See article by Sutter-Dallay et al

What Adversely Affects the Unborn—Psychotropic Drugs or Maternal Morbidity?

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Since the thalidomide disaster, there has been a heightened perception of fetal risk of medications, leading both pregnant patients and their health care providers to fear pharmacotherapy.[1] As a result, quite often women are not treated optimally even for life-threatening conditions. In reality, few medicinal drugs have been shown to be human teratogens, and only a handful are contraindicated due to undisputed evidence of fetal damage.[2] A substantial number of women of reproductive age suffer from serious psychiatric conditions that necessitate drug therapy, and because over half of all pregnancies are unplanned, large numbers of fetuses are exposed to psychiatric medications during the first trimester, when most embryogenesis takes place.[3] In several instances, exposure to psychiatric medications has increased exponentially over the last 2 decades. For example, while first-generation antipsychotic agents cause increased levels of prolactin, they clinically act as oral contraceptives; in contrast, the second-generation antipsychotics, introduced in the 1990s, do not tend to increase prolactin levels, leading to increased rates of pregnancies among women with schizophrenia.[4] While many psychiatric patients attempt to discontinue their medications after realizing they have conceived, large numbers need to continue medications to prevent deterioration of their medical condition.[5]

Neonatal Outcomes

The well-being of babies born to women with severe forms of psychiatric morbidity has been a focus of concern due to both peripartum exposure to medications and maternal morbidity, as well as the long-term ability of these women to optimally care for young children. A variety of adverse pregnancy outcomes have been associated with severe psychiatric conditions and the medications used to manage them, including, as examples, higher rates of miscarriage (eg, in depressed women),[6] increased risk of congenital malformations (eg, lithium, valproic acid),[7,8] more prevalent preeclampsia (eg, in schizophrenia),[9] and higher rates of intrauterine growth restriction and prematurity. A major methodological challenge in proving causation in many of these adverse events is the recognition that pharmacotherapy is given to women who exhibit more severe illness, so even when "matching" drug-exposed women to disease-matched untreated women, the severity of the condition is rarely similar.

In this issue of the *Journal,* Sutter-Dallay and colleagues[10] report on pregnancy outcome among neonates of French women experiencing severe psychiatric illness. The study is unique in its sample—a network of 13 French mother-baby units that focus on managing women with serious psychiatric conditions in pregnancy. For analysis of their network database, the authors have attempted to separate the mother-child pairs based on 4 classes of medications, rightly claiming that previous studies have not optimally addressed the effects of different groups of psychiatric drugs and their combinations. The large number of patients available to them—over 1,000, with 40% treated pharmacologically—has the potential to address differences among drug groups. The analysis suggests that mood stabilizers are associated with a 2-fold increased risk of low birth weight, whereas antipsychotics, antidepressants, and anxiolytics/hypnotics are associated with an increased risk of neonatal hospitalization, independent of birth weight and term delivery status.

Medication vs Psychiatric Morbidity

The title of the article by Sutter-Dallay et al[10] aims to address the "impact of prenatal exposure to psychotropic drugs on neonatal outcome." The term *impact* implies "effect," although the design of this study cannot prove or disprove causality, but rather suggests an association. Later on, the authors repeat this assertion by talking about "independent impact of each therapeutic class of antipsychotic drugs" and that "the risk of . . . was increased by. . . ." If women with more severe morbidity receive more drugs, or higher doses of a given drug, there is colinearity between the drug and disease state, and it is not easy to separate the impact of the 2 on neonatal outcome. The authors acknowledge this "bias by indication"; however, they do not offer ways to address it. This issue is not merely semantic, as many uninformed readers may conclude that the drug causes the adverse event and not the severity of the condition. In counseling women with serious psychiatric conditions, we commonly find in the Motherisk Program that patients are ready to avoid drug therapy even in grave clinical situations, not recognizing the dangers of remaining untreated.[5] Relevant to this point, the authors did have information on the course of pregnancy, but no variable addressed the severity of the psychiatric condition in pregnancy and its fluctuations throughout pregnancy.

Specific to the pregnancy outcomes the authors were interested in, it is noteworthy that they investigated birth

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weight but did not include maternal weight and pregnancy weight gain as independent variables in the analysis, despite these being well recognized to affect birth weight.[11]

The separation of drugs into different classes makes sense, as depression is different from bipolar disease and from schizophrenia. Yet, some of the decisions made by Sutter-Dallay and colleagues are not biologically based. For example, mood stabilizers include antiepileptic drugs, which are very different pharmacologically and toxicologically from lithium. Indeed, previous studies have shown lithium to be associated with increased birth weight, possibly due to an insulin-like effect,[7] while in the present study, mood stabilizers as a group lumped with antiepileptics showed reduced birth weight, similar to what several studies have shown in women with epilepsy.[12]

Another maternal characteristic that has important known effects on pregnancy outcome is body mass index (BMI), where overweight and obesity are associated with higher risk of miscarriages, gestational diabetes, hypertension, preeclampsia, and cesarean section, to mention a few.[13] Very relevant to the present study, the second-generation antipsychotics cause high rates of excessive weight gain among exposed mothers.[14] Yet, BMI was not included in the present study as a variable.

The present study is important in corroborating an overall understanding that pregnant women with serious psychiatric diseases have higher perinatal risks that need to be addressed by the physicians and other therapists involved in their care. Higher risks of pregnancy-induced conditions such as preeclampsia, hypertension, gestational diabetes, obesity, smoking, the use of recreational drugs, followed by higher risks for prematurity, low birth weight, neonatal morbidity, including neonatal abstinence syndrome, need a multidisciplinary team to address medically, obstetrically, and mentally.[15]

It is critical to remember that an erroneously perceived fetal risk of psychiatric medications may lead women to forego treatment of serious conditions.[5] For example, the strongest predictor of postpartum depression is depression in late pregnancy, which is often caused by unwarranted discontinuation of antidepressant drugs.[5]

In summary, to be able to better understand causation of adverse fetal outcomes in female patients with serious psychiatric conditions, improved understanding of the interactions between the woman's psychiatric morbidity and her pharmacotherapy will need to be developed, with more detailed data on the severity of the conditions and their changes during gestation.

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