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FPIN's Clinical Inquiries

Antidepressant Medications in Pregnancy

Clinical Inquiries provide answers to questions submitted by practicing family physicians to the Family Practice Inquiries Network (FPIN). Members of the network select questions based on their relevance to family medicine. Answers are drawn from an approved set of evidence-based resources and undergo peer review. The strength of recommendations and the level of evidence for individual studies are rated using criteria developed by the Evidence-Based Medicine Working Group (http://www.cebm.net/levels_of_evidence.asp).

This series of Clinical Inquiries is coordinated for American Family Physician by John Epling, M.D., State University of New York Upstate Medical University, Syracuse, N.Y. The complete database of evidence-based questions and answers is copyrighted by FPIN. If you are interested in submitting questions to be answered or writing answers for this series, go to http://www.fpin.org or contact CI2Editor@fpin.org.

Clinical Question

What is the safest and most effective antidepressant therapy in pregnant women?

Evidence-Based Answer

Selective serotonin reuptake inhibitors (SSRIs) are considered first-line agents for the treatment of depression in pregnant women. SSRIs and tricyclic antidepressants (TCAs) are considered safe and effective in pregnant women, although some studies have indicated increased short-term neonatal adverse effects after exposure to antidepressants in the third trimester.1-6 [Strength of recommendation: B, based on cohort studies]

SSRIs appear to have a more favorable side-effect profile than TCAs.7 [Strength of recommendation: B, based on extrapolation from a systematic review of randomized controlled trials (RCTs)] One small study8 supports the use of the phenethylamine agent venlafaxine (Effexor) in pregnant women. [Strength of recommendation: B, cohort study]

Evidence Summary

Decisions about which antidepressant to prescribe during pregnancy depend on assessments of efficacy and safety. Ethical considerations make randomized controlled trials of antidepressants during pregnancy impossible. Therefore, the best available evidence for assessing efficacy in pregnant women comes from an extrapolation of studies of nonpregnant women; for assessing safety, the best available evidence comes from prospective cohort studies. An analysis of 11

double-blind RCTs found that the SSRI fluoxetine (Prozac) and TCAs significantly reduced symptoms of depression; fluoxetine had fewer side effects.7

Studies assessing safety have measured rates of major malformations, spontaneous pregnancy loss, preterm delivery, neonatal toxicity, and adverse effects on childhood growth and development. The results of multiple studies have indicated no increased risk for major malformations when SSRIs or TCAs are used during pregnancy.1-4,8

One meta-analysis1 of prospective controlled and uncontrolled cohort studies examined the risk of major fetal malformations after fluoxetine use during the first trimester of pregnancy and identified two controlled studies that involved approximately 350 women taking fluoxetine. For these two studies, the odds ratio was 1.33 (95 percent confidence interval [CI], 0.49 to 3.58), which was not significant.

A second review2 of prospective controlled studies compared the effects of TCAs, fluoxetine, and newer SSRIs in approximately 625 pregnant women and found no significant difference in the rate of major fetal malformations. However, the review did find one study that reported a significantly higher rate of three or more minor anomalies in infants of women who took fluoxetine during the first trimester compared with women who did not take fluoxetine (15.5 versus 6.5 percent). There was no pattern to the anomalies.2 The number needed to harm was 11 (95 percent CI, 6 to 86).

A multicenter, prospective, controlled study8 compared 150 women who took venlafaxine, 150 women who took SSRIs, and 150 women who took nonteratogens. This study also found no difference in the rate of major malformations in infants of women taking antidepressants compared with those taking nonteratogens.

Results of studies evaluating the effect of antidepressants on pregnancies and on neonates in the immediate postpartum period have been mixed but, overall, reassuring. Rates of spontaneous pregnancy loss in women who took fluoxetine, TCAs, newer SSRIs, or venlafaxine were not significantly different compared with rates in control groups.2,8 While one study found an increased rate of preterm delivery in 70 women who took fluoxetine during the third trimester compared with a group of women who took fluoxetine before the 25th week of gestation (relative risk = 4.8; 95 percent CI, 1.1 to 20.8), other studies that included SSRI use during the third trimester reported no difference in gestational age or birth weight among the infants.2,4,5

Neonatal toxicity (e.g., jitteriness, respiratory distress, admission to a special care nursery) has been noted in studies of women taking TCAs through delivery and in one study of third-trimester fluoxetine use. However, neonatal toxicity was not consistently reported in all studies.2 A recent, large, prospective study6 of 997 infants whose mothers took antidepressants during late pregnancy reported increased risks for preterm birth (odds ratio = 1.96; 95 percent CI, 1.6 to 2.41) and adverse short-term neonatal effects. These results were slightly more pronounced in cases of TCA use than in cases of SSRI use.

Data on long-term neurodevelopment in children exposed to antidepressants in utero are limited but reassuring. Fifty-five children exposed to fluoxetine and 80 children exposed to TCAs were

compared with a control group of 84 children. There were no significant differences in IQ scores or development in language or behavior.2 More than one third of the women had continued antidepressant therapy throughout their pregnancy.

Recommendations from Others

A pediatric advisory subcommittee of the U.S. Food and Drug Administration recently suggested labeling changes for SSRIs and venlafaxine to inform patients and physicians of reports of neonatal toxicity and neonatal withdrawal syndrome associated with exposure to antidepressants during the third trimester. The labeling changes state that physicians should carefully consider the potential risks and benefits of therapy when treating a pregnant woman with depression. The American College of Obstetricians and Gynecologists does not have a guideline on the use of antidepressants in pregnant women.

Clinical Commentary

Depression affects approximately 10 percent of pregnant women. Although antidepressants appear to be safe and effective when used during pregnancy, the decision to continue or begin antidepressant therapy in a pregnant woman is complicated. Patients and their physicians must weigh the potential harm from depression to both mother and child against the possible neonatal and long-term effects from fetal exposure to antidepressants. Factors to consider include the severity of the depression, the availability and efficacy of nonpharmacologic treatments, past experience with specific medications, and whether to continue medication use throughout the entire pregnancy. Fortunately, data from cohort studies regarding safety for both SSRIs and TCAs are reassuring.

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