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Pharmacotherapy and Pregnancy: Highlights from the Third International Conference for Individualized Pharmacotherapy in Pregnancy

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Pharmacotherapy and Pregnancy: Highlights from the Third International Conference for Individualized Pharmacotherapy in Pregnancy

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Abstract

To address provider struggles to provide evidence-based, rational drug therapy to pregnant women, this third Conference was convened to highlight the current progress and research in the field. Speakers from academic centers, industry, and governmental institutions spoke about: the Food and Drug Administration's role in pregnancy pharmacology and the new labeling initiative; drug registries in pregnancy; the pharmacist's role in medication use in pregnancy; therapeutic areas such as preterm labor, gestational diabetes, nausea and vomiting in pregnancy, and hypertension; breast-feeding and medications; ethical challenges for consent in pregnancy drug studies; the potential for cord blood banks; and concerns about the fetus when studying drugs in pregnancy. The Conference highlighted several areas of collaboration within the current Obstetrics Pharmacology Research Units Network and hoped to educate providers, researchers, and agencies with the common goal to improve the ability to safely and effectively use individualized pharmacotherapy in pregnancy. Clin Trans Sci 2011; Volume 4: 204–209

Introduction

The use of medications in pregnancy is common and based on complex risk-benefit discussions between physicians and patients.^{1,2} Unfortunately, still there are deficits in the information used in the decision making process. Often, pharmacokinetic (PK) and pharmacodynamic (PD) information for drugs used in pregnancy is scanty if present at all. A good example of that is the recommendation about the use of oseltamivir for influenza. The Centers for Disease Control and Prevention's recommendation states that no clinical studies have been conducted to assess the safety of these medications for pregnant women. However, the available risk-benefit data indicate pregnant women should receive prompt therapy.³ This highlights the need for more data regarding medication therapy in pregnancy. An annual Conference continues to bring together leading researchers and representatives from government agencies to discuss this matter.

The Third International Conference for Individualized Pharmacotherapy in Pregnancy was convened in 2010. Bringing together top researchers in the field, the Third Conference focused on research and regulatory issues and objectives for regulatory agencies as well as specific advances in several key therapeutic areas. Below are the summaries of the discussions at the conference. Full notes from the panel discussions are available from the authors on request. Speaker video from the conference is available at the PREGMED website: <http://www.pregmed.org>.

An Overview of the FDA Office of Women's Health (OWH) Funded Pregnancy Studies and Their Impact

The Food and Drug Administration's (FDA) Office of Women's Health (OWH) was created in 1994 after the 1992 Government Accounting Office report⁴ showed that women were not adequately

included in clinical studies. The FDA OWH mission is to (1) protect and advance the health of women through policy, science, and outreach, and (2) advocate for inclusion of women in clinical trials and analysis of sex/gender effects. To that end from 2002 to 2010, OWH has funded several studies to address hypertension, anthrax prevention, depression, and infection during pregnancy.

The studies included: PKs and PDs of atenolol during pregnancy and postpartum;⁵ the PK of amoxicillin during pregnancy and postpartum;⁶ the PK and PD of sertraline in pregnancy and postpartum;⁷ the PK and PD of labetalol in pregnancy; and the PK and PD of selected anti-infective agents in pregnant women being treated for suspected or documented infections. All studies were conducted during the second and third trimesters of pregnancy. Clearance for all drugs with the exception of azithromycin was shown to increase during pregnancy. No data were available on ciprofloxacin. Due to the limited number of subjects in the studies, more data are needed in pregnant women.

Pregnancy Registries' Contributions to Informed Clinical Practice

Pregnancy registries are prospective active data-collection systems that can facilitate the early detection of teratogenicity and other serious adverse experiences in patients who inadvertently or purposefully use a medication or receive a vaccine during pregnancy. The use of the pregnancy registry design has allowed for the collection and analysis of data on the effects of drug exposure on human pregnancies that have otherwise been difficult to obtain.⁸ Information from animal studies is useful but not always applicable, and pregnant women rarely are enrolled in clinical trials. However, useful information about the outcomes

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of exposed pregnancies can be obtained by the careful collection and analysis of postmarketing surveillance data.

Pregnancy registries collect reports of exposure during pregnancy and, through intensive follow-up with health care providers and patients, obtain information about pregnancy events and outcomes. Reports are evaluated and outcomes are compared to rates in the background population and, if available, in subpopulations with the relevant disease states. Reports of birth defects are assessed for timing of exposure, maternal age and medical history, biologic plausibility, etc. Voluntary reporting is known to be subject to various biases and sample size is often limited in pregnancy registries. Their strength lies in their ability to obtain and analyze pregnancy outcomes early in the life of a product and to evaluate patterns in birth-defect reports. Potential birth-defect signals could then be evaluated in studies designed for hypothesis testing.

The FDA encourages the establishment of pregnancy registries for products intended for use by women of childbearing potential in its "Guidance for Industry: Establishing Pregnancy Exposure Registries"⁹ and maintains a list of active registries on its website (<http://www.fda.gov/ScienceResearch/SpecialTopics/WomensHealthResearch/ucm134848.htm>). Pregnancy registries can provide periodic (semiannual or annual) summary reports that are shared with regulatory agencies that monitor drug safety and with health care professionals who request information about use in pregnancy. Health care providers and patients who experience a drug or vaccine exposure during pregnancy are encouraged to request the summary reports and to enroll in pregnancy registries to add to the existing data on medication safety during pregnancy.

On the Front Lines: A Pharmacist's Perspective

Preliminary data from the National Center for Health Statistics regarding 2008 birthrates show a decrease in live births, in 2008 compared to 2006. However, the live birth-rates per 1,000 women increased from 9.4 (2006) to 9.9 (2008) in women 40 to 44 years of age and 0.6 (2006) to 0.7 (2008) in women 45 to 49 years of age.^{10,11} As women age, they are more likely to develop chronic medical conditions. Treatment may start before conception. There is a need to ensure optimal medication therapy prior to, during, and after pregnancy to protect the mother and fetus from potential side effects. These side effects may come from medications or untreated conditions. When chronically hypertensive women become pregnant, maintaining optimal blood pressure (BP) is the primary goal, with antihypertensive agents if necessary.¹² In an asthmatic pregnancy, continuing current therapy does minimize symptoms. Reinforcement of proper inhaler technique, medication adherence, control of environmental allergens and coexisting medical therapy, as well as smoking cessation, should also be emphasized.¹³ Diabetics should have preconception counseling to help maintain goal blood glucose levels throughout pregnancy. A concern in depressed pregnant women is the potential for complications if antidepressant therapy is discontinued. These women should be advised to continue treatment for their benefit as well as that of the fetus. Treatment includes appropriate nutrition and weight gain, treatment of underlying addictions, improving mood prior to conception, and routine follow-up.¹⁴

When assessing pregnant women with chronic medical conditions, a risk/benefit exists regarding treatment to the patient and the fetus.¹⁵ Pregnant women should be educated prior to conception, to understand and weigh the risks of the complications of their medical condition versus the side effects of treatment and medications. Once a treatment decision is made, these

patients should be monitored regularly to ascertain adherence to appropriate treatment goals and should be encouraged to utilize nonpharmacologic methods when appropriate.

A review of maternal/fetal considerations and pharmacotherapy of tocolytics for preterm labor

In 2006, preterm birth (PTB) complicated 12.8% of pregnancies in the United States, with 75% of these births resulting from spontaneous preterm labor (PTL) and preterm premature rupture of membranes.¹⁰ Long-term sequelae from PTB are more likely to occur in neonates born before 32 weeks of gestation and/or weighing less than 1,500 g. These sequelae include neurologic handicap, blindness, deafness, and chronic respiratory disease. Acute tocolysis of PTL is implemented in order to minimize maternal morbidity and prolong pregnancy (≥ 48 hours) by allowing for administration of glucocorticoids to hasten fetal lung maturity. Indomethacin, nifedipine, and magnesium are three of the more commonly used tocolytics. The use of tocolytic drugs should be individualized and based on the maternal condition, potential for side effects, and fetal gestational age.¹⁶ In addition, the physiologic changes of pregnancy can affect the PK and PD of administered tocolytics, which may alter the pharmacologic effect.

Indomethacin is an antiprostaglandin (PG) agent that inhibits the synthesis of PGE₂ and PGF_{2 α} —PGs known to be involved in both term and PTL. Although prolonged indomethacin use may be associated with vasoconstriction and persistent changes in the fetal ductus arteriosus and the developing cerebral, renal, and mesenteric circulations, it is the most common prostaglandin inhibitor used for tocolysis. With a 50-mg loading dose, the peak serum concentration of indomethacin is 2–3 mg/L, half-life (T_{1/2}) is 2.2 hours, plasma clearance is 0.044–0.109 L/h per kg, and volume of distribution (V_d) is 0.34–1.57 L/kg.¹⁷ Indomethacin crosses the placenta leading to fetal serum concentrations that are greater than amniotic-fluid levels. Nifedipine is a calcium-channel antagonist that induces vascular smooth muscle relaxation. Its absorption is rapid, but bioavailability is low due to first-pass metabolism and conversion of 40% of the drug into inactive metabolites.^{17,18} After a 10-mg oral dose, the peak serum concentration is 38.6 ± 18 μ g/L, T_{1/2} is 1.3 ± 0.5 hours; and plasma clearance is 2.0 ± 0.8 L/h per kg.¹⁹ Nifedipine also crosses the placenta and is found in the umbilical cord, fetal blood, and amniotic fluid. Although unlicensed and with several contraindications to its use, including maternal side effects, magnesium sulfate is commonly used for tocolysis in the United States. Maternal serum concentrations do not correlate with tocolytic effect, therefore, the infusion rate of magnesium sulfate is titrated according to clinical response and side effects.²⁰ With a 4-g intravenous loading dose of magnesium sulfate, the peak serum concentration is 5.56 ± 0.30 mg/dL; T_{1/2} is 610 ± 14 minutes; and V_d is 15.6 L.¹⁷ Magnesium sulfate crosses the placenta and is found in the amniotic fluid and fetal compartment. Due to the limited amount of information available regarding the appropriate dosing and frequency of administration of these drugs, research into the PK and PD of tocolytics is necessary in order to more effectively treat PTL and improve neonatal outcomes through the prolongation of pregnancy.

How sweet it is—taking a second look at hypoglycemic agents in pregnancy

Gestational diabetes mellitus affects nearly 18% of pregnancies and is associated with significant maternal, fetal, and neonatal complications. Oral hypoglycemic agents such as glyburide and

metformin are commonly used for the treatment of gestational diabetes based on the randomized trials demonstrating similar outcomes to insulin, in addition to their easy route of administration and schedule.^{21,22} The physiologic changes that occur during pregnancy such as alterations in CYP2C9, CYP3A, and CYP2C19 activities have been shown to alter the PK of glyburide, which may have significant implications for the optimum dosage range during pregnancy.²³ However, glyburide has been shown to cross the placenta, therefore, evaluation of alternate dosage regimens above the currently used dosage range (up to 10 mg twice daily) will need to consider fetal and neonatal safety.²³ The changes in renal filtration as well as active renal transport during pregnancy result in altered PK of metformin.²⁴ The changes may or may not result in the need to alter the metformin dosage range during pregnancy. In addition to considerations regarding dosage range optimization for gestational diabetes mellitus treatment, medication selection optimization requires further evaluation. The heterogeneity in underlying abnormalities in insulin sensitivity and beta-cell responsiveness²³ for women with gestational diabetes will likely play a role in individual response to the various hypoglycemic agents.

NIH update on pregnancy pharmacology programs and the OPRUs

In the United States, more than 50% of women take one or more medications during their pregnancies. But most of the medications do not have adequate dosage and safety recommendations for the pregnant women, which may adversely impact the health of both pregnant women and their unborn babies. The Obstetric-fetal Pharmacology Research Units (OPRU) network was funded by the National Institute for Child Health and Human Development in 2005 and was recompleted in 2009 to serve as a national resource for pharmacologic studies of drug disposition and effect during normal and abnormal pregnancies.

The OPRU network takes a multidisciplinary approach to maternal and fetal therapeutics, pairing clinical and basic science collaborative researchers within the sites and across the networks. During the first funding cycle, the OPRUs performed a study on glyburide's effects during and after pregnancy²³ and on the PKs of 17alpha-hydroxyprogesterone caproate in pregnancy to reduce the risk of recurrent PTB. The OPRU network also conducted opportunistic studies to determine the PK of the drugs that are being used for medications in women during their pregnancies. The currently funded sites are Indiana University, University of Pittsburgh, University of Texas Medical Branch in Galveston, and University of Washington, along with a Data Coordinating Center at Research Triangle International. Each site has unique clinical and basic science strengths that synergize across the network to be able to advance the field. In the current round of funding, which began in 2010, there are currently two new clinical trials moving forward: a trial of glyburide and metformin therapy for gestational diabetes and a study of different progestins for the prevention of PTB.

Breast-feeding and medication in mother's milk

Medications are commonly taken by women during pregnancy and postpartum to treat diseases that are specifically related to pregnancy or preexisting medical conditions. Just as ethical and medical considerations are necessary for pharmacotherapy in pregnancy, considerations are necessary to avoid the risk of drug exposure to the infant by means of breast-milk transfer. Current-

product labeling allows for the description of drug excretion to human milk and discusses the risks for serious adverse events. The case of the serious adverse event from codeine described by Koren's group highlights the importance of human and genetic research in the area of human lactation.²⁵ The FDA's upcoming pregnancy-labeling rule will include sections on risk summary, clinical considerations, and known data. The most valuable study data to help populate the new pregnancy label will come from studies that look at the total infant exposure, measured by ratios of areas under the concentration-time curve of drug in maternal plasma as compared with breast milk. Clinical lactation studies should be geared toward identifying the risk of drug exposures to neonates, the total infant daily dose, and the safety and adverse events due to drug exposure. While there is a paucity of this type of data currently, more is on the way. With more data, it will be possible to help nursing mothers and their physicians in counseling and in planning clinical investigations.

Ethical challenges in consenting pregnant women for medication research

Society's approach to the protection of human subjects in research might be captured best by the image of a slowly swinging pendulum. In the early years (post-Nuremberg Code), a strong protectionist ethic prevailed when concern about minimizing risk was so pervasive that, to paraphrase Hans Jonas, society was encouraged to accept slower progress in the conquest of disease if it meant that human dignity and important moral values were retained. As time passed and experience progressed, the absolutist stance was relaxed, evidenced by the somewhat more permissive *Declaration of Helsinki* that permitted (where Nuremberg did not), research on vulnerable persons, including children. The pendulum has rarely swung to a completely permissive (i.e., a rule-free) position. But efforts to more carefully calibrate risk and to define vulnerable populations in need of special additional protections have been underway for decades. Pregnant women, children, fetuses, and neonates are defined as "vulnerable" and in need of additional protection according to this reasoning and have at various times been either completely excluded from eligibility for research or been limited participants. But here too, times have changed and the pendulum has not remained static. *The NIH Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research*—Amended October 2001²⁶ is a clear statement on *how* to include vulnerable persons. Consistent with the ethical principle of justice, the policy requires a justification if these populations are to be excluded, suggesting that the pendulum's current trajectory has come to rest at a position of moderate protectionism.

Medication research involving pregnant women may have been previously discouraged, but not now. One reason for the change in stance is the important role of informed consent as a gatekeeper. No one questions the value of a robust consent process. Where the challenges lie are at the level of quality and quantity of information: how much information do researchers need to disclose to subjects? Whereas it might seem self-evident that patients should be given as much information as possible, some research suggests that potential subjects do not actually understand or want much of the information before making decisions. This finding should give pause if applied to a medication study (do we really want to give less rather than more information?), but, in other areas such as the development of biobanks, changes in the practice of informed consent are already underway.

Vanderbilt's BioVU biobank is an opt-out system (not unlike Spain's presumed consent approach to organ transplantation) where research subjects must indicate a preference not to have data or information used in research.

The pendulum is also influenced by researchers serving in multiple roles (e.g., health care provider and researcher), as do many health care providers. As demonstrated in a recent study, there is often a disconnect between what health care providers will support for their patients and for themselves.²⁷ Can we rely on the quality of the data that help us inform decisions? If the data are not robust, then are decisions truly informed? We also know that research is not confined by national borders. Research must also be sensitive to the social, political, and cultural issues in different locations. For instance, in parts of Kenya, women are culturally not allowed to consent for themselves. It is only in discussing and working on these ethical challenges that we can continue to see progress and meaningful and ethical benefits to human subjects' research in general, and specifically in pregnancy.

FDA and Maternal Health Update: Gathering and Communicating Data about Drug Use during Pregnancy and Lactation

There are more than 60 million American women of reproductive age, and about 10% of them become pregnant each year, only 50% of these pregnancies are planned. Pregnant women may require continued drug treatment for chronic conditions or treatment for new conditions that arise during pregnancy. While pregnant women use an average of four or five prescription drugs during pregnancy, they are usually excluded from clinical drug trials conducted prior to approval for marketing. Research and knowledge gaps remain following FDA approval and marketing of most drugs because studies of maternal and fetal effects and the amount of drug in human milk are not routinely studied. In turn, prescribers have little or no scientific evidence with which to inform clinical care, prescribing, and counseling for women of childbearing potential.

Over the past decade, new legislative authorities (FDA Amendments Act of 2007), multiple FDA initiatives, and efforts in the scientific and ethics communities have coalesced into a movement to improve data gathering and communication about drug use during pregnancy and lactation. The Pediatric and Maternal Health Staff (PMHS) in the Office of New Drugs at FDA's Center for Drug Evaluation and Research focuses on drug development and drug safety issues related to the use of medications in children, adolescents, and women of childbearing potential, especially those who are pregnant and breast-feeding. FDA's activities currently focus on three areas:

- (1) Development, clearance, and publication of the final regulations for pregnancy and lactation labeling for prescription drugs and biological products.
- (2) Development and publication of guidance for the drug development industry and FDA reviewers (e.g., PK during pregnancy and the postpartum period, clinical lactation studies, pregnant women in clinical trials: scientific and ethical considerations).
- (3) Working with review divisions in the Office of New Drugs to identify drugs that should be approved with requirements to study the effects of the drug in pregnant women and/or the amount of drug in human milk.

The new proposed regulations for pregnancy and lactation labeling for prescription drugs were published in May 2008. FDA received comments on the proposed regulations during a 90-day public comment period. These comments were considered and utilized by the FDA in development of the final regulations for publication, a process that is currently underway. The proposed regulations call for eliminating the confusing and often misused pregnancy categories (A, B, C, D, and X) from drug labeling for all drugs and will revise the content and format of pregnancy and nursing mothers labeling subsections for prescription drugs approved on or after June 30, 2001. Drug manufacturers will be able to voluntarily adopt the new format and content requirements for older drugs. The pregnancy subsection of labeling will include information about whether there is an ongoing prospective cohort study (pregnancy exposure registry) evaluating the effects of the drug in pregnant women using the drug therapeutically. This will be followed by a *Risk Summary* based on available human and animal data; a *Clinical Considerations* section; and a *Data* section that includes detailed information about the studies supporting the information in the *Risk Summary* and *Clinical Considerations*. The *Clinical Considerations* section provides information to prescribers to support clinical decision making and management. It includes information about the known risk to a pregnant woman and her fetus from the disease or condition the drug is intended to treat, dosing adjustments needed during pregnancy, maternal adverse reactions unique to or exacerbated by pregnancy, and potential neonatal complications and needed interventions. The *Clinical Considerations* section also includes information about known effects of the drug on labor and delivery.

FDA's greatest communication tool is drug labeling, but developing informed and balanced labeling is a complicated and challenging process. This is especially true for information about medication use during pregnancy and breast-feeding because there is often limited information at the time that a drug is approved. It is critical to our nation's public health to identify and communicate the risks and benefits of medication treatment for mothers and their fetuses/infants. This can only be accomplished with thorough scientific review of available human and animal data, identification of ethical and scientifically sound approaches to gathering more human data on medication use during pregnancy and breast-feeding, and clear and clinically relevant communication of this information to prescribers through drug labeling.

New Frontiers in Nausea and Vomiting of Pregnancy

Nausea and vomiting of pregnancy (NVP) affects an estimated 80% of all pregnancies. The condition has been trivialized in practice and research, assuming that it is merely an inconvenience. However, research in Motherisk has shown major impact on the quality of life of millions of women.²⁸

Treatment of symptoms of NVP has been challenged by limited research and less than optimal sample sizes to prove fetal safety. The drug most studied has been the combination of doxylamine and pyridoxine (vitamin B6). It is estimated that this antiemetic combination will reenter the American market as Diclectin® (a Canadian version of Bendectin®, used in the United States until 1982). Recent studies have shown that NVP associated with reflux symptoms is more severe, and that treatment of reflux symptoms with either H₂ blockers or Proton Pump Inhibitors alleviates the severity of NVP.²⁹

Cord blood (and tissue) banks—can they inform future therapies?

Maternal and fetal/newborn tissues (e.g., cord blood, placenta) are readily available, often discarded, and useful for both clinical and research needs. There is potential for cord blood and tissue banks to be repositories of cells and tissues for pharmacology research. Areas in which cells/tissues are used for maternal/fetal pharmacology research include transporter cellular/molecular biology; growth factor production and signaling; enzyme polymorphism studies; and drug metabolism studies. At the present time, a variety of cell and tissue models, such as malignant cell lines, isolated mature cells and/or microsomes, and *ex vivo* perfused tissues are used for this research. However, the extent to which these model systems represent normal maternal/fetal tissues is unclear, and problems also exist with standardization and reproducibility between laboratories. The use of primary stem/progenitor cells derived from maternal/fetal tissues provides potential solutions to some of these problems, since primary cultures can be isolated using standardized techniques, greatly expanded in culture, used to reproduce results using cells from the same donor instead of multiple donors, and widely distributed for validation of results in numerous laboratories.

The question remains regarding where these cells and tissues would be processed for widespread research use. Cord blood banks have been proposed as one potential source, since they routinely process and store cord blood hematopoietic stem cells for clinical use. However, cord blood banks perform minimal cell isolation and no culture/expansion since there is currently no clinical need for isolation and culture of hematopoietic cells, and in general process only cord blood and not other maternal/fetal tissues. Alternatively, tissue banks are well suited to providing cells and tissues to the research community. Tissue banks can store whole tissues but also isolate specific cells and often expand these cells prior to (or after) banking. Primary cells from maternal/fetal tissues that are potentially available from tissue banks include mesenchymal stem cells (MSC) from cord blood, cord tissues (e.g., Wharton's jelly), and placenta; endometrial (or uterine) regenerative cells (ERC); and human umbilical vein endothelial cells (HUVEC). MSC are expandable in culture to $>10^{12}$ cells or >30 population doublings, facilitating multiple reproducible experiments validated in many laboratories from a single donor. Placental MSC have been demonstrated to participate in placental tissue generation, maintenance, and repair, attesting to their utility as a model for normal tissues. HUVEC are more limited in their culture capacity than MSC and ERC, but are already widely used for pharmacologic research, particularly involving oxidative stress and vasogenic factors involved in pregnancy/labor. In summary, primary cells provided by tissue banks from maternal and/or neonatal tissues are readily available and expandable, are superior to immortalized malignant cell lines, may be able to mimic *in vivo* conditions by coculture of cell types (e.g., HUVEC with placental MSC; maternal with fetal-derived MSC), and may be amenable to additional manipulation, such as syncytialization of trophoblasts in culture. Moreover, not only normal cells but cells from neonates with genetic defects can be isolated; these cells may provide additional cellular research models and disease insights.

Preeclampsia and hypertension—individualizing therapy

Antihypertensive therapy in pregnancy and preeclampsia have evolved as the data have driven more individualization. The risk

of not intervening is severe hypertension and its adverse maternal sequelae. The risk of intervening too early is premature or small for gestational age babies. It is evident that treating hypertension in pregnancy prevents severe hypertensive crises.³⁰

Individualizing therapy based on maternal hemodynamics is based on the equation that Mean Arterial Pressure (MAP) = Cardiac Output (CO) \times Total Peripheral Resistance (TPR)/80. In order to control blood pressure, either the CO or TPR can be targeted by therapy. Additionally, simply because the majority of hypertensive pregnant women are in a vasoconstricted state does not mean that all subjects would benefit from lowering resistance. Studies have demonstrated that controlling BP before women get pregnant can reduce preterm deliveries. A small study demonstrated that atenolol therapy led to smaller babies.³¹ It is confirmed that there is a trade-off that as the BP is lowered, the birth weight does go down, however, there is less preterm delivery and respiratory distress syndrome. Individualizing therapy may actually indicate that it takes less drugs to control the BP as the pregnancy progresses. Hydralazine is a vasodilator that leads to a small increase in CO as the MAP decreases. Beta blockers such as atenolol decrease CO, leading to a decrease in MAP and a slight increase in TPR. Diuretics such as furosemide decrease CO in smaller amounts than beta blockers. Clonidine is a complex drug that has considerable variability in CO and TPR response. Thus, combination therapy can often achieve the normalization of maternal hemodynamic parameters that single-agent therapy is unable to provide. Individual variation in drug metabolizing enzymes may also play a role as certain drugs such as metoprolol are CYP2D6 substrates and can have profound differences in activities throughout pregnancy. The goal of the PK and PD principles in fostering individualized drug therapy for hypertension and preeclampsia is to promote maternal health, prevent PTB, and maintain fetal growth. Maternal hemodynamics can be used to effectively direct therapy to achieve these individualized pharmacotherapy goals.

Do not forget the baby—studying neonatal effects of drugs in pregnancy

Fetal development is an especially sensitive period, and alterations and interventions have the potential to produce lifelong consequences. As predicted by the fetal origins of adult disease hypothesis, it is becoming increasingly clear that altered fetal growth can significantly increase the risk of adult onset diseases such as hypertension, coronary artery disease, and type II diabetes. It is then reasonable to be concerned that maternal exposure to drugs may have the potential to produce similar long-term consequences.

The use of antenatal steroids to reduce respiratory distress syndrome in premature infants is probably the best-studied fetal drug exposure. Multiple randomized controlled trials have demonstrated that antenatal steroids provide significant benefits, including reductions in respiratory-distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and death. In addition, there is significant information about the effects of antenatal steroids beyond the neonatal period. Exposure to antenatal steroids has no detrimental effect in children or adults on hypothalamic-pituitary axis function, growth, blood pressure, or cholesterol concentrations. There is even a suggestion that blood-glucose concentrations may be lower in adults who have received antenatal steroids compared to those who have not. So for antenatal steroids, there is high-quality evidence supporting significant neonatal benefits and no long-term negative effects;

it is unlikely that this amount or quality of information will be produced for most other maternal drug exposures.

A drug class of current interest is the selective serotonin reuptake inhibitors (SSRIs). There are no available randomized-controlled trials, but observational studies have raised concerns about SSRI exposure and increased risk of premature delivery, although untreated depression may have a similar effect. Neonatal-abstinence syndrome after *in utero* exposure to SSRIs has been well documented, with approximately 30% of exposed infants having symptoms. A relationship between maternal use of SSRIs and persistent pulmonary hypertension of the newborn has also been observed; however, the increase in risk appears to be small, and not all studies have observed the relationship. Observational studies examining neurodevelopmental outcome after maternal use of SSRIs have not measured any adverse effects in children up to 6 years of age. However, the effects of fetal SSRI exposure beyond early childhood remain unknown. Some mechanism to evaluate the long-term effects of drugs in pregnancy is necessary; as electronic medical records become more prevalent, documenting maternal drug exposures in the medical record would be an important advance in evaluating long-term drug effects in children and the mothers.

Conclusion

As providers, pharmacists, FDA and NIH representatives, and patients make decisions every day about medication therapy in pregnancy, it is clear that more data are needed. Hypertension, diabetes, and PTL are just a few of the conditions that require drug therapy in pregnancy. Understanding the data through the current research, and upcoming pregnancy and lactation labeling changes, will aid in counseling pregnant women about their options. Cooperation and collaboration between government agencies, researchers, and people on the front lines of patient care will continue to strive to improve the care of pregnant women and their babies.

References

- Andrade SE, Gurwitz JH, Davis RL, Chan KA, Finkelstein JA, Fortman K, McPhillips H, Raebel MA, Roblin D, Smith DH, et al. Prescription drug use in pregnancy. *Am J Obstet Gynecol*. 2004; 191(2): 398–407.
- Engeland A, Bramness JG, Dalveit AK, Ronning M, Skurtveit S, Furu K. Prescription drug use among fathers and mothers before and during pregnancy. A population-based cohort study of 106,000 pregnancies in Norway 2004–2006. *Br J Clin Pharmacol*. 2008; 65(5): 653–660.
- Updated Interim Recommendations for Obstetric Health Care Providers Related to Use of Antiviral Medications in the Treatment and Prevention of Influenza for the 2009–2010 Season. The Centers for Disease Control and Prevention. 2009 [cited 2009 September 24]; Available from: http://www.cdc.gov/H1N1flu/pregnancy/antiviral_messages.htm.
- United States General Accounting Office GAO/HRD-93-17. Women's Health – FDA needs to ensure more study of gender differences in prescription drug testing. 1992.
- Hebert MF, Carr DB, Anderson GD, Blough D, Green GE, Brateng DA, Kantor E, Benedetti TJ, Easterling TR. Pharmacokinetics and pharmacodynamics of atenolol during pregnancy and postpartum. *J Clin Pharmacol*. 2005; 45(1): 25–33.
- Andrew MA, Easterling TR, Carr DB, Shen D, Buchanan ML, Rutherford T, Bennett P, Vicini P, Hebert MF. Amoxicillin pharmacokinetics in pregnant women: modeling and simulations of dosage strategies. *Clin Pharmacol Ther*. 2007; 81(4): 547–556.
- Freeman MP, Nolan PE Jr, Davis MF, Anthony M, Fried K, Fankhauser M, Woolsey RL, Moreno F. Pharmacokinetics of sertraline across pregnancy and postpartum. *J Clin Psychopharmacol*. 2008; 28(6): 646–653.
- Shields KE, Wilholm BE, Hostelley LS, Striano LF, Arena SR, Sharrar RG. Monitoring outcomes of pregnancy following drug exposure: a company-based pregnancy registry program. *Drug Saf*. 2004; 27(6): 353–367.
- Guidance for Industry Establishing Pregnancy Exposure Registries. Rockville, MD: U. S. Food and Drug Administration; 2002.
- Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S, Mathews TJ. Births: final data for 2006. *Natl Vital Stat Rep*. 2009; 57(7): 102 pp.
- Hamilton BE, Martin JA, Ventura SJ. Births: preliminary data for 2008. *Natl Vital Stat Rep*. 2010; 58(16): 1–17.
- Yoder SR, Thornburg LL, Bisognano JD. Hypertension in pregnancy and women of childbearing age. *Am J Med*. 2009; 122(10): 890–895.
- Schatz M, Dombrowski MP. Clinical practice. Asthma in pregnancy. *N Engl J Med*. 2009; 360(18): 1862–1869.
- Yonkers KA, Wisner KL, Stewart DE, Oberlander TF, Dell DL, Stotland N, Ramin S, Chaudron L, Lockwood C. The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *Obstet Gynecol*. 2009; 114(3): 703–713.
- Briggs GG, Nageotte MP, editors. *Diseases, Complications, and Drug Therapy in Obstetrics: A guide for clinicians*. Bethesda, MD: American Society of Health-Systems Pharmacists; 2009.
- Tan TC, Devendra K, Tan LK, Tan HK. Tocolytic treatment for the management of preterm labour: a systematic review. *Singapore Med J*. 2006; 47(5): 361–366.
- Tsatsaris V, Cabrol D, Carbone B. Pharmacokinetics of tocolytic agents. *Clin Pharmacokinet*. 2004; 43(13): 833–844.
- Abernethy DR, Schwartz JB. Calcium-antagonist drugs. *N Engl J Med*. 1999; 341(19): 1447–1457.
- Ferguson JE 2nd, Schutz T, Pershe R, Stevenson DK, Blaschke T. Nifedipine pharmacokinetics during preterm labor tocolysis. *Am J Obstet Gynecol*. 1989; 161(6 Pt 1): 1485–1490.
- Madden C, Owen J, Hauth JC. Magnesium tocolysis: serum levels versus success. *Am J Obstet Gynecol*. 1990; 162(3): 1177–1180.
- Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. *N Engl J Med*. 2000; 343(16): 1134–1138.
- Rowan JA, Hague WM, Gao W, Battin MR, Moore MP. Metformin versus insulin for the treatment of gestational diabetes. *N Engl J Med*. 2008; 358(19): 2003–2015.
- Hebert MF, Ma X, Narahariseti SB, Krudys KM, Umans JG, Hankins GD, Caritis SN, Miodovnik M, Mattison DR, Unadkat JD, et al. Are we optimizing gestational diabetes treatment with glyburide? The pharmacologic basis for better clinical practice. *Clin Pharmacol Ther* 2009; 85(6): 607–614.
- Eyal S, Easterling TR, Carr D, Umans JG, Miodovnik M, Hankins GD, Clark SM, Risler L, Wang J, Kelly EJ, et al. Pharmacokinetics of metformin during pregnancy. *Drug Metab Dispos*. 2010; 38(5): 833–840.
- Koren G, Cairns J, Chitayat D, Gaedigk A, Leeder SJ. Pharmacogenetics of morphine poisoning in a breastfed neonate of a codeine-prescribed mother. *Lancet*. 2006; 368(9536): 704.
- NIH policy and guidelines on the inclusion of women and minorities as subjects in clinical research. 2001. Available at: http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. Accessed October 14, 2008.
- Haas DM, Wunder K, Wolf JG, Denne SC. Women's health care providers' attitudes toward research in pregnancy. *J Reprod Med*. 2010; 55(3–4): 108–114.
- Mazzotta P, Stewart D, Atanackovic G, Koren G, Magee LA. Psychosocial morbidity among women with nausea and vomiting of pregnancy: prevalence and association with anti-emetic therapy. *J Psychosom Obstet Gynaecol*. 2000; 21(3): 129–136.
- Gill SK, Maltepe C, Koren G. The effect of heartburn and acid reflux on the severity of nausea and vomiting of pregnancy. *Can J Gastroenterol*. 2009; 23(4): 270–272.
- Magee LA, Elran E, Bull SB, Logan A, Koren G. Risks and benefits of beta-receptor blockers for pregnancy hypertension: overview of the randomized trials. *Eur J Obstet Gynecol Reprod Biol*. 2000; 88(1): 15–26.
- Butters L, Kennedy S, Rubin PC. Atenolol in essential hypertension during pregnancy. *BMJ*. 1990; 301(6752): 587–589.