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Pregnant Women Get Sick—Sick Women Get Pregnant

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The blunt statements above focus attention on the pregnant woman as “the last true therapeutic orphan.”¹ Because of ethical, medicolegal, and fetal safety concerns, they have been excluded from treatment studies. Pregnant women comprise a disadvantaged population who have been “protected” from participation in research, only to carry the burden, with their prescribers, of a paucity of information to inform treatment decision making. Through the *TR_x eating for Two* initiative, the Center for Disease Control and Prevention has promoted a conceptual shift from the dogma that medications during pregnancy must be avoided, to their use to “improve the health of women and babies by working to identify the safest treatment options for the management of common conditions before and during pregnancy.”²

Medication use by pregnant women is increasing across time and now is nearly universal. The average number of drugs (over the counter or prescribed, excluding vitamins/minerals) used any time in pregnancy increased from 2.5 in 1976–1978 to 4.2 in 2006–2008.³ In 2008, nearly 94% of women took at least one medication during pregnancy; in the first trimester, 82.3% used at least one and 27.6% reported taking four or more medications. These staggering statistics highlight the public health importance of research to inform pharmacotherapy for pregnant women.

For women with schizophrenia and bipolar disorder, medications are the mainstay of treatment and the recurrence risk following discontinuation is high.⁴ Huybrechts et al (this article) presented results from the Medicaid database (n=1,341,715) to provide critical new information on the risk for overall birth defects and specifically cardiac malformations in infants born to pregnant women treated with antipsychotic medications (APM). The sophisticated pharmacoepidemiologic methodology comprehensively tackles the major challenge in observational studies, that is, confounding by underlying disease factors that are (like the APM) potentially associated with pregnancy outcomes. The task is to separate the impact of two exposures (APM and psychiatric disease) on the reproductive outcomes. The

authors used propensity score stratification, which allows women with similar risk factors (such as obesity, other drug use, smoking), but who differ on APM exposure, to be compared. This strategy also addresses the differences in women with psychiatric disorders who choose to continue APM compared to those who do not on a broad range of potential confounders. The richness of the Medicaid database allowed for adjustment for potential confounders through the creation of 50 equally sized strata based on the distribution among the treated women of more than 250 variables in high dimensional analyses.

The authors found that associations between APM exposure and birth defects were attenuated after adjustment for confounding, which implies that these variables, rather than APM exposure, account for much of the impact on congenital malformations. *Unadjusted analyses* suggested a 36% increased risk of malformations overall for atypical APM (Relative Risk (RR) =1.36, 95% CI, 1.24–1.50) but not for typical APM (RR) =1.17, 95% CI, 0.81–1.68). After *adjustment for confounding* (which accounted for proxies of the severity of the underlying illness, associated behaviors and other potential confounding variables), the RR for atypical APM was near the null at 1.05 (95% CI, 0.96–1.16) for atypical APM, and 0.90 (95% CI, 0.62–1.31) for typical APM. The results for cardiac malformations were similar.

This landmark paper, with the largest population of women exposed to APM published to date, demonstrates that exposure to APM (other than risperidone) does not significantly increase the risk of birth defects, which has been a major source of concern for women and prescribers. Several methodological aspects of this study are important to highlight. The definition of exposure was filling a prescription for an APM during the first 90 days of pregnancy, which covers the period of organogenesis. Non-exposure was defined as no prescription filled during the 3 months before the start of pregnancy or during the first trimester. Use of *filling a prescription* to define exposure is preferable to having a prescription written because the woman is known to have obtained the drug from the pharmacy, although lack of certainty that the woman actually took the drug as prescribed remains. Restricting the sample to women with diagnoses for which APM have an FDA-approved indication, rather than the broad group of diagnoses associated with APM use, did not change the results. Sensitivity analyses demonstrated that having filled more than two prescriptions for an APM or having a supply that overlapped with the first trimester also did not meaningfully change the results. This paper increases the field's appetite for additional high-quality data on other maternal and offspring outcomes to improve the sophistication of risk-benefit decision-making. The existing literature suggests that the offspring of women treated with APM during pregnancy are at increased risk for stillbirth, preterm birth, large and small for gestational age, and neurodevelopmental difficulties.⁵ Clarification of the contribution of APM (if any) to these outcomes would be a major advance.

An intriguing finding is that one APM, risperidone, was associated with a 26% increased risk in overall malformations (RR=1.26; 95% CI, 1.02–1.56) and cardiac malformations (RR= 1.26, 95% CI, 0.88–1.81). Sensitivity analyses demonstrated that having filled more than two prescriptions for an APM or having a supply that overlapped with the first trimester strengthened the relationship between risperidone and birth defects (RR=1.46, 1.01–2.10) and for cardiac malformations specifically (RR=1.87, 1.09–3.19). As the authors state, this

association between risperidone and malformations merits further exploration. Although animal data do not indicate teratogenicity for risperidone, cross-species variability is always a concern. Why might exposure to risperidone differ from other APM with respect to birth defects?

The placental passage of risperidone does not exceed that of other APM. In a study of drug concentrations in maternal and cord plasma at delivery, the placental passage ratio was highest for olanzapine (mean=72.1%, SD= 42.0%), followed by haloperidol (mean=65.5%, SD=40.3%), risperidone (mean=49.2%, SD=33.9%), and quetiapine (mean=23.8%, SD=11.0%).⁶

Risperidone is unique among atypical APM in that induced prolactin levels are significantly higher than those produced by haloperidol and other first generation APM^{7,8} and may exceed 200 µg/liter.⁹ Hyperprolactinemia is associated with alterations in the concentrations of reproductive hormones such as estradiol and testosterone.¹⁰ Although risperidone-treated women with hyperprolactinemia are often amenorrheic and unable to conceive, those who become pregnant may have concentrations beyond what is typical during pregnancy. However, even in women with hyperprolactinemia unrelated to APM treatment, monitoring serum prolactin levels is not recommended in pregnancy because concentrations reach 150–300 µg/liter by term.⁹ We considered the possibility that women taking risperidone might be treated with cabergoline or bromocriptine for hyperprolactinemia, and that these drugs might affect the risk for birth defects; however, neither drug has been associated with congenital malformations.⁹ Alternatively, as the authors note in their discussion, the association between risperidone exposure and congenital defects may be due to chance or unmeasured confounding, and therefore it should not be viewed as causal, but as a safety signal that will require further study.

When the decision to treat a pregnant woman with an APM is made, clinicians are compelled to provide the highest quality pharmacologic intervention. The justification for treating a pregnant woman with medication is that the overall negative impact of the disease is greater than that of the drug treatment, which reduces the disease expression and thereby its impact on pregnancy outcomes. Optimization of APM treatment during pregnancy dictates several treatment goals. The drug must be at the most favorable dose for the woman, that is, the dose that produces the best therapeutic response with tolerable side effects. Maintaining optimal drug efficacy may be challenging because the clearance of drugs metabolized by cytochrome P450 (CYP) 3A4, 2D6, 2B6 and 2C9 increases during pregnancy, which reduces plasma concentrations; in contrast, the activity of CYP 2C19 decreases.^{11,12} Most APM are metabolized by CYP 3A4, although risperidone's major pathway is through CYP 2D6. Symptoms need to be monitored frequently across pregnancy and postpartum because adjustments may be required to maintain the efficacy of the APM across the dynamic physiologic milieu of pregnancy.^{13,14}

Finally, this publication is timely, given the revision of the FDA Pregnancy and Lactation Labeling Final Rule (12-04-2014).¹⁵ The labeling for drugs approved on or after June 30, 2001, must contain information to assist health care providers make prescribing decisions and counsel women about the use of the drug during pregnancy, including information on

disease-associated maternal and/or embryo-fetal risk, dose adjustments during pregnancy and after birth, maternal adverse reactions, fetal and neonatal adverse reactions, and the effect of the drug on labor or delivery. Resources such as MotherToBaby, a service of the Organization of Teratology Information Specialists, provide free evidence-based information about any drug in pregnancy.¹⁶ Nowhere in medicine is the need for personalization of care so crucial than during pregnancy--personalization of the treatment for serious mental illness with consideration of pregnancy physiology and the mother's capacity to provide sustenance for the growing fetus and newborn.

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