DRUGS, PREGNANCY, AND LACTATION

Antipsychotics and Pregnancy

Previous columns on the reproductive safety of psychiatric medications have focused on the attendant risks of fetal exposure to antidepressants, benzodiazepines, and mood stabilizers such as lithium and sodium valproate. But less attention has been given to the risks of in utero exposure to antipsychotic medications, as new data regarding these agents are sparse. It has been years since any new systematic data on the reproductive safety of the older, typical antipsychotics have become available. For example, over a decade ago, my associates and I reported that a meta-analysis of studies of the teratogenicity of older typical antipsychotics failed to find an increased risk for organ malformation associated with first trimester exposure to this class of molecules (Am. J. Psychiatry 1996;153:592-606).

LEE COHEN, M.D.

Over a decade later, there are even fewer data on the risk for organ malformations associated with prenatal exposure to the widely prescribed newer, atypical antipsychotics.

This void of information regarding medicines used widely by reproductive-age women prompted the founding of the National Pregnancy Registry for Atypical Antipsychotics, based at Massachusetts General Hospital in Boston (www.womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry).

In the registry, we are enrolling pregnant women aged 18-45 years who are treated with one or more atypical antipsychotics, and prospectively following them for a spectrum of outcomes, including organ malformations and maternal or newborn complications. Those drugs include aripiprazole (Abilify), clozapine (Clozaril), ziprasidone (Geodon), paliperidone (Invega), risperidone (Risperdal), quetiapine (Seroquel), olanzapine (Zyprexa), asenapine (Saphris), and lurasidone (Latuda).

In an ancillary investigation, we also plan to do a prospective study of a subset of newborns exposed in utero to atypical antipsychotics in which we will evaluate these infants for the presence of withdrawal symptoms, such as tremulousness, jitteriness, and potential extrapyramidal symptoms. This pilot investigation follows the drug safety communication from the Food and Drug Administration in February 2011 in which health care providers were notified that the pregnancy section of the medication label for the entire antipsychotic drug class was being changed to reflect the potential risks for extrapyramidal symptoms (EPS) or withdrawal symptoms noted in newborns whose mothers had been treated with these drugs during the third trimester of pregnancy.

The FDA label change is based on 69 cases of neonatal EPS or withdrawal symptoms associated with exposure to both atypical and typical antipsychotics used during pregnancy that were reported to the agency's Adverse Event Reporting System (AERS) through October 2008. Symptoms included abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding. In some newborns, symptoms subsided within a few hours or days and did not require specific treatment; other newborns required longer hospital stays. Presumably, the frequency of reports reached a threshold that prompted the FDA to change the pregnancy section across the family of compounds, making this information more consistent.

While reports of EPS symptoms associated with fetal exposure to older antipsychotics date back several decades, with periodic case reports describing EPS with increased muscle tone and tremor, data regarding the risk for these symptoms associated with the atypicals have been sparse and typically limited to small case series or adverse event reporting systems.

As the FDA communication notes, one of the problems with these reports is that symptoms observed following in utero exposure have typically not been limited to monotherapy. In fact, most – but not all – of the reported cases were confounded by maternal use of other medications during pregnancy, including benzodiazepines, opiates, or antidepressants, as well as by the presence of obstetric and perinatal complications. Accordingly, the FDA acknowledged the limitations of these reports when the other medications known to be associated with similar withdrawal symptoms – such as benzodiazepines – were coadministered. One has to wonder whether some of the reported cases also were associated with late trimester exposure to selective serotonin reuptake inhibitors (SSRIs).

The FDA communication and label change is an example of another situation where drug safety monitoring provides some data, which at first pass may raise appropriate concern. However, estimating prevalence of the noted adverse events is extremely difficult, if not impossible, to calculate, because the total number of individuals exposed (denominator) is not known. Moreover, severe outcomes in adverse event reporting systems tend to be overreported in any voluntary reporting system.

So what is the clinician to do, particularly given the fact that the newer antipsychotics are being used across disease states – not only for chronic mental illness such as schizophrenia, but for bipolar disorder, obsessive compulsive disorders, anxiety disorders, and as an adjunct treatment for depression? Clinicians will likely see more women who are treated with these drugs during pregnancy and should at least be aware of the potential risk for EPS and some of the other associated symptoms described in the communication, particularly in women treated closer to term.

However, it should be appreciated that for many patients, the use of atypical antipsychotics across pregnancy may be required to sustain psychiatric well-being. In fact, the FDA does not recommend arbitrary discontinuation of these agents, but rather notes that health care professionals "should be aware of the effects of antipsychotic medications on newborns when the medications are used during pregnancy."

Clearly, given the nature of the psychiatric disorders for which these medicines are being used, the clinician needs to be particularly mindful that abrupt discontinuation of this class of medicines can increase the risk of recurrence of the underlying illness. Perhaps the most prudent clinical approach in this situation is one of careful observation – as opposed to arbitrary discontinuation of a typical or atypical antipsychotic, which is neither suggested nor implied in the FDA's communication. The FDA communication, which is not a warning, presumably serves to provide extra data for the clinician to factor into risk-benefit decisions.

Clearly, only a prospective study with clear knowledge of exposure and concomitant drug therapy with prospective assessment of the exposed newborns will yield information that refines our knowledge of this signal, which the FDA has suggested may exist. Eligible patients for the MGH National Registry of Atypical Antipsychotics can enroll by calling 866-961-2388. ■

DR. COHEN directs the perinatal psychiatry program at Massachusetts General Hospital, Boston, which provides information about pregnancy and mental health at www.womensmentalhealth.org. He is principal investigator of the National Pregnancy Registry for Atypical Antipsychotics, which is funded by the manufacturers of some antipsychotics. To comment, e-mail him at obnews@elsevier.com.

Study: Be Cautious When Using Anti-TNFs in Pregnancy

BY DENISE NAPOLI

FROM ANNALS OF THE RHEUMATIC DISEASES

Pregnant women taking tumor necrosis factor inhibitors at conception experienced a higher rate of spontaneous abortion than did patients who did not.

The data, culled from the British Society for Rheumatology Biologics Registry, are from the "largest detailed prospective collection of pregnancy outcomes in women with arthritis-related diseases exposed to anti-TNF therapy" to date, according to the authors. However, the study was unable to control for the possibility that disease severity itself plays a role in adverse pregnancy outcomes.

Nevertheless, "no firm conclusions can be drawn about the safety of anti-TNF therapy during pregnancy and, without further evidence, guidelines which suggest these drugs should be avoided at the time of conception must remain," recommended Dr. Suzanne M.M. Verstappen of the University of Manchester's Arthritis Research UK Epidemiology Unit, and her colleagues. They looked at women who received adalimumab, etanercept, or infliximab either at conception or at any time prior to conception. A subset was also exposed to methotrexate and/or leflunomide at time of conception in addition to the anti-TNFs. A fourth cohort with active rheumatoid arthritis had no history of anti-TNF use, but rather received nonbiological disease-modifying antirheumatic drugs (DMARDs), excluding methotrexate and leflunomide (Ann. Rheum. Dis. 2011 [doi:10.1136/ard .2010.140822]).

Among cohort Ia, which included 20 women (21 pregnancies) who took anti-TNFs plus either methotrexate and/or leflunomide at conception, there were 10 live births, 4 terminations, and 7 (33%) spontaneous abortions (miscarriages occurring prior to 20 weeks or to viability outside the womb). Among cohort Ib, which included 44 women who took anti-TNFs at conception, but not methotrexate or leflunomide, there were 50 pregnancies. They included 32 live births among this cohort, 4 terminations, 12 spontaneous abortions (24%) and 2 intrauterine deaths (occurring post 20 weeks). There was also one neonatal death registered. The women who had taken anti-TNFs in the past, but not at the time of conception (cohort II), did have seemingly better outcomes: the 59 pregnancies (54 women) resulted in live births in 46 cases (including one of two twins), terminations in 2, and spontaneous abortions in 10 (17%). There were two intrauterine deaths, including the twin death. Among the 10 pregnancies in 10 women who had no history of anti-TNF use (cohort III), there were zero terminations and one spontaneous abortion (10%).

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