See brief report by Cohen et al p986

Psychotropic Medication Use During Pregnancy: Changes to the Labeling System and the Importance of Exposure Registries

In this issue of *JCP*, Cohen et al[1] present the methodology of the National Pregnancy Registry for Atypical Antipsychotics (NPRAA). In full disclosure, the investigators are my colleagues, and I have great interest in the topic of pregnancy registries, including this particular registry, as a perinatal psychiatrist and from a scientific perspective. Highlighting the importance of this paper is intuitive because we are at a defining moment in the application of data to inform the care of pregnant women.

Many women arrive at reproductive age already having experienced the onset of psychiatric illness and the initiation of treatment.[2] Considering that many, if not most, psychiatric disorders are chronic and/or relapsing in course, many individuals require maintenance treatment to stay well. A substantial number of women with serious illnesses require treatment during pregnancy. Therefore, it is essential to have a sound knowledge base about the impact of psychiatric disorders and pharmacologic treatments during pregnancy. Since many pregnancies are unplanned, reflecting about half of pregnancies in the United States, women of reproductive potential, not just those trying to conceive a pregnancy, need to be aware of the potential risks and the reproductive safety profiles of any medications they are taking. It is also important to remember that since many women are treated on an ongoing basis throughout the reproductive years, their plans for having children are likely to change during their treatment. Because medications used for acute treatment frequently become the cornerstones of maintenance pharmacotherapy, reproductive safety must be considered from the very initiation of treatment in women of reproductive potential and among girls prior to reaching the reproductive years.

Historically, the US Food and Drug Administration (FDA) has had a pregnancy category labeling system that uses letters—*A, B, C, D,* and *X*—to convey reproductive and lactation safety. The shortcomings of this system have been substantial, including absence of information about the risk of the untreated disorder, lack of clear priority of human data in informing risk of use during pregnancy, and an unmet need for a systematic mechanism to update labeling as new data become available. When new drugs become approved, systematic human pregnancy data are typically nonexistent. As a result, category assignment has largely been based on animal data. New medications have frequently received a category label that seems particularly favorable, when actually there is an absence of data supporting safety; ironically, older drugs that have received years of study including sizable numbers of pregnant women followed prospectively, with even inconsistent reports of worrisome outcomes, may be placed in a category that strikes fear in patient and clinician hearts—notably the *C* or *D* that most psychotropics have received, even if the risk/benefit for a particular patient is in favor of using the drug.

The letter categories have been more than just potentially misleading and incomplete. They have been seductively easy to use and rely upon. Clinicians and patients are understandably drawn to their simplicity. A letter grade is succinct, and one would expect, or at least hope, that the letters represent data that allow comparisons between drugs. However, reducing the evidence to a letter reflects neither the quantity or quality of the data nor how a particular medication compares to other drugs used for similar indications.

After much effort and many years of deliberation, the FDA has proposed a new system, titled the "Pregnancy and Lactation Labeling Rule" (PLLR) or "final rule."[3] In this system, which will supersede the previous one, labels will be subdivided into sections, including pregnancy, lactation, and topics related to females and males of reproductive potential. There will be formatting differences for label changes, as well as cross-referencing between sections. The system mandates timeliness, requiring updates when new information becomes available. Strong priority is placed on human data, with much focus on postmarketing data. Importantly, context for risks will be provided, as labels will include information about background population rates of adverse events that are reported. Prospective data will be prioritized within the pregnancy section, with pregnancy registry data prioritized and included whenever a registry exists. Contact information for registries will be provided. The pregnancy section will include a risk summary that includes human, animal, and pharmacologic data (in that order).

Sources of human data will include pregnancy exposure registries, clinical trials, and other large-scale epidemiologic studies. Ideally, data on incidence of use and adverse effects, effect of dose, effect of duration of exposure, and effect of gestational timing of exposure will be presented. Importantly, the risk of an outcome will need to be quantified by comparing the risk in infants born to women who took a particular drug versus those born to women who have the condition for which the drug is approved but who did not take the drug. This is a pivotal change, as controls appropriate to the exposure group need to be included to round out the risk/benefit picture of exposure to a medication during pregnancy.

The FDA published guidance for industry regarding the establishment of pregnancy registries in 2002.[4] In this report, prospectively oriented pregnancy exposure registries were endorsed, as they provide margins of reassurance regarding lack of risk, monitor for suspected risks, and identify factors that affect adverse outcomes. Pharmaceutical products are considered good candidates for registries if there is a high likelihood of use by women of reproductive age, as inadvertent exposures are likely to occur. The publication also explains the importance and types of control groups that may be used, including internal and external controls. Optimally, internal controls and exposed women would share a common indication for treatment and/or underlying risk factors and be concurrently enrolled. The FDA has suggested that multidrug registries may provide an efficient and economical way to implement such methodology,[4] which is the model of the NPRAA described by Cohen and colleagues.[1] The FDA has also called for independent data monitoring of outcomes to bring expertise to the assessment and interpretation of results, such as classification of birth defects and obstetric outcomes.

The changes proposed are laudable. We will be moving from the alluring but flawed category label of a letter followed by fine print, to just the fine print. This fine print will include clinically meaningful information, with an emphasis on human data, updated information, consideration of maternal illness, and comparative statistics about adverse effects. This is a daunting and necessary endeavor, and important questions remain. For example, the collection of rigorous human pregnancy data is emphasized, but how will such work be funded? The FDA has outlined pregnancy registry recommendations for industry, but it has not petitioned companies to formally support registries. It is also unclear how the new labeling will be understood and utilized by health care providers and the public. The shift may require more education in order for the new labeling to translate into better patient care and outcomes. The new labeling has the potential to enrich the conversation about relevant issues regarding the use of medications in pregnancy between health care providers and patients to include what is known, what is not, and the relative risks.

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