# Three Databases Studied

**Pregnancy** *from page 1*

1998 and June 30, 2003. The pregnancy registry consisted of three linked databases: the RAMQ, which provides information on medical diagnoses and procedures and drugs dispensed; the MedEcho, which provides hospitalization data; and the ISQ, which provides birth and death data, as well as demographic information about the mother, father, and infant.

To be included in the study, women had to be between 15 and 45 years of age on entry into the pregnancy registry, which was defined as the first day of gestational age based on the last menstrual period. Other inclusion criteria were having a live singleton birth, being covered by the RAMQ drug insurance plan at least 12 months before and during pregnancy, and being prescribed an NSAID or other medications during pregnancy.

Women who used indomethacin, aspirin, diclofenac, or misoprostol were excluded from the study.

The researchers used ICD-9 codes 740-759 to identify offspring with congenital anomalies. They also stratified analyses by anomalies of major organ systems.

Up to 10 mothers of infants with no congenital anomalies were selected as controls for each case. The cases and controls were matched for maternal age, region of residence, diabetes status, and year of conception. Definition of exposure to an NSAID was a filled prescription for an NSAID in the first trimester.

Dr. Bérard reported that 36,387 women met inclusion criteria for the study. Of those, 2,571 (7%) had offspring with at least one malformation.

Mothers who used NSAIDs during the first trimester of pregnancy were similar to nonusers in regard to maternal age at conception and place of residence. However, they were more likely to be on welfare or living alone, and they were also generally less educated.

**Babies born to first-trimester NSAID users were 2.2 times more likely to have any congenital anomaly.**

**DR. BÉRARD**

Multivariate analysis revealed that mothers who used NSAIDs during the first trimester were 2.2 times more likely than controls to have a baby with any congenital anomaly. In addition, NSAID users were 3.3 times more likely than controls to give birth to an infant with anomalies of the cardiac septal system.

"Our study suggests a strong association between first-trimester exposure to NSAIDs and the anomalies of cardiac septal closure," Dr. Bérard said. The study will appear in a future edition of Birth Defects Research. ■

# Early Epidurals Don't Increase Risk of Operative Delivery

HOLLYWOOD, FLA. — Epidural analgesia given in early labor has been shown to have no significant effect on the risk of operative delivery in patients with spontaneous labor, and the same appears to hold true for patients with induced labor, according to data presented at the annual meeting of the Society for Obstetric Anesthesia and Perinatology.

In a series of 796 consecutive women with induced labor who requested early pain relief, the operative delivery rates were similar in those who did and did not receive early labor epidural analgesia (28% and 27%, respectively), Dr. Philip E. Hess reported in a poster at the meeting.

Because labor induction is known to be associated with higher operative delivery rates, there was concern that the effects of epidural analgesia in induced labor might be different than its effects in spontaneous labor, Dr. Hess wrote.

In the current study, patients undergoing labor induction who requested early pain relief (before 4-cm dilation) received parenteral opioid or labor epidural analgesia according to their obstetrician's protocol, reported Dr. Hess of Beth Israel Deaconess Medical Center, Boston.

A total of 350 women received epidural analgesia, and 446 received parenteral opioid. The groups were demographically similar, except the average body mass index was higher in the group that did not receive early epidural analgesia.

The groups were also similar demographically to a comparison group of 503 women with spontaneous labor. Consistent with the literature, that group had a 21% operative delivery rate, which was significantly lower than the rates in the induced labor groups, Dr. Hess noted.

**—Sharon Worcester**

## DRUGS, PREGNANCY, AND LACTATION

# A Clinician's Approach to Anticonvulsants

Historically, lithium has been a mainstay of treatment for bipolar disorder. However, over the last decade, anticonvulsant drugs such as sodium valproate and lamotrigine (Lamictal) have become more widely used to treat this disorder.

The use of lithium in the first trimester is associated with a 0.05%-0.1% risk for Ebstein's anomaly, a well-described and frequently serious cardiac malformation. But data from the North American Antiepileptic Drug (NAAED) Pregnancy Registry and other international registries indicate that first-trimester exposure to sodium valproate is associated with an 8%-10% risk of major congenital malformations, notably neural tube defects and cardiac malformations.

BY LEE COHEN, M.D.

As a result, many clinicians have been relieved to have the option of lamotrigine, which is an effective treatment for bipolar disorder and for which there had been extremely reassuring reproductive safety data over the last 5-7 years.

And until recently, several global teratovigilance programs had not found any indication that first-trimester use of this medication was associated with an increased risk for major congenital malformations.

In what is an important development, recent data from the NAAED registry note a prevalence rate of 2.7% for overall major malformations; however, five infants (8.9/1,000) had oral clefts. (See accompanying article.)

The baseline incidence of oral clefts in the general population has been calculated to be between 0.5 and 2.16 per 1,000 births; thus the data from the NAAED registry suggest at least a fourfold increase in the risk of cleft lip and palate or an absolute risk of approximately 0.9%. Interestingly, in five other registries surveyed, the frequency of oral clefts was 2.5 per 1,000 births, far less than reported by the NAAED Registry.

So how is the clinician to understand these new data, which suggest a signal of teratogenic risk, and how do the data inform the clinical care of patients who rely on the medication for control of chronic relapsing illnesses such as epilepsy or bipolar illness?

While stopping medication for the first trimester may appear to be an option for patients with bipolar disorder, unfortunately, a significant proportion of bipolar patients who do so will relapse.

Pregnancy does not appear to protect women with bipolar disorder against relapse if the mood stabilizer they are using is discontinued: In both a retrospective and prospective study, approximately 50% of patients relapsed during the first 6 months of pregnancy following discontinuation of mood stabilizer. It is also noteworthy that women with bipolar disorder are already at a fivefold increased risk for postpartum depression, compared with the general population, a risk that increases further if they relapse during pregnancy.

Therefore, many women with bipolar disorder who want to conceive are caught between a rock and a hard place, because many compounds used to treat bipolar disorder are either known teratogens, or are agents for which the available reproductive safety data are extremely sparse, such as the atypical antipsychotics, i.e., olanzapine (Zyprexa), risperidone (Risperdal), quetiapine (Seroquel), and aripiprazole (Abilify).

Clinicians need to work collaboratively with patients to make treatment decisions, making every effort to minimize risk of relapse and fetal risk, realizing that some patients may have to assume some risk if they are to sustain affective well-being during pregnancy. For women who are on lamotrigine and are planning to conceive, the patients and prescribing clinician should now discuss the increased risk for oral clefts.

Patients who require treatment with a mood stabilizer, particularly those with recurrent disease, may consider a trial of lithium, which, while a teratogen, is associated with an extremely small risk for a cardiovascular malformation.

Certainly, the risk associated with lamotrigine is dramatically more modest than the risk associated with first-trimester exposure to sodium valproate, and many patients may elect to continue lamotrigine.

While it may seem intuitive to consider one of the atypical antipsychotics as an alternative to lamotrigine or lithium, given their efficacy in bipolar illness, the total absence of systematically derived data regarding the reproductive safety of atypicals makes them a less attractive alternative, and frankly the last resort, as compared with medications with known reproductive safety data.

When drug choice during pregnancy is considered, proceeding with a drug with known small risks as opposed to one with totally unknown risks is advantageous, particularly if the known risk is a modest one, which is the case with lamotrigine and lithium.

Ultimately, the clinician is left having to make decisions on a case-by-case basis, in collaboration with the patient, realizing that no decision is absolutely risk free. But decisions can be made that minimize morbidity associated with recurrence of bipolar illness, as well as prenatal exposure to any potentially harmful compound.

When presented with the options, women may make very different decisions. Some women in fact may decide to assume a small risk of oral cleft over a 0.05% risk for a heart malformation because they feel that oral clefts can be repaired more easily, while the morbidity and mortality of Ebstein's anomaly is high, even though the risk is exceedingly small. That is why these decisions have to be made individually, because such decisions will be made not based on relative risk or even absolute risk but rather on each patient's perception of risk.

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