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No Simple Decisions for Psychiatrically Ill Pregnant Women

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"The world is a radically uncertain place."[1]

Clinical researchers seek data that will enable physicians and patients to choose the safest and most effective treatments. When it comes to pregnant women with psychiatric conditions, research is stymied by ethical concerns. No institutional review board will allow studies that randomly assign pregnant subjects to active treatment and placebo groups. Yet psychiatric illness affects over 20% of pregnant women worldwide[2,3]—and these women and their physicians need data to help guide treatment decisions.

In this issue of the *Journal*, Viguera and colleagues[4] report on results from the National Pregnancy Registry for Atypical Antipsychotics (NPRAA), based at Massachusetts General Hospital. The Registry, formed in 2008, prospectively evaluates rates of malformations in infants exposed in utero to second-generation antipsychotics (SGAs). The database now numbers close to 2,000 and is growing, with a goal of refining risk estimates for birth defects associated with atypical antipsychotic medication as well as gathering data about neonatal, obstetric, and neurobehavioral outcomes. Registries like this one are essential to clinical decision-making, as they allow access to real-world information from women who have decided to continue their medication during pregnancy.

The updated results of the NPRAA are consistent with those from 2016,[5] suggesting that SGAs are not likely to be major teratogens. The registry compared 621 pregnant women (with 631 live births) exposed to SGAs during the first trimester with 690 pregnant women (with 704 live births) with psychiatric illness who were not exposed to SGAs and found similar rates of major malformations in both groups (n = 16 or 2.5% in the exposure group vs n = 14 or 2% in the control group). Notably, both groups had rates of major malformations that were lower than the 3% baseline risk in the United States,[6,7] reminding us that pregnancy is inherently risky while providing reassurance that SGA do not increase the level of risk.

This is welcome news for pregnant women whose psychiatric conditions require treatment with an antipsychotic medication. Still, there are other factors to consider. As time passes and the number of subjects in the registry increases, information regarding neurobehavioral outcomes and differences between individual agents will be a welcome addition to the database. And a persistent question relevant to all psychotropic exposure in pregnancy remains: even when we do have long-term neurobehavioral data, how do we distinguish between the effects of prenatal exposures (to medication or psychiatric illness) and the postnatal environment?

The NPRAA was designed to account for confounders, including women with psychiatric illness as a control group and gathering prospective data on alcohol, cigarettes, other medications, and psychiatric history. The clinical characteristics of the registry population reveal the complexity of the problem: 41% of the exposed group and 36% of the control group had a history of postpartum depression and/or psychosis, the mean number of lifetime psychiatric hospitalizations was 3.9 in the exposed group and 2.7 in the control group, and polypharmacy was common in both groups. In a sample that is overwhelmingly White (91%), married (84%), and college-educated (80%), the degree of impairment from psychiatric illness is significant. Behind the reassuring finding that SGAs are not teratogens is another reality: that the women who need answers about the teratogenicity of SGAs are quite ill.

Over the last decade, studies of psychiatric medication in pregnancy have become increasingly sophisticated, employing propensity matching, multivariate logistic regression, and other modalities to reduce the impact of confounders, both known and unknown. The push for more comprehensive data is essential for progress, since treatment decisions affect both the psychiatric and the obstetric health of expectant mothers and the health of their babies. Furthermore, while antenatal exposure to medications may directly affect fetal health, the mental health of expectant mothers also affects fetal outcome. A patient's antenatal psychiatric condition often predicts how she will fare postnatally—and there are ample data to suggest that maternal emotional well-being has a bearing on infant emotional, cognitive, and behavioral outcomes.[8–11] As we consider risk assessment, it is important to think beyond risks and also consider the benefits of psychopharmacologic treatment in pregnant psychiatrically ill women.[12] The indication for a particular medication matters: treatment with an SGA is often a reasonable and even *necessary* choice for the psychotic or deeply depressed bipolar patient; the choice becomes less clear for the patient suffering from insomnia.

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In the years since the NPRAA's inception, the US Food and Drug Administration has shifted its approach to medication labeling regarding use in pregnancy, abandoning the categorization of A, B, C, D, and X in favor of a summary of published literature. The shift to a new system is in process, and national registries such as the NPRAA are now highlighted in medication package inserts, encouraging patients to enroll to continue to expand our knowledge. As clinicians, we are no longer asked to distill safety into a letter grade, but rather to help our patients apply the existing literature to their particular situation.

While patients and physicians alike want and need clear algorithms based on rigorous studies to direct treatment decisions, the reality is that uncertainty permeates all of medicine. Some difficult questions can and will be answered with more data, and the NPRAA makes a valuable contribution to that effort. But there is another category of decision-making facing pregnant women that no amount of data can completely address. While we might be tempted to ask the question about whether a particular medication is safe in pregnancy, another question our patients want answered is, "Should *I* take this medication in pregnancy?" By shifting our object of analysis away from the medication and toward the individual, we shift away from the binary, letter-grade analysis into an infinitely more complex form of risk assessment. Here, we ought to consider not only the published data and the patient's psychiatric history, but also her social context, priorities, and values.

The concept of "satisficing" is useful here. Developed in the 1950s by the Nobel Laureate behavioral economist Herbert Simon,[13] satisficing is a decision-making strategy that aims for a satisfactory ("good enough") outcome rather than a perfect one. For situations in which every course of action has risks, satisficing encourages us to choose the path with the highest likelihood of an acceptable outcome. To expect perfection is to guarantee disappointment. A person who satisfices focuses not on finding the best or optimal rational solution (eg, the *safest* medication in pregnancy) but rather on coming to a solution that is realistic given the constraints of her particular circumstances—the *most livable* combination of risks and benefits. During the COVID-19 pandemic, we have all been using this strategy in our personal lives. Although we have access to the same information about disease transmission, mitigation strategies, community prevalence, and vaccines, individuals and families make vastly different decisions about what risks they are willing to take and different assessments of what they stand to gain from taking them.

Although data such as those from the current rigorous registry study by Viguera and colleagues are important and encouraging, we can never ensure a perfect outcome to our perinatal patients no matter what treatment choices they make. After all, pregnancy is risky by nature, and no one can predict long-term outcomes for an unborn baby with any degree of certainty. Even if the odds do favor a healthy baby, that prediction does not and cannot take into account what it feels like to choose to subject oneself to those odds. By satisficing, we ask what decision will most likely produce a *satisfactory* outcome, given the reality that uncertainty is an inherent condition in medicine, and in life.

We are never going to get the answers that we need until we begin asking more nuanced questions. Psychiatric research provides us with desired and important data meant to inform clinical decision-making. But we deceive ourselves if we imagine that the data alone can dictate a course of action. How we frame data for a patient often tips the scale as she struggles with decisions about whether to accept psychotropic medication. It is important to acknowledge that how we do so has as much to do with our own perception of the seriousness of particular risks as it does with absolute risks based on published data. While doctors tend to aim for universal and true predictions with the goal of providing clear, unambiguous recommendations for patients, risk assessment invariably incorporates subjective judgments based on a wider understanding and appreciation of personal, psychosocial, and cultural factors. This is particularly true for psychiatrically ill pregnant women. Because of the inherent limitations of research methodology available to this patient population, as well as wide variation in judgments of what constitutes an acceptable outcome, we need to recognize that we do not have all the answers and we never will.

Studies like that of Viguera and colleagues significantly advance our knowledge in the area of reproductive psychiatry. As clinicians, we help put that information to work in the context of our patients' imperfect and complex lives. If we can let go of our own desire for certainty and recognize that some questions are ones that no amount of data can dispel, we will be better equipped to help our patients make decisions they can comfortably live with.

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