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 NEWS

Antidepressants and Pregnancy

By Arline Kaplan | April 10, 2013



The extent to which antidepressant use during pregnancy is associated with increased risks of postnatal adaptation syndrome (PNAS), persistent pulmonary hypertension in the newborn (PPHN), first-trimester teratogenicity, stillbirth, and infant mortality is explored in 2 recent studies.^{1,2}

In a recent interview, lead author Nancy Byatt, DO, MBA, a perinatal psychiatrist and Assistant Professor of Psychiatry and OB-GYN at the University of Massachusetts Medical School, said that depression and anxiety are very common during pregnancy and the postpartum period. Approximately 18.4% of women suffer from antenatal depression, and as many as 19.2% experience postpartum depression. In the third trimester, 1 of 5 women (21.7%) experiences anxiety disorders, and in the first 3 postpartum months, 11.1% have an anxiety disorder.¹

In economically developed countries, the prevalence for depression during pregnancy ranges between 7% and 19%, according to obstetrician and epidemiologist Olof Stephansson, MD, PhD, of the Karolinska University Hospital Solna in Stockholm, who is also lead investigator on a recent study that assessed the relative risks of stillbirth and infant mortality associated with SSRI use during pregnancy.²

Byatt told *Psychiatric Times* that conflicting data have led to major controversies regarding antidepressant use during pregnancy. To help providers “understand the risks and benefits of using antidepressants during pregnancy and apply that knowledge to enhance clinical care,” she and colleagues conducted an extensive review of the literature between 1966 and 2012.

Antidepressants considered in the review included SSRIs, SNRIs, and [norepinephrine](#) (Drug information on [norepinephrine](#)) reuptake inhibitors. According to Byatt, the review focused on outcomes that “have the most controversy surrounding them.” These are congenital malformations, PNAS, and PPHN.

Results

“The current evidence for malformations is limited because of inconsistent findings and limited methodology of the published studies,” the review authors wrote. “Few studies have controlled for maternal illness, and therefore do not take into account whether reproductive outcomes are due to maternal illness or antidepressant exposure.”

“There are some individual studies that show a risk between specific SSRIs and birth defects, but if you look at the overall evidence, it has not been consistently observed, which is very reassuring,” Byatt said. “There has not been any single malformation that has been consistently observed across studies with any commonly used antidepressant.” The investigators concluded that PNAS occurs in up to 30% of neonates who are

exposed to antidepressants in late pregnancy. But, it is a transient syndrome that typically resolves in days and in rare cases, a few weeks.

“The PPHN literature is limited by small and/or uncontrolled studies,” according to Byatt and her group. In addition, “there are other reported risk factors, including race, method of delivery, obesity, asthma, and diabetes that many studies do not take into account.” The evidence regarding the risk of PPHN because of in utero antidepressant exposure remains inconclusive. Some studies suggest a small association, and other studies suggest no association.

Byatt pointed to changes in drug safety advisories on SSRIs and PPHN over the years. In 2006, the FDA issued a Public Health Advisory warning of a possible link between SSRI antidepressant use during pregnancy and reports of PPHN. However, in 2011, the FDA, in a Drug Safety Communications, said that given conflicting results from different studies, it is “premature to reach any conclusion about a possible link between SSRI use in pregnancy and PPHN.”

“Overall, we do not recommend discontinuing SSRIs in pregnant women because of the risk of PPHN,” Byatt said. The literature and her communications with other experts in the women’s mental health field indicate that “the overall data on SSRI use in pregnancies is reassuring. SSRIs are considered to be relatively safe for use during pregnancy and the postpartum period.” There are limited data regarding other classes of antidepressants. “The available studies are reassuring, but not definitive,” she said.

Risks of untreated depression/anxiety

Understandably, providers may worry about the medication risks for the pregnant woman and her fetus/child, Byatt said, but equally important are the risks of untreated depression and anxiety. “Prenatal depression and anxiety can lead to missed obstetrical appointments, poor nutrition, poor sleep, and substance abuse,” she said. “Depression also has been associated with poor birth outcomes, including preterm birth, preeclampsia and an increased risk for delivery of a low birth weight infant.”

To assist clinicians in working with their pregnant patients, Byatt and colleagues included a Table of treatment recommendations in their article. These include using the lowest medication dose possible while avoiding undertreatment; avoiding polypharmacy; and maximizing nonmedication, evidence-based treatments.

At about the same time their literature review on antidepressant use in pregnancy was published, an article by Nulman and associates³ appeared on the neurodevelopment of children following prenatal exposure to venlafaxine (Effexor), SSRIs, or untreated maternal depression. Those investigators concluded that factors other than antidepressant exposure during pregnancy predicted children’s intellect and behavior and that children of depressed mothers may be at risk for future psychopathology.

“You can extrapolate from the study that if you can help mom go into the postpartum period well and healthy with her symptoms in remission as much as possible, you can set the stage for mom to be in a position to care for the baby in such a way that would mitigate the child’s risk of having his or her own future mental health symptoms,” Byatt said.

Byatt was somewhat critical of a review that discussed the impact of SSRIs on fertility, pregnancy, and neonatal health.⁴ Domar and colleagues⁴ contended that there is evidence of risk with the use of SSRI antidepressants by pregnant women, that there is no evidence of improved pregnancy outcomes with SSRIs, and that pregnant women, providers, and the public should be advised of this. Byatt said that rather than conducting a systematic review of all the available evidence and coming to a nonbiased conclusion, Domar and colleagues cited a “few articles that support their conclusions,” which can worsen the stigma and confusion surrounding depression treatment during pregnancy.

SSRIs and infant death

Byatt described the recent population-based cohort study by Stephansson and colleagues² as a “well done and very reassuring study.” Analyzing data from Denmark, Finland, Iceland, Norway, and Sweden, Stephansson and colleagues looked at the use of SSRIs during pregnancy and the risk of stillbirth and infant mortality. The large size (more than 1.6 million births) facilitated the study of rare pregnancy outcomes, such as stillbirth, neonatal death, and postneonatal death, Stephansson told *Psychiatric Times*.

For the study funded by the Swedish Pharmacy Company and the authors’ affiliations, the researchers obtained information on maternal use of SSRIs from prescription registries. Exposure was defined as 1 or more filled prescriptions for an SSRI from 3 months before the start of pregnancy until birth. The researchers also gathered information on maternal characteristics, pregnancy, and neonatal outcomes from patient and medical birth registries. They then estimated relative risks of still-birth, neonatal death, and postneonatal death associated with SSRI use during pregnancy, taking into account maternal characteristics and previous psychiatric hospitalizations.

Among 1,633,877 singleton births in the study from 1996 to 2007, there were 6054 stillbirths, 3609 neonatal deaths, and 1578 postneonatal deaths. A total of 29,228 mothers (1.79%) had filled a prescription for an SSRI during pregnancy.

“Women taking SSRIs had slightly increased rates of stillbirth and postneonatal death,” said Stephansson, Associate Professor at Karolinska University’s Clinical Epidemiology Unit. Women exposed to an SSRI had higher rates of stillbirth (4.62 vs 3.69 per 1000) and postneonatal death (1.38 vs 0.96 per 1000) than those who did not. The rate of neonatal death was similar between groups (2.54 vs 2.21 per 1000).

However, when the researchers considered maternal factors, there was no association with SSRIs and stillbirth or infant death rates, Stephansson said. Such factors included a history of the severity of the psychiatric disorder among women taking SSRI drugs during pregnancy, their older age, the tendency for them to be smokers, and the greater incidence of diabetes and high blood pressure.

The researchers acknowledged that they might have overestimated the actual use of antidepressants, because having a drug prescribed doesn’t always equate with using it. Stephansson noted that the study findings need confirmation by other studies in different settings. He added that the Nordic team of researchers has been looking at various issues involving SSRI use and pregnancy. Last year, in a large, multinational cohort study, Kieler and colleagues⁵ found the risk of PPHN “after exposure to any SSRI in late pregnancy was more than doubled.”

The results indicate that out of 11,014 mothers who used antidepressants in late pregnancy (later than gestational week 20), 33 babies (0.2%) were born with PPHN (absolute risk, 3 per 1000 liveborn infants compared with the background incidence of 1.2 per 1000). With regard to SSRI use in early pregnancy, the results indicated that risk for PPHN was “slightly increased.” Specific SSRIs had similar increased risks of PPHN, suggesting a class effect.

Currently, the Nordic collaboration team, according to Stephansson, is investigating spontaneous abortions and congenital malformations and their possible association with antidepressant exposure.

References

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