Novolog's Risk in Pregnancy Gets Downgraded

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 analogue 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 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.

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 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," he 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 analogue and is classified as pregnancy category B. The drug's label 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 analogues 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, analogues, 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."

A third insulin analogue on the market, insulin glulisine (Apidra), approved in 2004, has a pharmacokinetic profile that is similar to insulin aspart and lispro. Its 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. ■

Insulin Pump Beats Injection In Pregnant Diabetes Patients

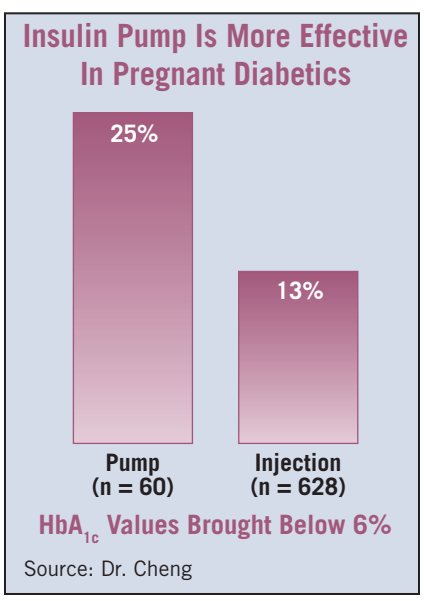
BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — Pregnant women with type 1 diabetes mellitus were more likely to improve glycemic control and less likely to deliver by cesarean section if they used insulin pumps rather than self-injections of insulin, Dr. Yvonne W. Cheng said.

Among 60 women in the pump group, 25% had hemoglobin A_{1c} (HbA_{1c}) values below 6%, compared with 13% of 628 women in the injection group of a retrospective cohort study, she reported in a poster presentation at the annual meeting of the Society for Maternal-Fetal Medicine.

Half of women in the pump group delivered by C-section, compared with 63% in the injection group, said Dr. Cheng of the University of California, San Francisco, and her associates.

After controlling for the effects of maternal age, parity, ethnicity, body mass index, gestational weight gain, and gestational age at enrollment in the California Diabetes and Pregnancy Program, women in the pump group were three times as likely to have HbA_{1c} values below 6% and were half as likely to have a C-section, compared with the injection group.



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The conclusions support results from a 2004 study that found improved glycemic control with use of an insulin pump instead of injections by pregnant women with type 1 diabetes.

Three other studies in 1988, 2000, and 2005 found no significant differences in results among groups, she noted. All the previous studies were smaller than the present study, with only 11-36 patients in the pump groups.

The current study also found that women in the pump group were more likely to be white, to speak English as their primary language, and to have a higher education level than did women in the injection group.

There were no differences between the pump and injections groups in rates of preterm delivery, large-for-gestational-age babies, or admissions to intensive care nurseries.

"In nonpregnant diabetics, most people are switching over to pumps" because studies have shown better glycemic control, Dr. Cheng said in an interview.

The pump provides continuous release of insulin, functioning more like the pancreas than do timed injections of insulin.

To be candidates for pumps, women must be able to count carbohydrates, operate the machine, and program it.

Dr. Cheng has no association with companies that make insulin pumps or injection products. ■

High Fracture Rate Found Among Women in Rosiglitazone Trials

BY ELIZABETH MECHCATIE
Senior Writer

The maker of rosiglitazone is notifying health care professionals about an increased rate of fractures found in women participating in two large, long-term controlled trials of the drug, and the company is advising providers to consider these findings when prescribing rosiglitazone.

In a letter to health care professionals posted on the Food and Drug Administration's MedWatch site, GlaxoSmithKline notes that in ADOPT (A Diabetes Outcome and Progression Trial), significantly more women who received rosiglitazone monotherapy had fractures, compared with women who received metformin or glyburide.

ADOPT, a randomized, double-blind parallel group study of 4,360 recently diagnosed type 2 diabetic patients, compared glycemic control with rosiglitazone to metformin and glyburide monotherapies over 4-6 years, and was published last year (N. Engl. J. Med. 2006;355:2427-43). The trial showed that rosiglitazone monotherapy was associated with a lower treatment failure rate at 5 years than was either metformin or glyburide.

In addition, a preliminary review of interim fracture data in another large, ongoing, long-term controlled rosiglitazone study was "reported to [GlaxoSmithKline] as being consistent with the observations from ADOPT," the letter said. The review was conducted by an independent safety committee at GlaxoSmithKline's request. The committee has recommended that the study, which is looking at cardiovascular end points in patients with type 2 diabetes, continue with no modifications; final results are expected to be available in 2009.

In ADOPT, about 9% of the women on rosiglitazone experienced a fracture during the course of the study, for a rate of 2.74 fractures per 100 patient-years. This was significantly higher than the 5% of women on metformin and 3.5% of women on glyburide who experienced a fracture, for 1.5 fractures and 1.3 fractures per 100 patient-years, respectively.

Most of the fractures among the women on rosiglitazone were in the humerus, hand, or foot, which are different from the fracture sites associated with postmenopausal osteoporosis. The number of women with a hip or spine fracture—the kind typically associated with postmenopausal osteoporosis—"was low and similar among the three treatment groups," according to the letter, which was signed by Dr. Alexander R. Cobitz, senior director, metabolism, in clinical development and medical affairs at GlaxoSmithKline.

The incidence of fractures among the men in the study was similar in all three treatment groups.

"Presently, our understanding of the clinical significance of the findings from these two long-term trials is incomplete," the letter said. For now, the company "believes the risk of fracture should be considered in the care of patients, especially female patients, with type 2 diabetes mellitus who are currently being treated with rosiglitazone, or when initiation of rosiglitazone treatment is being considered."

Rosiglitazone, approved by the FDA in 1999, is marketed as Avandia and is also available in combination with metformin (Avandamet) and with glimepiride (Avandaryl) for treating type 2 diabetes. ■

Read the letter at www.fda.gov/medwatch/safety/2007/Avandia_GSK_Ltr.pdf. Adverse reactions to rosiglitazone can be reported to GlaxoSmithKline at 888-825-5249. Report serious adverse reactions to the FDA's MedWatch program by calling 800-FDA-1088 or online at www.fda.gov/medwatch.