



BY LEE COHEN, M.D.

DRUGS, PREGNANCY, AND LACTATION

Yet More Reproductive Safety Data on SSRIs

Over the last 5 years, several studies analyzing the reproductive safety of the SSRIs, individually and as a group, have been published in the United States and elsewhere. Earlier studies that failed to show an association between first-trimester exposure to SSRIs and an overall increased risk of major congenital malformations were typically small cohort studies; subsequent meta-analyses of the cohort studies have also failed to show an increased risk, which has been reassuring.

The cohort study is the gold standard for evaluating the teratogenic potential of drugs. However, such a study is limited by the difficulty in enrolling enough exposed subjects to demonstrate a statistically significant difference between the two groups (which is particularly true for relatively rare outcomes that can easily be missed).

Recently, several large case-control studies have questioned the safety of SSRIs with respect to teratogenic risk. These case-control studies have included an analysis of records from a large managed care organization, which found an increased risk of heart defects in the babies of women who were prescribed paroxetine (Paxil) during pregnancy, compared with the babies of women prescribed other antidepressants during pregnancy. Another study, using data from the Swedish Medical Birth Registry, also found an increased risk

of cardiac defects among infants with first-trimester exposure to paroxetine.

Two large case-control studies published in June represent the latest efforts to use birth defect surveillance programs to refine our understanding of the reproductive safety of SSRIs. Based on their size, these studies might be expected to refine the risk estimate for congenital malformations following fetal exposure to SSRIs, but these investigations had divergent results.

The National Birth Defects Prevention Study compared 9,622 infants with birth defects with 4,092 control infants born in the United States from 1997 to 2003 and found no significant association between use of any SSRI from 1 month before to 3 months after conception and congenital heart defects or most other birth defects analyzed.

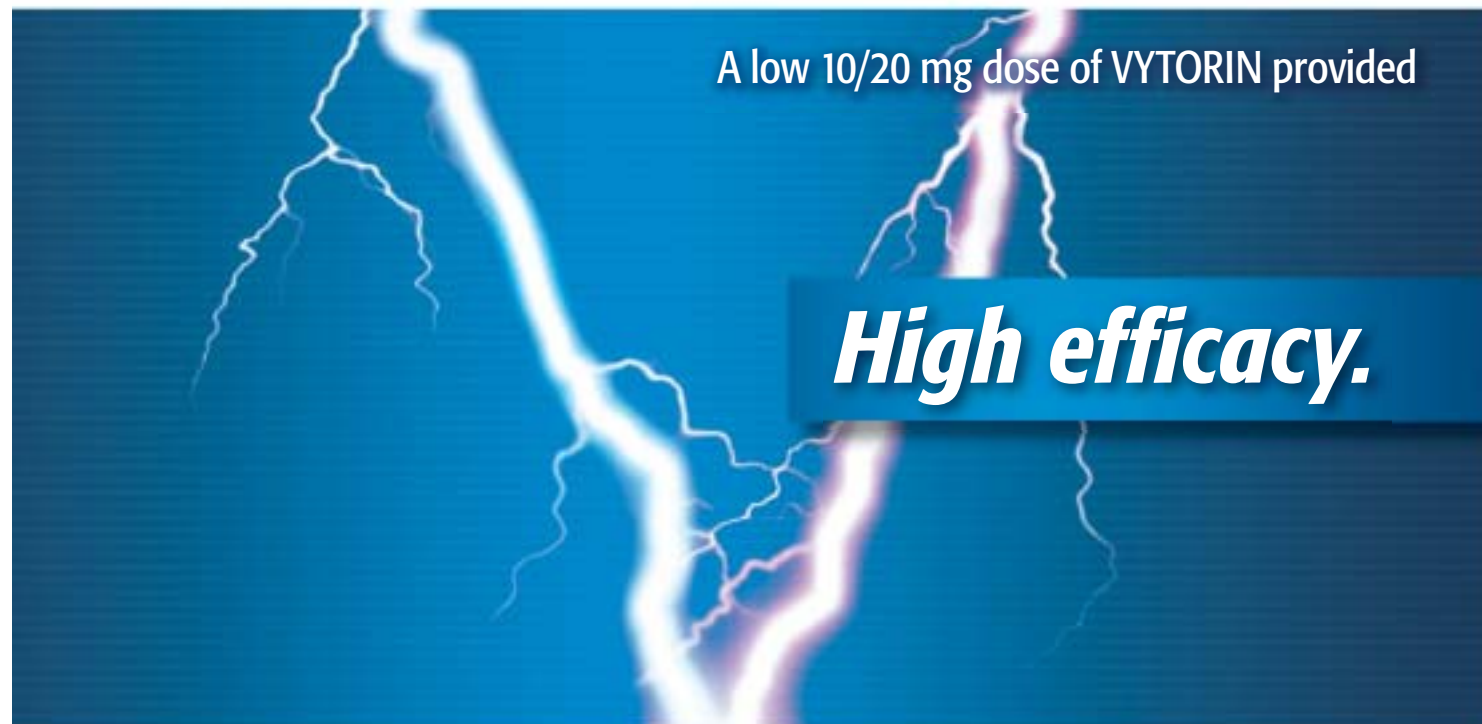
There was, however, a significantly increased risk for anencephaly (odds ratio 2.4), craniosynostosis (OR 2.5), and om-

phalocele (OR 2.8) associated with SSRI use in early pregnancy; these are birth defects that have not been associated with in utero exposure to SSRIs in previous studies. The relationship was particularly strong with paroxetine (N. Engl. J. Med. 2007;356:2684-92).

But no associations were identified between maternal SSRI use in early pregnancy and these three anomalies or congenital heart defects overall in the accompanying

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Diabetes Not Linked to Specific Birth Defects

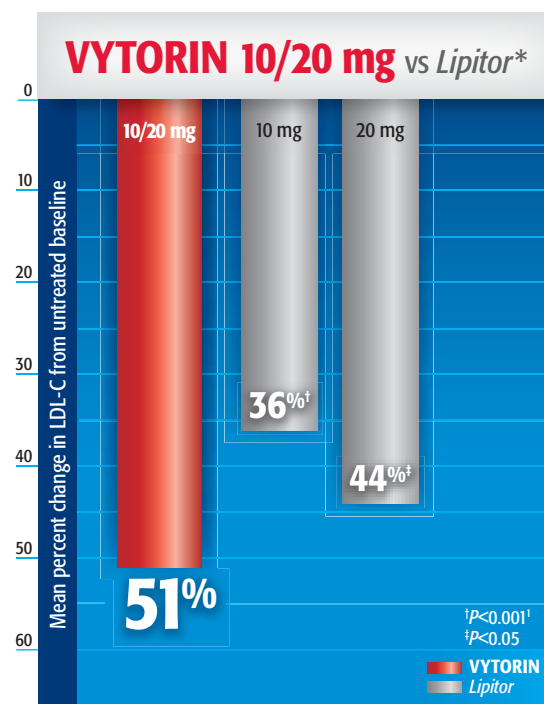
CHICAGO — Pregnant women with diabetes have a two- to four-times higher risk of having a child with a birth defect, but a review of a national birth defects registry does not show that any one type of defect is associated with diabetes, Dr. Adolfo Correa said at the annual scientific sessions of the American Diabetes Association.

The review looked at data from the National Birth Defects Prevention Study, which had reports on 9,778 cases of live births with birth defects and 4,086 control live births, said Dr. Correa of the division of birth defects and developmental disabilities at the Centers for Disease Control and Prevention, Atlanta.

The analysis found a significantly increased risk in 25 of 37 categories of defects, with odds ratios of 5.0 or higher for 17 categories. However, no one category stood out. The highest odds ratio was for sacral agenesis, but out of 25 cases, only 9 involved mothers with diabetes.

“Pregestational diabetes is associated with an increased risk for a wide variety of defects,” but the study found only weak associations, he said.

—Timothy F. Kirn



Reference: 1. Ballantyne CM, Abate N, Yuan Z, King TR, Palmisano J. Dose-comparison study of the combination of ezetimibe/simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia: the Vytorin Versus Atorvastatin (VYVA) study. *Am Heart J*. 2005;149:464-473.

▶ VYTORIN 10/40 mg was superior to atorvastatin 40 mg at lowering LDL-C (57% vs 48%, $P<0.05$).

▶ VYTORIN 10/80 mg was superior to atorvastatin 80 mg at lowering LDL-C (59% vs 53%, $P<0.05$).

*Mean percent change in LDL-C from untreated baseline in a multicenter, double-blind, randomized, active-controlled, 8-arm, parallel-group study (6 weeks of active treatment) (N=1,902). Patients with hypercholesterolemia who had not met their LDL-C goal as defined by NCEP ATP III were randomized to VYTORIN 10/10, 10/20, 10/40, or 10/80 mg or atorvastatin 10, 20, 40, or 80 mg. Mean pooled baseline LDL-C values for VYTORIN and atorvastatin were 178 mg/dL and 179 mg/dL, respectively.¹ VYTORIN 10/10 mg reduced LDL-C by 47% from baseline vs 36% with atorvastatin 10 mg ($P<0.05$).

▶ The dosage should be individualized according to the baseline LDL-C level, the recommended goal of therapy, and the patient's response.

The clinical impact of comparative differences in lipid changes between products is not known.

VYTORIN is indicated as adjunctive therapy to diet for the reduction of elevated TOTAL-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and nonfamilial) hypercholesterolemia or mixed hyperlipidemia when diet alone is not enough.

Contraindications: hypersensitivity to any component of this medication; active liver disease; unexplained persistent elevations of serum transaminases; and women who are pregnant, nursing, or may become pregnant.

No incremental benefit of VYTORIN on cardiovascular morbidity and mortality over and above that demonstrated for simvastatin has been established.

case-control study of 9,849 infants with birth defects and 5,860 infants with no birth defects enrolled in the Slone Epidemiology Center Birth Defects Study, at Boston University (N. Engl. J. Med. 2007;356:2675-83). However, there was a significant association between the use of sertraline (Zoloft) specifically and both omphalocele (odds ratio 5.7) and septal defects (2.0). There was also a significant association between paroxetine exposure and right-ventricular outflow tract obstruction defects (odds ratio of 3.3). It should be noted that the number of actual exposures in these studies to a specific SSRI was particularly small, fewer than 10 actual reported exposures.

Where do these two important studies leave the patient and the clinician? Despite the divergent findings, both studies suggest that the absolute risk of overall major congenital malformations or even particularly rare malformations is extremely small, as pointed out by the respective authors and the accompanying editorial (N. Engl. J. Med. 2007;356:2732-3). For example, the Slone study authors point out that the estimated prevalence of right-ventricular outflow tract obstruction defects is about 5.5 cases per 10,000 live births, so the risk of this defect would be only 0.2% if an SSRI increased the risk fourfold. It also has been noted that in such studies the search

for numerous outcomes associated with potentially numerous exposures may result in a finding by chance.

Clinicians and patients deciding about treatment during pregnancy will need to continue to make decisions on a case by case basis, weighing the risks and benefits using the available, incomplete data on the relative risks of exposure to the medicine or to depression, and the patient's wishes.

In addition, clinicians and patients should consider that, while we have not yet absolutely quantified the risk of prenatal exposure of SSRIs (which might not be achievable), a critical finding influencing treatment decisions is that untreated

depression during pregnancy dramatically increases risk for postpartum psychiatric relapse. In fact, perhaps nothing trumps the importance of sustaining maternal emotional well-being during pregnancy, even given the small absolute risks that may be associated with an individual SSRI during pregnancy. ■

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 also is a consultant to manufacturers of antidepressants, including SSRIs.

reduction vs *Lipitor*

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VYTORIN contains 2 active ingredients: ezetimibe and simvastatin.

SELECTED CAUTIONARY INFORMATION

Skeletal Muscle: Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria, and rare fatalities have occurred. The risk of myopathy/rhabdomyolysis is dose related. Tell patients to promptly report muscle pain, tenderness, or weakness. Discontinue drug if myopathy is suspected or CPK levels rise markedly.

Myopathy Caused by Drug Interactions: Use of VYTORIN with itraconazole, ketoconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, or large quantities of grapefruit juice (>1 quart daily) should be avoided because of the increased risk of myopathy, particularly at higher doses.

The concomitant use of VYTORIN and fibrates (especially gemfibrozil) should be avoided. Although not recommended, the dose of VYTORIN should not exceed 10/10 mg if used with gemfibrozil.

The benefit of further alterations in lipid levels by the combined use of VYTORIN with niacin should be carefully weighed against the potential risks of myopathy. The dose of VYTORIN should not exceed 10/10 mg daily in patients receiving cyclosporine or danazol, and 10/20 mg daily in patients receiving amiodarone or verapamil.

Liver: It is recommended that liver function tests be performed before the initiation of treatment and thereafter when clinically indicated. Additional tests are recommended prior to and 3 months after titration to the 10/80-mg dose, and semiannually for the first year thereafter.

VYTORIN is not recommended in patients with moderate or severe hepatic insufficiency.

In clinical trials, the most commonly reported side effects, regardless of cause, included headache (6.8%), upper respiratory tract infection (3.9%), myalgia (3.5%), influenza (2.6%), and extremity pain (2.3%).

VYTORIN tablets contain ezetimibe and simvastatin: 10 mg of ezetimibe and 10, 20, 40, or 80 mg of simvastatin (VYTORIN 10/10, 10/20, 10/40, or 10/80 mg, respectively).

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