Gestational Diabetes Affirmed as Precursor

BY MIRIAM E. TUCKER
Senior Writer

The risk of developing diabetes after a history of gestational diabetes increased over time and reached nearly 20% by 9 years post partum, according to results from a large, population-based study involving Canadian women.

The finding confirms those from the United States and elsewhere regarding the rise in both gestational diabetes and type 2 diabetes, as well as the highly elevated risk for the development of subsequent diabetes among women who have gestational diabetes. "This estimate should be used by clinicians to assist in their counseling of pregnant women and by policy makers to target these women for screening and prevention," said Dr. Denice S. Feig of the University of Toronto and her associates (CMAJ;2008:179:229-34).

They utilized data from two sources: a database of hospital discharges for deliveries that occurred in Ontario from April 1, 1995, to March 31, 2002; and a database of all Ontario residents diagnosed with diabetes through March 31, 2004. Of 659,164 women aged 16-49 years without pre-existing diabetes who delivered a baby between 1995 and 2002, a total of 21,823 were diagnosed with gestational diabetes. The overall incidence of gestational diabetes in Ontario rose from 3.2% in 1995 to 3.6% in 2001.

The incidence of having gestational diabetes was higher among women with higher Charlson Comorbidity Index scores (an estimate of the risk of death from comorbid disease), those with lower incomes, and those living in urban areas, compared with rural. Women who had 10 or fewer primary care visits in the 2 years prior to the index delivery were less likely to be diagnosed with gestational diabetes than were women with more than 10 visits (2.7% vs. 3.7%), and those without a usual care provider were less likely to be diagnosed with gestational diabetes than were those who did have one (3.0% vs. 3.4%).

Following delivery, the probability of developing diabetes among the women with gestational diabetes during pregnancy rose rapidly during the first 9 months post partum, and remained more or less constant thereafter over the 9-year follow-up period of the study.

At 9 months, 3.7% of the women had been diagnosed with diabetes. Most of these women probably had pre-existing type 2 diabetes that was only discovered via screening for gestational diabetes. The database doesn't distinguish between type 1 and type 2 diabetes, but most were probably type 2, Dr. Feig and her associates noted.

The probability of developing diabetes among those with a history of gestational diabetes was 5% at the end of 15 months and 13% at 5 years. By the end of the 9-year follow-up, 19% had developed diabetes, compared with just 2% of those without gestational diabetes. The women with gestational diabetes who delivered during 1999-2001 had a higher risk of subsequent diabetes than did those who delivered during 1995-1996. Among the women in the later group, diabetes had developed in 16% by 5 years, whereas it took 9 years for the earlier group to reach a rate of 16%, they said.

Other factors increasing the risk of diabetes following gestational diabetes included Charlson index, greater age, a higher number of primary care visits prepregnancy, and the development of hypertension after delivery. On the other hand, living in a rural area, having a higher income, and having a prior pregnancy within 4 years of the index pregnancy decreased the risk. However, previous gestational diabetes was a more significant predictive factor than all the others were, the investigators said.

In an accompanying editorial, Dr. David Simmons of the Institute of Metabolic Science, Cambridge University Hospitals NHS Foundation Trust, England, called the study "timely, allowing renewal of attention to an important condition where we could do better." Among the areas needing improvement, he said, are increased efforts to prevent progression to diabetes in these women, particularly those who might become pregnant again, and to improve the diagnosis of type 2 diabetes prior to pregnancy.

"Even if there were no primary prevention programs in place, there should be secondary prevention programs to detect diabetes as near to its development as possible. Such programs would allow control of hyperglycemia before a subsequent pregnancy, something clearly of benefit to any future fetus," he commented. ■

Drugs, Pregnancy, And Lactation

Estimating Pregnancy Risk in the Absence of Human Data

BY GERALD G. BRIGGS, B.PHARM, FCCP

In 2007, the FDA approved 16 new molecular entities and several new biologics. None of these agents have human pregnancy experience, but some will be prescribed to women of reproductive age and exposure in early gestation is inevitable. There also are situations when a woman's condition requires drug therapy, regardless of pregnancy. New antineoplastics are indicated when other therapies have failed to fit into this category. Examples are ixabepilone (Ixempra) and lapatinib (Tykerb), used for breast cancer; nilotinib (Tasigna), used for leukemia; and temsirolimus (Torisel), used for advanced renal cancer.

Regardless of the circumstances, clinicians caring for women of reproductive age will be faced with the dilemma of how to counsel patients when there are few or no human pregnancy data. One method, using some of the drugs approved in 2007 as examples, is described here. When an exposure has already occurred, or when the maternal benefit for starting therapy clearly exceeds the fetal risk and there are no other alternatives, the estimation of fetal risk can be based on four questions:

- Is there human pregnancy experience for the drug?
- Is there human pregnancy experience with other drugs in the same class or with similar mechanisms of action?
- Does the drug cross the human placenta?
- Does the drug cause developmental toxicity in animals at doses less than or equal to 10 times the human dose?

Timing of the exposure is critical, and must be included in any estimation. Although organogenesis (5-10 weeks) is usually the most vulnerable period and exposure at that time should be avoided if possible, drugs can cause developmental toxicity throughout gestation. The only requirement is that the exposure coincides with a critical event in development.

For the new drugs described, the answer to the first question is no.

There are several examples that fit the second question. Aliskiren (Tekturna) is an antihypertensive that acts as a renin inhibitor. Two other classes of drugs that act on the renin-angiotensin system, angiotensin-converting–enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs), are known to cause marked fetal toxicity in the second and third trimesters; a similar effect might occur with aliskiren. Nebivolol (Bystolic) is a β-blocker that is used for hypertension. It has no intrinsic sympathomimetic activity (ISA), so, as with other β-blockers without ISA, its effects may include restricted placental and fetal weights when used during the second half of gestation.

Levocetirizine (Xyzal), the L-isomer of cetirizine (Zyrtec), is an antihistamine. There is no evidence of fetal harm from antihistamines, so the risk from exposure to levocetirizine is probably low. On the other hand, lisdexamfetamine (Vyvanse), which is indicated for attention-deficit/hyperactivity disorder, is a prodrug of dextroamphetamine, a drug known to cause human developmental toxicity.

Package inserts typically provide at least four important factors that help answer the third question: maternal concentration, elimination half-life, plasma protein binding, and molecular weight. For example, a small percentage of nonpregnant adults had measurable plasma concentrations of retapamulin (Altabax), a topical antibiotic, but the levels were very low (less than 1 ng/mL). The elimination half-life is unknown, but the medium molecular weight (518) suggests that the drug will cross the placenta. However, the amounts available for transfer appear to be clinically insignificant.

Although there are no definite methods to interpret animal studies, nearly all drugs known to cause human developmental toxicity also cause such toxicity in at least one animal species

The dose that causes toxicity in animals is critical, as is its relationship to the maximum recommend human dose (MRHD). Guidelines released by the Environmental Protection Agency in 1991 stated that if a drug did not cause developmental toxicity at doses less than or equal to 10 times the human dose based on body surface area (BSA) or systemic exposure (AUC), then the drug could be considered low risk for human fetal toxicity. Conversely, if a drug did cause toxicity at doses less than or equal to 10 times the human dose (in the absence of maternal toxicity), then it could be classified as having risk, but the risk magnitude would be unknown. These conclusions were similar to those reached by a panel convened in 2004 (Birth Defects Res. 2004;70[Part A]:7-12).

This information can be applied to sapropterin (Kuvan), an antidote for phenylketonuria. No evidence of teratogenicity was observed in rats at doses up to three times the MRHD based on BSA, but in rabbits, a nonsignificant increase in holoprosencephaly was noted at about 10 times the MRHD.

For the antiretroviral maraviroc (Selzentry), no increase in defects was observed in rats and rabbits at exposures that were 20 times and 5 times higher, respectively, than the MRHD based on AUC. Using this system, I would classify the risk of these drugs, based only on animal data, as moderate (sapropterin) and low (maraviroc).

The strength of any risk estimation increases if two or more of the responses concur. For example, animal studies with retapamulin found no fetal toxicity after high systemic doses. These results, combined with the low systemic levels, reinforce the estimation that this is a low-risk drug. Conversely, animal studies with aliskiren observed fetal growth restriction. Thus, the estimation that this drug may cause fetal growth restriction is strengthened.

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