DRUGS, PREGNANCY, & LACTATION

Azathioprine Use In Bowel Disease

An increasing number of women of reproductive age are being treated with azathioprine (Imuran) for inflammatory bowel disease (IBD) because the peak incidence of the disease is among women in this age group.

The immunosuppressant, also used to treat other autoimmune diseases and renal transplant patients, is a prodrug that is metabolized to 6-mercaptopurine (6-MP); 6-MP is available and is used to a lesser extent to treat IBD.

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Concerns about the safety of the drug during pregnancy are reflected in the many calls we receive at Motherisk from women with IBD who are worried about the risks of exposure – and numerous queries from women on Internet message boards and IBD patient websites.

Many clinicians also choose not to prescribe azathioprine during early pregnancy or in the third trimester. Contributing to this anxiety are warnings in the drug's label that it "can cause fetal harm" when used in pregnancy, and the fact that azathioprine and 6-MP are purine antimetabolites. Moreover, studies of animals exposed to very high doses found an increased risk of congenital malformations, although the doses used to treat women and others are orders of magnitude smaller than those used in the animal studies.

Addressing these concerns, we recently conducted a meta-analysis of studies of women treated with azathioprine, and to a lesser extent, 6-MP, during pregnancy. A search of the medical literature found nine studies of about 500 women with IBD treated with these drugs during any stage of pregnancy and a group of disease-matched controls who were not treated with either drug, who were included to avoid the confounding effects of other diseases on outcomes measured in the studies, which included congenital malformations, spontaneous abortions, low birth weight, and prematurity.

The incidence of prematurity was about 70% higher among the women treated with azathioprine or 6-MP, compared with another control group of healthy women who were not treated with the drug. This was a trend that we believe is due in large part to the disease because other autoimmune diseases also are associated with an increased risk of prematurity.

When compared with the group of healthy women who did not have IBD, the risk of congenital malformations was increased by about 45% among women with IBD who were treated with azathioprine or 6-MP. But when the women on azathioprine or 6-MP were compared with women with IBD who were not on one of the purines, there was no increased risk in malformation – which indicates that it is not prenatal exposure to azathioprine or 6-MP but the condition itself that may increase the risk of malformations to some extent.

We concluded that the previously reported association of thiopurines with congenital malformations is likely due to the confounding effects of disease activity. The results of the study, which was recently completed, supports the use of azathioprine during pregnancy because the benefits of the treatment outweigh any minimal theoretical risks that may exist.

At the time a new drug enters the marketplace, there are typically case reports of malformations following drug exposure in pregnant women. Yet since azathioprine became available, there have been no case reports of malformations associated with prenatal exposure. This trend further supports our recent meta-analysis that it is not associated with an increased risk for malformations.

Other reassuring reproductive safety information includes evidence that levels of maternal 6-MP found in cord blood and the placenta are very low, which possibly means the placenta blocks some of the passage of 6-MP from the mother to the fetus.

A study we published in August, which involved perfusing term placentas obtained after cesarean section in healthy women showed that transfer of 6-MP is limited from the mother to the baby (Reprod. Toxicol. 2011 [doi:10.1016/j.reprotox.2011.8.008]).

Both studies provide helpful information for counseling patients with IBD who are doing well on azathioprine. These results also provide some reassurance regarding the relative safety of azathioprine during pregnancy for other conditions as well – although the effects of the underlying maternal disease on pregnancy must always be considered as an important factor.

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Gestational Diabetes, BMI Over 25 Raise Cardiac Risk

BY MIRIAM E. TUCKER

FROM THE ANNUAL MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES

LISBON – Women with a history of gestational diabetes had an overall 50% higher risk for cardiovascular events later in life, and the risk was doubled among overweight women, based on the results of a large, population-based, case-control study in Sweden.

Gestational diabetes is associated with increased risk for type 2 diabetes later in life. The relationship between gestational diabetes mellitus (GDM) and cardiovascular disease has been less well studied.

Also, this appears to be the first analysis to adjust for possible confounders. The increased risk for cardiovascular disease among women with previous GDM was significant among women with body mass indexes (BMIs) of at least 25 kg/m^2, but not below that value.

Moreover, hypertension and smoking during pregnancy were stronger risk factors for later cardiovascular disease than was GDM. "Preventive strategies after pregnancy might need to be individualized depending on each woman's characteristics and risk profile," said Dr. Erik Schwarcz, an endocrinologist and senior physician at University Hospital Orebro, Sweden.

Cases in the study, which used data from Swedish National Healthcare Quality registers from 1991 through 2008, were 4,590 women who died of cardiovascular disease or had a first cardiovascular event – ischemic heart disease, ischemic stroke, peripheral arterial disease, or atherosclerosis – and who gave birth to at least one child during the study period. Each of those women was matched with about five age-matched controls – total 22,398 – who did not have cardiovascular disease and who gave birth during the same year.

At the time of the cardiovascular event, the cases' mean age was 41 years (range 19-61), with a mean of 9 years between the pregnancy and the event. There were 130 deaths among the 2,660 cases, compared with 2 in the 13,357 controls. Ischemic heart disease and stroke were the most common diagnoses, affecting 56% and 35%, respectively.

A history of GDM was present for 2.4% of the cases, compared with 1.2% of the controls, a significant difference. Also significantly increased among the cases were chronic hypertension (2.1% vs. 0.3%), smoking (35.3% vs. 18.1%), non-Nordic ethnicity (14.1% vs. 11.5%), mean BMI (25.4 vs. 23.9 kg/m^2), and low education (23.4% vs. 15.1%).

After adjustment for hypertension, smoking, BMI, parity, education level, and ethnicity, all of the risk factors remained significant except for non-Nordic ethnicity, with odds ratios of 1.50 for GDM, 5.15 for chronic hypertension, and 2.24 for smoking. Using a BMI of 20-25 as the referent, a BMI of 25-29 gave an odds ratio of 1.32, while a BMI of 30 or greater doubled the risk (OR, 2.00).

Dr. Schwarcz disclosed that he has received lecture fees and has conducted clinical trials for Sanofi-Aventis, Novo-Nordisk, and AstraZeneca. ■

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