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Are Antidepressant Medications Safe for Pregnant Women With Epilepsy? The Signs Point to Yes

The Use of Antidepressant Drugs in Pregnant Women With Epilepsy: A Study From the Australian Pregnancy Register

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Objective: To study interactions between first-trimester exposure to antidepressant drugs (ADDs) and antiepileptic drugs (AEDs) and a history of clinical depression and/or anxiety on pregnancy outcomes and seizure control in pregnant women with epilepsy (WWE). Methods: We examined data from the Australian Pregnancy Register of Antiepileptic Drugs in Pregnancy, collected from 1999 to 2016. The register is an observational, prospective database, from which this study retrospectively analyzed a cohort. Among the AED-exposed outcomes, comparisons were made among 3 exposure groups: (1) pregnancy outcomes with first-trimester exposure to ADDs, (2) outcomes with mothers diagnosed with depression and/or anxiety but who were not medicated with an ADD, and (3) those with mothers who were not diagnosed with depression and/or anxiety and were not medicating with ADD. Prevalence data were analyzed using Fisher exact test. Results: A total of 2124 pregnancy outcomes were included in the analysis; 1954 outcomes were exposed to AEDs in utero, whereas 170 were unexposed. Within the group of WWE taking AEDs, there was no significant difference in the prevalence of malformations in infants who were additionally exposed to ADDs (10.2%; 95% confidence interval [CI]: 3.9-16.6), compared to individuals in the non-ADD-medicated depression and/or anxiety group (7.7%, 95% CI: 1.2-14.2), or those without depression or anxiety (6.9%, 95% CI: 5.7-8.1; $P = .45$). The malformation rates in pregnancy outcomes unexposed to AEDs were also similar in the above groups ($P = .27$). In WWE medicated with AEDs and ADDs, the frequency of convulsive seizures ($P = .78$), or nonconvulsive seizures ($P = .45$) throughout pregnancy, did not differ across comparative groups. Significance: Comedicating with ADDs in WWE taking AEDs does not appear to confer a significant added teratogenic risk, and it does not affect seizure control.

Commentary

Over the last decade, our understanding of the risks associated with use of antiepileptic drugs (AEDs) during pregnancy has greatly expanded. Thanks in large part to the work of international epilepsy pregnancy registries, providers can now give informed counsel to women about the likelihood of major congenital malformations associated with first-trimester exposure to commonly utilized AED as well as on expectations for maternal seizure control during pregnancy. However, managing epilepsy well across all stages of life requires a focus that expands beyond just treatment of seizures. Psychiatric comorbidities of epilepsy are critical determinants of quality of life in epilepsy. One in 5 people with epilepsy have depression and anxiety, and the rate is significantly higher among people with medically refractory seizures.[1] Suicide rates are 3 times higher in people with epilepsy than in the general population.[2] Despite the recognized prevalence of mood disorders and anxiety in people with epilepsy, these conditions continue to be generally underdiagnosed and undertreated. One often cited barrier to treatment is physician's fear that antidepressant medications may contribute to poor seizure control. For women with childbearing potential, there may be additional concern that psychotropic medication use could further increase the risk of adverse pregnancy outcomes. In fact, women with epilepsy (WWE) have been shown to be less likely to take antidepressant medication during pregnancy than other women, including women with other chronic diseases.[3]

In the United States, the use of antidepressant medications during pregnancy has markedly increased over the last 30 years, with a 2008 estimate of 8% of pregnant women using drugs of this class.[4] Nevertheless, the relative risk versus benefit of using these drugs during the perinatal period remains an area of active controversy. Infants exposed to antidepressant medications during pregnancy have been variably reported to be at heightened risk for major congenital malformations, adverse neurodevelopmental and behavioral outcomes, and low birth weight.[5] However, just as there are potential risks in discontinuing AED therapy in WWE prior to conception,

withdrawal of antidepressant medications prior to or during pregnancy can be a risky proposition. Maternal depression itself has been potentially correlated with these same adverse pregnancy outcomes.[5] Furthermore, failure to adequately treat significant depression during pregnancy can lead to significant harm to the mother including suicide, substance abuse, lower adherence with appropriate prenatal care, and harm to the child including maternal neglect and abuse.[6] Absent definitive evidence, guidance from the American College of Obstetrics and Gynecology has been to utilize counseling when depression and anxiety in the perinatal period are mild and to prescribe antidepressant medications when moderate to severe.[6] For women with both depression and epilepsy, evidence is limited on the potential risks associated with concurrent use of an AED and antidepressant drug (ADD) for the developing fetus or the mother.

This study by Sivathamboo et al is the first to specifically examine pregnancy outcomes related to pharmacologic treatment of depression in WWE. The authors utilized data from the Australian Pregnancy Register of Antiepileptic Drugs in Pregnancy to address 2 questions about the combined use of AED and antidepressants: First, if there was an increased risk of congenital malformations in exposed infants, and second, if there was an adverse impact on maternal seizure control. Among the 159 WWE and depression/anxiety, 94 were on an antidepressant medication, primarily selective serotonin reuptake inhibitors (n = 57) or selective norepinephrine reuptake inhibitors (n = 13). As expected from prior analyses, there was a 3-fold increased risk of major malformations in AED exposed infants versus AED unexposed. For WWE taking an AED, congenital malformation rate was not significantly influenced by additional exposure to an ADD (10.2%; 95% confidence interval: 3.9-16.6; n = 87) nor was it influenced by the presence of depression/anxiety. Fetal birth weight was also similar between the exposure groups. Over the course of pregnancy, seizure control for both convulsive and nonconvulsive seizures was overall similar between women on an AED with nonmedicated versus medicated depression/anxiety. The only noted difference was in the time frame between 7 months' gestation and delivery during which 16% of women on an ADD had a nonconvulsive seizure versus 9.7% of those with nonmedicated depression/anxiety ($P < .001$). The authors did examine the same comparisons among WWE not taking an AED during pregnancy and similarly found no significant effect of antidepressant exposure on congenital malformation risk. However, the sample sizes were small with only 7 women with treated and 3 with untreated depression and anxiety. Limitations of the study include that the presence of depression and anxiety were based on self-report by the study participants. These diagnoses were not validated or rated by severity. Furthermore, dosage of antidepressant medications was not included in the analysis. This is significant because if the analysis included a high percentage of women with mild depression/anxiety or who were on low-dose antidepressant medication, the potential risks may be underestimated. Hopefully, future studies will address these variables and can validate these findings from the Australian Pregnancy Register in larger sample sizes. In the meantime, WWE and their providers should feel more confident in continuing antidepressant medications through pregnancy when the clinical need is present.

By Katherine Noe

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