



## Legacy Building

### Pharmacoepidemiology

Julia Beck is an upbeat, can-do woman. A marketing strategist in Washington, DC, Beck survived a rare, deadly disease in her twenties. One unfortunate by-product was epilepsy, one of the most common neurological disorders in the U.S. Her seizures were frequent and unpredictable.



In her early thirties, Beck and her former husband began their quest to have a baby. To limit the risks associated with multiple medications, Beck's physician recommended she go on a one-drug-only regimen. The trial-and-error period that ensued triggered not only more seizures, it also provoked a cascade of concerns that her medications would cause deformities in her child. Though she was surrounded by "brilliant medical minds" and did extensive research—"I was on top of my game," she says—information about how anti-epilepsy medications might affect her baby was hard to come by. "It was a bit of the Wild West," says Beck.

An astonishing—and growing—number of women face such daunting dilemmas. Some 50% of pregnant women—about two million annually in the U.S.—take at least one prescription drug during their pregnancy. The number taking prescription drugs during the first trimester, when the fetus' organs are just forming, has jumped 60% in the past 30 years, and the number using at least four medications has more than doubled in the same period. An even higher proportion, close to 80%, take at least one over-the-counter drug. What's more, half of all pregnancies are unplanned, giving women no reason to even think about the possible hazards of medications considered safe.

With all this pill-taking, no published data exists to assess the potential birth defect risk for 79% of medications approved between 2000-2010. That's because pregnancy often puts a game-stopping vise on medical research trials. While all medications must pass a series of tests for safety and efficacy before gaining approval, pregnant women are excluded to protect mother and child. Somehow, after approval, this lack of evidence is often construed as evidence of safety.

Entering the fray of such fraught situations is Sonia Hernandez-Diaz, MD, DrPH, one of a handful of epidemiologists worldwide devoted to studying drug safety during pregnancy. "There's a glaring informational gap to be filled," she says. "I want women and their clinicians to avoid risks, as well as unnecessary anxiety, during pregnancy. It's a public health problem."

## **New Finding, New Thinking, New Treatment**

With that aim in mind, Hernandez-Diaz is bringing her finely-honed epidemiologic research skills to three large-scale studies exploring the issue. Her goal: To optimize medical decision-making and improve health outcomes.

In an effort to obtain valid, precise and timely information, Hernandez-Diaz joined a huge case-controlled surveillance study, launched in 1978, that identifies fetuses and newborns with birth defects, as well as a sample of control infants without malformations. Specific medication-related information for some 30,000 women was collected. The mothers are interviewed retrospectively to determine their use of medications during pregnancy.

Hernandez-Diaz chooses to study common exposures, where the public health impact could be immense. Her unique contribution was devising a systematic approach to assess the risks of the most commonly-used medications during pregnancy, both prescription and over-the-counter—pain relievers, antibiotics, asthma medications, anti-histamines, cough medicine and anti-allergy drugs—assumed safe for pregnant women. Initial findings for pain relievers and antibiotics are reassuring, showing no association between these commonly-used drugs and common birth defects. The impact of cough medications and antihistamines are still being evaluated.

To further arm women and physicians with facts, Hernandez-Diaz is also concentrating on the risks and benefits of anti-depressants on pregnant women. Working with anonymized national Medicaid data from all 50 states compiled by the Centers for Medicare and Medicaid Services, she spearheaded the creation of a database of one million pregnant women (“a bureaucratic nightmare,” she quips).

For the 280,000 pregnant women who use anti-depressants in the US—seven percent of all pregnant women—Hernandez-Diaz’ heartening results offer information on the risks and benefits of alternative approaches to managing depression during pregnancy. Contrary to previous medical thinking, her research shows that certain anti-depressants taken during pregnancy may not be the culprits connected to an increased risk of cardiac malformations.



Professor in Epidemiology, Sonia Hernandez-Diaz

## On the Epilepsy Front

It's well-known that a mother's seizures are dangerous for her developing fetus. The same holds true for classic anti-convulsants, such as Depakote. Yet it could be equally dangerous for women with epilepsy to continue or change their medication prior to or during pregnancy, as Julia Beck so poignantly reflects. The dilemma is all the more acute for newer anti-epilepsy drugs, for which little or no pregnancy-related safety and effectiveness research exists. To give women like Beck and their clinicians the solid information they need to make the most effective treatment decisions, Hernandez-Diaz compared the safety and effectiveness of newer anti-convulsants with that of older varieties. By doing so, she brought the relatively new comparative-effectiveness and patient-centered outcomes research movement into reproductive and perinatal research. Rather than studying large, undifferentiated populations, these approaches look at the best interventions for specific groups of patients—often the vulnerable or those excluded from clinical trials, such as pregnant women and the elderly.

Using information obtained through phone interviews with more than 7,000 pregnant women who had enrolled in the North American Anti Epilepsy Drug (AED) Pregnancy Registry over 14 years (1997 - 2011), she discovered highly-useful evidence: Newer anti-convulsants are safer for the fetus.

Pregnant women taking traditional drugs—valproate and phenobarbital, for example—in the first trimester have a higher risk of giving birth to babies with cardiac malformations, cleft palates and neural defects such as spina bifida than those taking newer AEDs such as lamotrigine, the most commonly prescribed drug for epilepsy in the study population. Additionally, Hernandez-Diaz found that topiramate, which now has been approved for the hefty weight-loss market, increases the probability of oral clefts in infants. For pregnant women and their developing infants, there is still a dearth of information on the safety of newer, recently-introduced AEDs, which may be prescribed for women not responding to traditional drugs.



Professor of Epidemiology, Murray Mittleman



Professor of Epidemiology, Alexander Walker

These and other data that Hernandez-Diaz is discovering contribute to a health care conversation that has been replete with conflicting information for decades. “In the big picture,” she says, “we produce solid, verifiable evidence to fill the gap of information that women and their clinicians face every day. From a public health point of view, I’m hoping this research will impact international treatment guidelines and regulations and enable millions of women who are either pregnant or planning to be to make the best therapeutic decisions with the least risk and most benefit.”

Her work, along with that of her HSPH colleagues Alexander Walker, MD, DrPH, Sebastian Schneiweiss, MD, ScD, and Murray Mittleman, MD, DrPH, DEc, will potentially affect the health of millions. Walker, who pioneered pharmacoepidemiology research, studies the intended and unintended effects of drugs and medical

procedures. Schneiweiss applies his expertise in advanced methodology to comparative effectiveness research, particularly as it relates to biotech products, drug policy and evaluating risk management programs. Mittleman, who leverages his vast clinical expertise and connections to train practitioners worldwide, focuses on preventive cardiology— clinical and behavioral factors that increase the risk of heart attack, triggers of acute cardiac events, and premature heart disease in women.

“Our collective interest is to teach the next generation of leaders in the field,” says Hernandez-Diaz. “We build a pyramid of good methodology by training academicians, clinicians, regulators, policy makers, consultants, and industry professionals to analyze and interpret the data. That is an important legacy.”