NovoLog Moves Up to Pregnancy Category B

Study compared rapid-acting insulin analog with regular human insulin in 322 pregnant women.

BY ELIZABETH MECHCATIE
Senior Writer

The Food and Drug Administration has upgraded the pregnancy risk category for NovoLog insulin from category C to B, based on the results of a large multinational study of pregnant women with type 1 diabetes.

The change was announced by the manufacturer, Novo Nordisk, early this year. NovoLog is the trade name for insulin aspart (rDNA origin) injection, a rapid acting insulin analog that was approved by the FDA in 2000.

The study, conducted at 63 sites in 18 countries, compared NovoLog with regular human insulin in 322 pregnant women with type 1 diabetes. The study found that changes in HbA_{1c} and the rate of maternal hypoglycemia were comparable in both groups, according to the company. The study was too small to make any conclusions about the risk of congenital malformations associated with NovoLog, according to a statement issued by Novo Nordisk.

The study found low rates of major maternal hypoglycemia and fewer preterm deliveries among the women who were treated with NovoLog.

The study also found that there was a reduced risk of neonatal hypoglycemia (glucose below 2.6 mmol/L) requiring treatment and "consistently low rates" of major maternal hypoglycemia and fewer preterm deliveries among the women treated with NovoLog, compared with those treated with regular human insulin. These data are on file with the company and will be published, a company spokesperson said.

Dr. Gideon Koren, director of the Motherisk Program, a teratogen information service at the Hospital for Sick Children, Toronto, said that he was pleased to see a decision regarding the safety of a medication during pregnancy that was based on a large, well-designed study.

"This is more the exception than the rule, because very few such studies are being conducted and reported in pregnancy," Dr. Koren noted in an interview.

"Insulin, being a very large molecule, is not expected to cross the human placenta, as was shown for regular insulin numerous times, and by us recently for insulin lispro," added Dr. Koren, professor of pediatrics, pharmacology, pharmacy, medicine, and medical genetics at the University of Toronto.

Lispro, marketed by Eli Lilly as Humalog, is another rapid-acting human insulin analog and is classified as pregnancy category B, based on animal reproduction studies that have not demonstrated any signs of harmful effects to the fetus, according to the drug's label. (The label also states that there are no adequate well-controlled studies in pregnant women, and that because animal reproduction studies "are not always predictive of human response," the drug should be used during pregnancy only if clearly needed.)

Gerald G. Briggs, B.Pharm., pharmacist clinical specialist, Women's Pavilion, Miller Children's Hospital, Long Beach, Calif., noted in an interview that both insulin analogs are commonly used in pregnancy, but are usually reserved for type 1 diabetics, particularly those whose diabetes is considered difficult to control. He considers all insulins—human, pork, analogs, as well as inhaled insulin—as category B drugs, even though some are classified as C. All are large molecules that are closely related to human insulin and it is unlikely that insulin crosses the placenta, at least in clinically significant amounts, said Mr. Briggs, coauthor of the reference book "Drugs in Pregnancy and Lactation." He is not aware of any developmental toxicity reported in association with these agents, other than indirect effects related to severe maternal hypoglycemia.

A third insulin analog on the market, insulin glulisine (Apidra), approved in 2004, has a pharmacokinetic profile that is similar to insulin aspart and lispro, but Mr. Briggs said he is not aware of any information on its use in pregnancy. (Glulisine's label says that the effect of pregnancy on the drug's pharmacokinetics and pharmacodynamics has not been studied.)

Under the current system of pregnancy risk categories used by the Food and Drug Administration, a drug is classified in category B if animal studies show no risk or human data are reassuring. A drug is classified as category C when animal studies have demonstrated adverse effects on the fetus, or have not been done, and studies in women are not available. Drugs in this category should be given only if the potential benefit justifies the potential risk to the fetus. ■

Kit on Benefits of Folic Acid in Diet

The University of Florida Institute of Food and Agriculture Sciences in Gainesville offers an interactive kit for health professionals to help educate patients about the health benefits of daily dietary folic acid for everyone, not just to prevent birth defects.

The kit contains handouts and a video and is available in Spanish. For more information, contact the institute by visiting www.ifasbooks.ufl.edu. ■

DRUGS, PREGNANCY, AND LACTATION

Glyburide for Gestational Diabetes

When treatment for gestational diabetes is indicated, the drug of choice, insulin, can be problematic for some women because of the need for daily injections, which can affect compliance. The cost of therapy may also be an issue for women in lower socioeconomic groups.

The use of oral hypoglycemic agents for treating women with gestational diabetes has not been recommended in the past because many of these drugs cross the placenta, increasing the risk of neonatal hypoglycemia. But there are now several studies that provide encouraging data suggesting that the second-generation sulfonylurea glyburide is a safe option for both the woman and baby.

BY GIDEON KOREN, M.D.

The first study indicating that glyburide might be a safe option for treating gestational diabetes was conducted in 1994, using the human placental perfusion model, which entails taking the term placenta after birth and reconstructing the blood vessels of the mother and newborn to determine whether a drug crosses the placenta. The investigators showed that while most of the oral hypoglycemic drugs tested crossed the placenta, a minimal amount of glyburide passed the placenta (Am. J. Obstet. Gynecol. 1994;171:653-60).

One of the investigators, Dr. Oded Langer, and associates conducted a randomized, controlled trial comparing insulin with glyburide in 404 women with singleton pregnancies and gestational diabetes who started treatment between 11 and 33 weeks' gestation. The study was published in 2000. Both treatments were equally effective in achieving the target level of glycemic control in the women, with 4% of women on glyburide requiring treatment with insulin.

Importantly, there were no significant differences in neonatal complications between the two groups: The percentages of babies who were large for gestational age, had macrosomia, had lung complications, were hypoglycemic, were admitted to neonatal intensive care units, or had fetal anomalies were similar in both groups. Serum insulin levels in the cord were similar in both groups, and no glyburide was detected in the cord serum of babies in the glyburide group, confirming the 1993 study (N. Engl. J. Med. 2000;343:1134-8).

A recent meta-analysis completed by Motherisk of all studies on this topic also found no evidence of an increased risk to the newborn associated with glyburide treatment, corroborating the 2000 study.

Why glyburide does not cross the placenta is an interesting question, one that several research groups are investigating. The placenta is not just a passive barrier, and it has different carrier systems that can selectively efflux different drugs from the baby back to the mother. We also know that the opposite occurs. For example, the placenta carries iron from the mother to the baby; even when the mother is anemic, the placenta ensures that the baby receives iron.

We published a paper earlier this year using the same placental perfusion model used in the 1993 study, but put glyburide on both sides of the placenta and found that it is actively pumped from the baby to the mother (Am. J. Obstet. Gynecol. 2006;195:270-4). The central thinking now is that the most likely placental transporter for glyburide is the breast cancer–resistant protein abundantly available in the placenta.

Glyburide provides an example of a drug that has not been given to women with gestational diabetes because of the false impression that it does cross the placenta, but the available data indicate that despite being a small molecule, it does not.

These novel findings may have major implications for women with gestational diabetes who require treatment because many would be happy not to have to use insulin daily. In many parts of the world, glyburide is already widely used for treating gestational diabetes. And although some women will require insulin, or a combination of glyburide with insulin, there are many women with gestational diabetes who will do well with glyburide. Glyburide is available as a generic, which is a significant cost advantage.

Finally, this may be one of the first examples of a medication that is considered safe to use in pregnancy because it has been found not to cross the placenta. In the future, drug therapy in pregnancy may involve the development of drugs that are pumped by the placenta back to the mother, using placental transporters to control fetal exposure (Placenta 2006;27:861-8).

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