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FDA rankings of drugs' teratogenic potential are guided by the lowest tier of evidence-based medicine

Pregnant and mentally ill A labor-intensive clinical challenge

Life in the womb is fraught with hazards. Any deviation from a healthy pregnancy can damage a major organ system (first trimester), impair brain structural/functional development (second trimester), or cause prematurity and low birth weight (third trimester).

So many things can go wrong in the intrauterine environment that it is miraculous most babies are born with no apparent physical malformations. But behavioral teratogenesis is more subtle than physical defects and might not manifest until years later. Numerous studies have linked prenatal and obstetric complications to serious psychiatric disorders later in childhood or adulthood.

No wonder, then, that the pharmacologic management of mentally ill pregnant women is a high-stakes challenge. Consider the article in this issue by Louann Brizendine et al on treating anxiety during pregnancy with selective serotonin reuptake inhibitors vs benzodiazepines (page 38).

Risk vs benefit. Psychotropics can have unpredictable, serious effects on fetal growth and development, but fetal repercussions may be equally devastating if we do not stabilize the mentally ill mother and guard her against self-neglect, nonadherence to prenatal care, suicide, or infanticide. Thus, the benefit:risk ratio is sufficiently high to justify pharmacologic intervention during pregnancy—with the requisite caution this treatment deserves.

The greatest risk to the fetus is teratogenicity, which 1 review article¹ defined as “the dysgenesis of fetal organs as evidenced either structurally or functionally (eg, brain functions). The typical manifestations of teratogenesis are restricted growth or death of the fetus, carcinogenesis, and malformations, defined as defects in organ structure or function. These abnormalities vary in severity (eg, hypospadias that is mild and may be missed, or is severe, necessitating several corrective operations). Major malformations may be life-threatening and require major surgery or may have serious cosmetic or functional effects.”

continued

To comment on this editorial or other topics of interest, contact Dr. Nasrallah at henry.nasrallah@currentpsychiatry.com or visit CurrentPsychiatry.com and click on the “Contact Us” link.



Table

FDA classification of medications' teratogenic potential

Category	Examples
A: Controlled studies in pregnant women demonstrate no fetal risk	Folic acid, levothyroxine
B: Controlled animal studies have not shown a fetal risk, but there are no studies done on women OR controlled studies in animals have shown a fetal risk that was not reproduced in controlled human studies	Amoxicillin, ceftriaxone
C: Controlled animal studies have demonstrated adverse fetal effects and there are no human studies OR there are no controlled studies in humans or animals	Nifedipine, omeprazole
D: Controlled studies in humans demonstrate adverse fetal effects but the benefits of using the drug may be greater than the risks	Propylthiouracil
X: Controlled studies in animals and humans have demonstrated adverse fetal effects OR there is evidence of fetal risk based on human experience. The risk of using these drugs outweighs any possible benefit. The drug is absolutely contraindicated in pregnancy	Misoprostol, warfarin, isotretinoin

Source: Adapted from Food and Drug Administration. Current categories for drug use in pregnancy (www.fda.gov/fdac/features/2001/301_preg.html)

Because of teratogenicity concerns, pregnant women are excluded from clinical trials of investigational drugs. Thus, new drugs are not approved for use in these patients, and FDA rankings of drugs' teratogenic potential (Table) are guided by nonblinded, noncontrolled, naturalistic, after-the-fact observations—the lowest tier of evidence-based medicine.

Proceed with caution. Against this background, I follow these principles when treating pregnant patients:

- **Counsel all mentally ill women** about the potential risks of conceiving while receiving a psychotropic before they consider pregnancy. Counseling should include all prescription and nonprescription drugs.
- **Obtain a family history** of psychiatric disorders from all pregnant patients.
- **Make an accurate psychiatric diagnosis** in pregnant patients, and assess the risks of providing vs withholding needed pharmacotherapy.

- **Use nondrug treatments** (if evidence-based) before medications. Options include behavioral therapies, interpersonal therapy, supportive therapy, and somatic treatments such as electroconvulsive therapy, repetitive transcranial magnetic stimulation, and light therapy.

- **When using psychotropics**, select the lowest-risk agents (Category A) first, and use the lowest efficacious dose.

- **Collaborate with** the patient's obstetrician. I coined the term "psychiatric dystocia" to describe the complicating potential of mental illness on pregnancy.

- **Completely avoid drugs** with established teratogenicity, and educate the patient not to take these drugs if another physician prescribes them to her.

- **Prescribe high-dose folate** (4 to 5 mg/d) for psychotic, bipolar, or depressed pregnant patients to protect against neural tube defects and enhance fetal CNS development.

- **Regularly check** the patient's nutrition, sleep hygiene, substance use (smoking, alcohol, coffee, illicit drugs), and use of over-the-counter supplements.

- **Use stress-reduction techniques** to reduce potential deleterious effects of stress-induced hypercortisolemia on the fetus, and involve the patient's partner.

- **See the mentally ill pregnant patient frequently** for check-ups on response and/or side effects.

- **Arrange for a child psychiatrist** to examine the infant of a seriously mentally ill patient shortly after birth. A newborn's irritability, crankiness, or insomnia may be perceived as withdrawal symptoms or behavioral teratogenesis, whereas it could very well be a genetically inherited temperament instability from a mother suffering from anxiety, depression, or psychosis.

Helping the mother without harming the child is like walking a tightrope: it calls upon all our skills, experience, and sound judgment.



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P.S. To help you manage potential medico-legal issues such as prescribing during pregnancy, CURRENT PSYCHIATRY welcomes Douglas Mossman, MD, as editor of *Malpractice Rx*. This month, Dr. Mossman discusses documentation and invites you to submit questions about liability.

Reference

1. Koren G, Pastuszak A, Ito S. Drugs in pregnancy. *N Engl J Med* 1998;338:1128-37.