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We Don't Know What We Don't Study: The Case for Research on Medication Effects in Pregnancy

Melissa A. Parisi[1], **Catherine Y. Spong**[2], **Anne Zajicek**[3], and **Alan E. Guttmacher**[4]

[1] Intellectual and Developmental Disabilities Branch *Eunice Kennedy Shriver* National Institute of Child Health and Human Development National Institutes of Health Bethesda, MD

[2] Pregnancy and Perinatology Branch *Eunice Kennedy Shriver* National Institute of Child Health and Human Development National Institutes of Health Bethesda, MD

[3] Obstetric and Pediatric Pharmacology Branch *Eunice Kennedy Shriver* National Institute of Child Health and Human Development National Institutes of Health Bethesda, MD

[4] Office of the Director *Eunice Kennedy Shriver* National Institute of Child Health and Human Development National Institutes of Health Bethesda, MD

Abstract

This Commentary addresses issues related to exposures to teratogens and makes the case for increased research into the safety of medications during pregnancy for mothers and fetuses. Not only are medications commonly used during pregnancy, but evidence points to an increasing prevalence and number of drug exposures experienced by the embryo or fetus, particularly during the critical first trimester of pregnancy. Although the first trimester represents a particularly vulnerable period of organogenesis, exposures during other gestational time periods may also be associated with deleterious outcomes. In addition to the changing (and in many cases unknown) risks to a developing fetus, other challenges to studying medication exposures and their effects during pregnancy include the dramatic changes in physiology that occur in pregnant women and the ethical dilemmas posed by including this vulnerable population in randomized controlled trials of safety and efficacy. However, without adequate knowledge of the pharmacokinetics, pharmacodynamics, efficacy, and safety of medication use in pregnancy, women may be under-dosed to minimize exposure or not treated at all, resulting in inadequate treatment and potential harm to the mother and her baby. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is undertaking studies on medications and teratogenic exposures during pregnancy, including alcohol, maternal diabetes, oral hypoglycemic agents, and antiviral medications, through several of its research networks. Although this is a start, there is a critical need for further research on medications used during pregnancy, especially their effects on both the mother and her developing child.

Keywords

medication; exposure; pregnancy; teratogen; research

"Pregnant women become ill, and sick women become pregnant" is certainly a truism, but do we really understand how best to treat women during pregnancy? The past decade has witnessed the development of treatments for several disorders, in part due to efforts of the

Corresponding author: Melissa A. Parisi, MD, PhD, Intellectual and Developmental Disabilities Branch, Center for Developmental Biology and Perinatal Medicine, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, 6100 Executive Boulevard, Room 4B09, MSC 7510, Bethesda, MD 20892-7510. Tel: (301) 435-6880 Fax: (301) 496-3791 parisima@mail.nih.gov .

National Institutes of Health (NIH) and the Food and Drug Administration (FDA) to promote translational research to develop compounds that can enter the pipeline of drug development and to support clinical trials of new therapeutics [Collins, 2010]. However, a glaring lack of knowledge remains about the safety and efficacy of the vast majority of medications used during pregnancy and other exposures that pregnant women experience. There is also a paucity of drugs indicated for use in pregnancy, and near complete absence of development of new medications for this population [Fisk and Atun, 2008]. Further research on medication use in pregnancy is critically needed.

Although a teratogen is broadly defined as an environmental agent capable of causing abnormal prenatal variation in form or function, most individuals immediately think of medications as the most suspect of teratogenic agents. A prime example is the vitamin A derivative, isotretinoin (Accutane), which can cause hearing and visual loss, malformed ears, other dysmorphic features, and intellectual impairment in exposed fetuses. In fact, teratogens include many agents in addition to medications: (1) infectious (e.g., syphilis, toxoplasmosis, cytomegalovirus infection); (2) physical (e.g., radiation, heat, uterine constriction); (3) maternal metabolic/genetic (e.g., maternal diabetes, maternal phenylketonuria); and (5) paternal (e.g., cumulative exposures resulting in DNA damage and new dominant mutations) [Robinson and Linden, 1993]. The period of greatest teratogenic risk is the first trimester, the most critical period of organogenesis [Mitchell et al., 2011]. Although the majority of exposures that result in birth defects are presumed to do so because they affect development of the embryo during organ development in early gestation, some teratogens have effects later in pregnancy.

Medications are commonly used in pregnancy. Approximately 64% of women in the US are prescribed one or more drugs, excluding vitamins and minerals, during pregnancy [Andrade et al., 2004; Chambers et al., 2008]. Since around half of all pregnancies are unplanned, and fewer than half of pregnancies are recognized before the 4th week of gestation, some of this drug use occurs before a woman knows pregnancy has begun or could plan to limit her exposures. In addition, many common acute or chronic conditions such as urinary tract infections, depression, hypertension, or asthma require medication usage during pregnancy [Chambers et al., 2008]. Over-the-counter (OTC) medications and herbal supplements are also commonly used during pregnancy. Survey data collected from over 30,000 women by the Slone Epidemiology Center Birth Defects Study (BDS) from 1976-2008, and the National Birth Defects Prevention Study (NBDPS) from 1997-2003, provide several important observations about medication usage and trends over time. In the BDS survey, the average number of medications (prescription and OTC) used in pregnancy was 2.5 between 1976 and 1978 and had risen to 4.2 by the last two years of the study (2006-2008) [Mitchell et al., 2011]. In addition, medication usage increased by 63% *during the first trimester alone* between the earliest and latest study periods of the BDS, with an average of 2.6 medications used during this most sensitive of periods. By the last year of the study, 94% of women took at least one medication during pregnancy [Mitchell et al., 2011]. Similar trends were observed in the NBDPS. The proportion of women taking at least one *prescription* medication has dramatically increased over the past three decades, despite the fact that many formerly prescription medications are now available OTC. Some of the most commonly used prescription drugs include antibiotics, asthma medications, and anti-nausea medications. While fewer than 1% of pregnant women took an antidepressant during the 1988-1990 period, 7.5% used antidepressants during the most recent period, with a significant proportion taking selective serotonin-reuptake inhibitors (SSRIs) [Mitchell et al., 2011].

Studying medications requires specific trial design, including pharmacokinetics, pharmacodynamics, efficacy, and safety. Pregnancy complicates these studies. Dramatic

physiologic changes occur during pregnancy, including a 50% increase in glomerular filtration rate, a 40-45% increase in blood volume, and alterations in serum binding proteins [Cunningham et al., 2009]. In addition, there are potential critical time periods of vulnerability of the embryo or fetus during the gestational period. Most clinical trials of medications exclude pregnant women due to these issues and because of ethical considerations, focusing instead on determining safety, efficacy, and dosing in the non-pregnant state. However, this is not rectified after completion of the initial studies – rather the pharmacokinetic and dosing information is, at best, extrapolated to the pregnant state without additional data.

The FDA classifies drugs into five categories to describe their risk of teratogenicity (A, B, C, D, and X). However, the vast majority of medications are characterized by the FDA as pregnancy category B ("Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women") or category C ("Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks"). In an article in this issue by Adam et al., their recent survey of safety information for 176 drugs approved by the FDA between 2000 and 2010 documents that 97.7 % had an "undetermined" teratogenic risk in human pregnancy, and 73.9% had no data available regarding safety in pregnancy [Adam et al., 2011]. In cases where a drug is a known teratogen (pregnancy category D), the impact of the type of adverse outcome is not incorporated into the pregnancy category rating, so a medication such as doxycycline that may cause dental staining is in the same category as valproic acid, which can cause birth defects such as myelomeningocele [Chambers et al., 2008]. In fact, the majority of data used to derive pregnancy categories is based on animal data, with uncertain ability to translate these preclinical toxicity studies to risks to human fetuses [Chambers et al., 2008]. Most randomized clinical trials of medications do not include pregnant women because of study design issues and ethical concerns related to including this "vulnerable population" in trials of safety and efficacy. However, because the current system relies on voluntary case reports and registries [Leen-Mitchell et al., 2000; Lim et al., 2009], the consequence is either inadequate data or, at best, a long delay in obtaining adequate data about drug safety during pregnancy. It may take several decades to identify enough rare cases of an adverse fetal outcome to recognize a drug as a teratogen; the recent case of mycophenolate mofetil, a common immunosuppressant, is one such example where the pattern of malformations was only recognized when "astute clinicians" identified a pattern of birth defects in enough newborns to make the association with the drug [Carey et al., 2009]. Another example is that of SSRIs for the treatment of depression. Early studies with small sample sizes in the 1990s suggested no increased risk of birth defects, but more recent studies have indicated a small but increased risk of rare congenital defects in exposed infants [Alwan et al., 2007; Chambers et al., 2006; Kallen and Otterblad Olausson, 2007; Louik et al., 2007]. The fundamental problem is the lack of adequate information to draw conclusions about the safety, efficacy, and proper dosing of drugs during pregnancy.

When left with inadequate data on which to base a decision about use of a medication during pregnancy, the clinician and patient often make decisions that can have serious consequences for the health of the pregnant woman or of the developing child. Underdosing to reduce teratogenic risk may result in inadequate treatment, particularly if the dose of a specific medication needs to be increased to meet the dramatic physiologic and metabolic changes during pregnancy. For example, levothyroxine requirements markedly increase in women with hypothyroidism during pregnancy [Alexander et al., 2004]; thus, maternal thyroid levels need to be monitored at least once per trimester, and more frequently with any dosing changes to ensure adequate fetal levels of this hormone. Recommended amoxicillin

dosing for post-exposure anthrax prophylaxis is likely inadequate in pregnant women due to various renal changes [Andrew et al., 2007]. Furthermore, some women treated with SSRIs for depression have discontinued their medication because of concerns of fetal risks, with disastrous consequences, including a relapse of major depression or suicidal ideation [Cohen et al., 2006; Einarson et al., 2001]. In other cases, women have chosen to terminate a pregnancy because of perceived high risks when, in fact, the risks were quite low [Koren and Pastuszak, 1990].

This dearth of pharmacokinetic/pharmacodynamic data for medication use in pregnant women is particularly alarming. During the recent influenza A H1N1 pandemic in 2009, pregnant women were at increased risk of hospitalization, death, and adverse infant outcomes. The Centers for Disease Control and Prevention (CDC) recommended treatment with oseltamivir, but limited data were available to suggest a safe or efficacious dose in the pregnant population [Rasmussen et al., 2009]. In fact, although many experts advocated for increased doses of oseltamivir because of physiologic and metabolic changes of pregnancy, particularly for the sickest pregnant patients [Saleeby et al., 2009], the CDC did not make this recommendation because data were not available to address dosage adjustment during pregnancy [Greer et al., 2011]. Basic information about the metabolism of the majority of medications used during pregnancy is completely unavailable, leaving pregnant women and their providers in the dark about an appropriate dosing strategy.

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) has as part of its mission to “ensure that every person is born healthy…” and as part of that effort, supports research on reproductive health, pregnancy, and pregnancy outcomes, including the effects of a broad range of medications and interventions during pregnancy. Research is ongoing for some of the more common exposures recognized as teratogenic, alcohol and maternal diabetes. The Prenatal Alcohol and SIDS (Sudden Infant Death Syndrome) and Stillbirth (PASS) Network, funded jointly by NICHD and the National Institute on Alcohol Abuse and Alcoholism (NIAAA), examines the role of prenatal alcohol exposure in the risk for SIDS and adverse pregnancy outcomes, such as stillbirth and fetal alcohol syndrome, and how these risks may be interrelated. This study will follow 10,000 women and their children, focusing on two groups with particularly high current rates of exposure to this teratogen, the Northern Plains Native American community and the South African Western Cape population. Diabetes in pregnancy, specifically uncontrolled hyperglycemia, is a known teratogen resulting in caudal regression sequence and a broad spectrum of malformations including heart defects, with the major effects in the first trimester during organogenesis. Recent studies have suggested that use of oral hypoglycemics instead of insulin injections can be efficacious in pregnant women; however, their pharmacology and dosing in pregnancy are not known. The NICHD’s Obstetric-Fetal Pharmacology Research Units Network (OPRU) is examining the pharmacokinetics and pharmacodynamics of several medications in pregnancy, including oral hypoglycemic agents for treatment of gestational diabetes. The NICHD’s Maternal-Fetal Medicine Units Network has assessed the exposure and safety of oseltamivir in a 2009 H1N1 influenza registry, and the OPRU provided critical data assessing its pharmacokinetics in pregnant and nonpregnant women, as a start to providing information on which to base dosing decisions during pregnancy [Beigi et al., 2011].

This is only a beginning. More research is needed to better understand the effects of medications during pregnancy, not only the pharmacodynamics so that effective doses can be given to pregnant women, but also the risks that these medications and other exposures pose for fetal growth, organ formation, and neurological function. With improved federal regulations and a research commitment by granting agencies, pharmaceutical companies,

and investigators, we can and must expand our knowledge of both the efficacy of medications for pregnant women, and the effects on their developing babies.

Biography

Melissa A. Parisi, M.D., Ph.D., is a board-certified pediatrician and clinical geneticist. She is Chief of the Intellectual and Developmental Disabilities Branch of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) at the National Institutes of Health (NIH).

Catherine Y. Spong, M.D., is an obstetrician gynecologist with subspecialty training in maternal fetal medicine. She is the Chief of the Pregnancy and Perinatology Branch at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD).

Anne Zajicek, M.D., Pharm.D., is a board-certified pediatrician and pediatric clinical pharmacologist. She is Chief of the Obstetric and Pediatric Pharmacology Branch at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD).

Alan E. Guttmacher, M.D., is a pediatrician and medical geneticist. He is the Director of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD).

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