## DRUGS, PREGNANCY, AND LACTATION

# Use of Antidiabetic Agents During Pregnancy

In a previous column, I looked at the ways uncontrolled hyperglycemia during pregnancy causes significant toxicity for the mother, embryo, fetus, newborn, and adolescent ("Toxicity of Diabetes in Pregnancy," December 2009, p. 52).

This column examines the use of antidiabetic agents, other than insulin, that are used for non–insulin-dependent diabetes during pregnancy and lactation. With insulin excluded, there are eight classes of antidiabetic agents, two of which are given by subcutaneous injections.

BY GERALD G. BRIGGS, B.PHARM., FCCP

Although insulin therapy remains the standard, other agents are sometimes used for people with type 2 and gestational diabetes because of their ease of administration and relatively simple dosing. However, finding the proper dose to adequately control maternal glucose levels throughout a 24-hour period can be challenging. There are situations where combining insulin with another antidiabetic agent gives the best results.

Type 2 and gestational diabetes are characterized by high insulin resistance with calorie-to-insulin ratios ranging from 5:1 to 15:1. So, a patient with a ratio of 5:1 consuming 2,000 kcal/day would require a daily insulin dosage of about 400 U. In our clinic, if a patient requires 300 U/day or more, we add metformin 500 mg twice daily to reduce the insulin dosage by 60%, or about 180 U/day. Metformin appears to be compatible with pregnancy and breastfeeding, but should not be used alone because it will not provide adequate glucose control.

The first-generation sulfonylureas currently available are chlorpropamide (Diabinese), tolazamide (Tolinase), and tolbutamide (Orinase). They can cause marked and persistent neonatal hypoglycemia if taken close to birth. To prevent this toxicity, therapy should be changed to insulin in the third trimester or, at least, several days before birth.

The second-generation sulfonylureas glipizide (Glucotrol), glimepiride (Amaryl), and glyburide (DiaBeta, Glynase, and Micronase) are prescribed much more frequently than the first-generation agents because they do not cause animal developmental toxicity, and can be considered low risk. Although structural anomalies have been reported with these agents, the cause appears to be hyperglycemia rather than the drugs.

The two alpha-glucosidase inhibitors acarbose (Precose) and miglitol (Glyset) delay the digestion of carbohydrates within the gastrointestinal tract, thereby reducing the rise in blood glucose following meals. In people with type 2 diabetes who are not pregnant, the drugs may be used alone but are more commonly used in combination with a second-generation sulfonylurea. Animal data suggest a low risk for acarbose, but animal toxicity (reduced fetal weights and an increase in nonviable fetuses) has been observed with miglitol. Less than 2% of acarbose is absorbed, but higher amounts of its metabolites are measured in the maternal circulation. Miglitol is readily absorbed into the systemic circulation, but it is not metabolized. The human pregnancy data for these agents are very limited.

There is no human pregnancy experience with pramlintide (Symlin), a synthetic analogue of human amylin given by subcutaneous injection, but the animal data suggest moderate risk (structural anomalies in rats). The drug—which slows the rate of gastric emptying, prevents a postprandial rise in plasma glucagon, and promotes satiety—is best avoided in pregnancy.

Saxagliptin (Onglyza) and sitagliptin (Januvia), inhibitors of the enzyme dipeptidyl peptidase–4, are indicated as monotherapy or in combination with metformin or a thiazolidinedione to control hyperglycemia in type 2 diabetes. Saxagliptin has no reported human pregnancy experience, but sitagliptin has limited data from the manufacturer's registry. No congenital anomalies attributable to sitagliptin (either alone or combined with metformin) have been observed. Nevertheless, these agents probably will not provide the tight glucose control needed in pregnancy and are best avoided.

Two glucagonlike peptide–1 receptor agonists, exenatide (Byetta) and liraglutide (Victoza), are peptides given as subcutaneous injections. They are indicated as adjunctive therapy in type 2 diabetics who have not obtained adequate control with diet, exercise, and oral agents. Neither drug has reported human pregnancy experience, but the animal data suggest an associated risk. Insulin, not these agents, should be added if improved glucose control is needed.

Similar to the sulfonylureas, the meglitinides nateglinide (Starlix) and repaglinide (Prandin) are oral insulin secretagogues that are used either alone or with metformin for type 2 diabetes. The very limited human pregnancy data consist of cases exposed before and during early gestation. In all cases, therapy was changed to insulin when the pregnancy was discovered. No developmental toxicity was observed in the newborns.

Pioglitazone (Actos) and rosiglitazone (Avandia), thiazolidinediones used as adjuncts to diet and exercise, lower insulin resistance but do not promote insulin release. Animal reproduction data suggest risk, but the human experience is too limited to assess the risk, so they should be avoided in pregnancy.

In summary, only metformin and glyburide have sufficient human pregnancy experience for them to be classified as low risk in pregnancy. Although many of the remaining agents will probably eventually be shown to be low risk, they are best avoided until such data are available.

In a nursing infant, hypoglycemia is a potential complication with insulin secretagogues such as the first-generation sulfonylureas and the meglitinides. Although the second-generation sulfonylureas also are insulin secretagogues and are excreted in milk, studies have shown that they do not cause infant hypoglycemia or other toxicities. The same is true for metformin. Miglitol is excreted into milk, but based on one case, the amounts were clinically insignificant. None of the remaining agents have human data during lactation but are probably compatible with nursing. However, both of the thiazolidinediones are weak bases and will accumulate in milk, resulting in milk concentrations exceeding those in the mother's plasma. ■

MR. BRIGGS *is a pharmacist clinical specialist in perinatal support services at the Memorial Care Center for Women at Miller Children's Hospital, Long Beach, Calif. He also is coeditor of "Diseases, Complications, and Drug Therapy in Obstetrics." He said he had no disclosures related to the topic of this column.*

# Women With Higher BMI at Lower Risk for Glaucoma

BY JEFFREY S. EISENBERG

FROM OPHTHALMOLOGY

Higher body mass index is not associated with a higher risk of primary open-angle glaucoma, and in women, it may be associated with a reduced incidence of normal-tension glaucoma, a study has shown.

Even so, clinicians and patients must be cautious about these findings until further research substantiates them and clarifies the related biologic mechanisms, cautioned lead researcher Dr. Louis R. Pasquale of the department of ophthalmology, Harvard Medical School, and the Massachusetts Eye and Ear Infirmary, both in Boston, and his colleagues.

The findings are based on data from a prospective cohort study of 78,777 women in the Nurses Health Study and 41,352 men in the Health Professionals Follow-Up Study. Researchers followed participants in the NHS from 1980 through 2004 and participants in the HPFS from 1986 through 2004 (Ophthalmology 2010 [doi:10.1016/j.ophtha.2009.12.017]).

Eligible patients were aged 40 years and older, did not have primary open-angle glaucoma (POAG) at baseline, and underwent eye examinations during follow-up.

VITALS

**Major Finding:** Higher BMI is not associated with a higher risk of POAG, and in women, it was associated with a 6% risk reduction in normal-tension glaucoma.

**Data Source:** Prospective cohort study of 78,777 women in the Nurses Health Study and 41,352 men in the Health Professionals Follow-Up Study, from which 980 cases of POAG were identified.

**Disclosures:** The investigators reported no conflicts of interest. The study was funded by grants from the National Institutes of Health.

Participants in both studies completed questionnaires with information about anthropometric measures, potential confounders, and ophthalmic status. Also, researchers evaluated medical records, including visual field data, from participants who self-reported glaucoma.

For statistical analysis, they divided the incident cases by person-years accrued for each category of anthropometric measure, controlled for known risk factors for POAG, and determined the relationship between anthropometric measures and POAG subtype, namely high tension (more than 21 mm Hg) and low tension (21 mm Hg or less).

The researchers identified 980 cases of POAG during follow-up. Overall, they found no associations between cumulatively averaged BMI and either POAG subtype, and no association between height and the risk for POAG. In women, however, they found that every unit increase in BMI was associated with a 6% reduction in the risk for normal-tension glaucoma.

"Although the inverse association between weight residuals and normal-tension POAG among women may be the result of chance, it is reasonable to entertain [biologic] mechanisms that may support such an association," the researchers reported. "Perhaps some measure linked to adiposity or lean mass that is under sex hormonal influences may protect against the development of POAG. It is possible that higher circulating estrogen levels in postmenopausal women with higher BMI bind to estrogen receptors expressed on retinal ganglion cells to mediate neuroprotection."

By determining how anthropometric measures influence a patient's risk of developing POAG, the researchers wrote, they may one day unlock important clues regarding disease pathogenesis. ■