COMMENTARY

Are Antipsychotic Medications Safe During Pregnancy?

Hema Madhuri Mekala, MD; Priyanga Jayakumar, MD; Tina Thomas, MD; Simrat Kaur Sarai, MD; Steven Lippmann, MD

Dr. Mekala is Research Coordinator at the Griffin Memorial Hospital in Norman, Oklahoma. **Dr. Jayakumar** is a first-year Family Medicine Resident at the Baylor Scott & White Medical Center in Round Rock, Texas. **Dr. Thomas** is a first-year Psychiatry Resident at the University of Texas Health Science Center in Houston. **Dr. Sarai** is a Research Scholar and **Dr. Lippmann** is an Emeritus Professor, both at the University of Louisville in Kentucky. **Correspondence:** Dr. Lippmann (steven.lippmann@louisville.edu)

Psychiatric illnesses are prevalent in about 25% of the US adult population.[1] Approximately 21% to 33% of women are prescribed antipsychotic drugs during pregnancies, and about 50% experience a relapse of symptoms related to mental illness.[2,3] In 2015, the Pregnancy and Lactation Labeling Rule removed the A, B, C, D, and X categories for medications prescribed during gestation. Labels now include more information and detail about these pharmaceuticals regarding potential risks to a mother and fetus.[4] As with all other pharmacotherapies during pregnancy, teratogenicity and medicinal adverse effects (AEs) must be balanced against the risk of nonpharmacotherapy.

MEDICATIONS

Antipsychotic medications often are prescribed to treat people with a wide range of psychiatric conditions, including schizophrenia, bipolar disorder, depression, anxiety, and personality disorders.[5] Commonly, second-generation antipsychotic medications are selected for pregnant women. Olanzapine, haloperidol, risperidone, and quetiapine freely pass through the placenta.[5] During gestation, when an antipsychotic agent is strongly indicated, it is prudent to select one of the second-generation versions or haloperidol.

Risks vs Benefits

Physicians should always consider the risk-to-benefit ratio of these medicines for both the pregnant woman and the fetus.[6] The National Pregnancy Registry for Atypical Antipsychotics was established to evaluate the safety and efficacy of these drugs during pregnancy and the postpartum period.[4,6]

Even during the first trimester of pregnancy most antipsychotic medications prescribed to women, are documented to cause few major fetal malformations.[7] Research during 487 pregnancies revealed that the risk of a malformed infant previously exposed in utero to antipsychotic drugs was 1.4%, compared with 1.1% for those not exposed.[6] Risperidone, however is an exception, because evidence has shown that it results in more cardiac malformations and congenital anomalies than do other medications.[7]

Complications

Maternal complications, such as increased weight gain, gestational diabetes mellitus, hypertension, and venous thromboembolism, are reported in pregnant women prescribed antipsychotic medications.[3] Sudden discontinuation of these drugs might interfere with activities of daily living, allow more psychotic symptoms in the mother, impair prenatal self-care, and increase the risk for suicide or infanticide.[8] Fetal complications might include prematurity, intrauterine growth retardation, distress, suboptimal birth weights, low Apgar scores, neonatal hypoglycemia, and congenital defects. Stillbirths can occur as well.[9]

Neonates exposed to antipsychotic medications in utero can experience withdrawal symptoms after delivery. They might exhibit agitation, feeding disorders, hypotonia, hypertonia, respiratory distress, somnolence, and tremor.[10] Extrapyramidal symptoms, such as abnormal movements, restlessness, stiffness, and tremors, may occur more often when prescribing first-generation rather than with second-generation antipsychotic drugs.[11] These clinical manifestations occur from a few hours

after birth to 1 month later. The management of withdrawal symptoms is not clear, though symptomatic intervention is recommended.[11]

However, studies have shown that documented AEs are not significantly increased in the patients or infants exposed to antipsychotic medications compared with those of a control group.[7] Furthermore, pregnant women with mental illness who remain untreated or who discontinue these drugs during a gestation evidence increased maternal morbidity[12]; they also exhibit more complications, such as placental abnormalities, antepartum hemorrhage, or preeclampsia.[6] Hence, when medications are indicated, physicians should encourage patients to continue taking these medications after being educated about the risks and benefits of pharmacotherapy.[6]

CONCLUSIONS

The advantages of prescribing antipsychotic drugs during pregnancy include better psychiatric, obstetric, and neonatal health. Although antipsychotic medications continue to be safe during pregnancy, only necessary prescribing of indicated antipsychotic medicine and maintaining the safest possible therapeutic profile is an optimal approach to treat pregnant women requiring these medications.[12] The efficacy of these medications also depends on an individual assessment of the patient's health and lifestyle. When obtaining a patient history, physicians should include a review of smoking, alcohol consumption, substance abuse, and prior and/or concomitant use of other medications. Demographics, medical comorbidities, and psychiatric illnesses have a role in the clinical outcome.[13] Physicians also should consider dosage, timing, and duration of medication exposure.

A baby born with birth defects can be devastating to the mother and is always balanced against the risk of less intervention. Apart from guiding patients regarding antipsychotic medication intake, pregnant women should be educated about regular prenatal checkups, taking vitamins and other supplements, monitoring for gestational diabetes mellitus, a proper diet, and exercise. Physicians and their patients should always minimize exposure to smoking or drugs and medications, especially polypharmacy.[13] A higher level of prenatal care is advised whenever a physician suspects complications, including a referral to a maternal-fetal specialist.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

Disclaimer

References

1. Centers for Disease Control and Prevention. CDC report: mental illness surveillance among adults in the United States. https://www.cdc.gov/mentalhealthsurveillance/fact_sheet.html. Archived document. Updated December 2, 2011. Accessed April 10, 2018.
2. Levenson JL, ed. *The American Psychiatric Publishing Textbook of Psychosomatic Medicine: Psychiatric Care of the Medically Ill.* 2nd ed. Arlington, VA: American Psychiatric Publishing; 2011.
3. Kulkarni J, Worsley R, Gilbert H, et al. A prospective cohort study of antipsychotic medications in pregnancy: the first 147 pregnancies and 100 one year old babies. *PLoS One.* 2014;9(5):e94788.
4. US Food and Drug Administration. Content and format of labeling for human prescription drug and biological products; requirements for pregnancy and lactation labeling. https://www.fda.gov/downloads/aboutfda/reportsmanualsforms/reports/economicanalyses/ucm427798.pdf. Accessed April 10, 2018.
5. Ennis ZN, Damkier P. Pregnancy exposure to olanzapine, quetiapine, risperidone, aripiprazole and risk of congenital malformations. A systematic review. *Basic Clin Pharmacol Toxicol.* 2015;116(4):315-320.
6. Cohen LS, Viguera AC, McInerney KA, et al. Reproductive safety of second-generation antipsychotics: current data from the Massachusetts General Hospital National Pregnancy Registry for Atypical Antipsychotics. *Am J Psychiatry.* 2016:173(3):263-270.
7. Huybrechts KF, Hernández-Díaz S, Patorno E, et al. Antipsychotic use in pregnancy and the risk for congenital malformations. *JAMA Psychiatry.* 2016;73(9):938-946.
8. Galbally M, Snellen M, Power J. Antipsychotic drugs in pregnancy: a review of their maternal and fetal effects. *Ther Adv Drug Saf.* 2014;5(2):100-109.
9. Crawford MB, DeLisi LE. Issues related to sex differences in antipsychotic treatment. *Curr Opin Psychiatry.* 2016;29(3):211-217.
10. Chisolm MS, Payne JL. Management of psychotropic drugs during pregnancy. *BMJ.* 2016;352:h5918.
11. US Food and Drug Administration. FDA drug safety communication: antipsychotic drug labels updated on use during pregnancy and risk of abnormal muscle movements and withdrawal symptoms in newborns. https://www.fda.gov/Drugs/DrugSafety/ucm243903.htm. Updated August 4, 2017. Accessed April 10, 2018.
12. Tosato S, Albert U, Tomassi S, et al. A systematized review of atypical antipsychotics in pregnant women: balancing

between risks of untreated illness and risks of drug-related adverse effects. *J Clin Psychiatry.* 2017;78(5):e477-e489.

13. Petersen I, Sammon CJ, McCrea RL, et al. Risks associated with antipsychotic treatment in pregnancy: comparative cohort studies based on electronic health records. *Schizophr Res.* 2016; 76(2-3):349-356.