# Experts Debate Insulin Analogue Use in Pregnancy

*While the analogues appear safe, there is reason to be cautious until more data are available.*

BY CHRISTINE KILGORE

EXPERT ANALYSIS FROM THE ANNUAL MEETING OF THE DIABETES IN PREGNANCY STUDY GROUP OF NORTH AMERICA

WASHINGTON – Short-acting insulin analogues appear to be safe in insulin-requiring pregnancies and have clinical advantages, including increased freedom of meal timing, better matching of insulin dose with meal content, and improved glycemic control with a reduction in the frequency of hypoglyemic events, said Dr. Marshall W. Carpenter.

The analogues lispro (Humalog) and aspart (Novolog) may be advantageous, for instance, for the pregnant woman "with a toddler around who may not know when she is going to sit down to eat," Dr. Carpenter said at the meeting.

"The benefit is reflected in the [higher, faster] peak insulin values seen with both lispro and aspart compared with human insulin," said Dr. Carpenter of the department of obstetrics and gynecology at Tufts University, Boston.

Dr. Virginia R. Lupo, who chairs the department of obstetrics and gynecology at the Hennepin County Medical Center in Minneapolis, offered a different take on the utility of short-acting insulin analogues.

Diabetes disproportionately affects women who have annual household incomes below $25,000 and who are more likely to be black, Hispanic, American Indian, or Asian Pacific Islanders than white, she said. For many of these women, a regimen including short-acting insulin analogues is too complex for their lifestyle, eating habits, functional health literacy, and other life circumstances.

"A lot of my patients eat by grazing – there are no distinct meal times," she said. And because of evening-long food availability and ingestion, these patients "require elevated basal insulin through the evenings."

"I'm not convinced that insulin analogues are the right way to go," she said. "I like the idea of NPH twice a day, before breakfast and before supper. It's better to take [insulin] twice a day than not take it five times a day."

The utility of long-acting insulin analogues in pregnancy, Dr. Carpenter said, is still uncertain considering the lack of substantive real-life clinical experience with these analogues and the safety implications raised in the literature thus far. "And really," he added in an interview after the meeting, "there's no evidence that glargine (Lantus) offers any benefit over NPH insulin – and NPH insulin is cheaper."

Questions about the safety of analogues overall stem from the molecular modifications involved in their creation, and specifically the implications of modifying the C-terminal end of the insulin beta chain. Such modifications appear to increase affinity for the insulinlike growth factor–1 (IGF-1) receptor – a receptor that has "a broad array of effects," from induction of mitogenesis and inhibition of apoptosis, to stimulation of angiogenesis, he said.

Analogues' increased "stimulation of [this receptor] has thus appropriately raised concerns about safety," he said.

While the current safety profile of the short-acting analogues "suggests no independent effect on retinopathic change or carcinogenesis," there is reason to be cautious about long-acting analogues until more data are available, he said.

A study published in 2000 comparing the toxicopharmacologic properties of insulin analogues showed that glargine had a six- to eightfold increase in IGF-1 receptor affinity and associated mitogenic potency compared with human insulin, he noted. The two rapidly acting insulin analogues resembled human insulin on all parameters, except for a slightly elevated IGF-1 receptor affinity for lispro (Diabetes 2000;49:999-1005).

**Studies and commentary since an initial study by John L. Kitzmiller have shown no adverse impact of insulin analogues on the progression of diabetic retinopathy in pregnant patients.**

A possible association of lispro with proliferative retinopathy was "put on the map" more than a decade ago when Dr. John L. Kitzmiller and his colleagues reported that 3 out of 10 lispro-treated patients with no detected background retinopathy progressed to proliferative retinopathy during pregnancy (Diabetes Care 1999;22:874-5), Dr. Carpenter said.

Studies and commentary since then have shown no adverse impact of insulin analogues on the progression of diabetic retinopathy in pregnant patients, he said. A Finnish study of 69 pregnant women treated with either lispro or conventional human insulin, for instance, showed no significant differences in retinopathy progression (Diabetes Care 2003;26:1193-8).

Experts have also noted that the hemaglobin $A_{1c}$ levels in women in Dr. Kitzmiller's series were initially high, indicative of poor prepregnancy metabolic control, which raises the question of whether the rapid change to euglycemic control may have been the primary contributor to the advancing retinopathy among these patients rather than a specific lispro effect.

Regardless of insulin choice, rapid tightening of glycemic control is among the predictors of proliferative diabetic retinopathy during pregnancy, along with the duration of diabetes, $HbA_{1c}$ or plasma glucose at the onset of care, and other factors, he said. "We really ought to have informed consent for the rapid achievement of normal blood sugars from a nonpregnant state to a pregnant state … for patients who are in denial before becoming pregnant, with very poor metabolic control, and who are then enlisted in very careful management to dramatically improve their glycemic control," Dr. Carpenter said in an interview. "These are the patients we know are at risk of worsening retinopathy."

Dr. Lupo and Dr. Carpenter said they had no relevant financial disclosures. ■

# Type 2, Gestational Diabetes Are Genetically Linked

BY CHRISTINE KILGORE

EXPERT ANALYSIS FROM THE ANNUAL MEETING OF THE DIABETES IN PREGNANCY STUDY GROUP OF NORTH AMERICA

WASHINGTON – Most of the gene variations identified thus far as risk factors for type 2 diabetes also appear to increase risk for gestational diabetes – a trend that reaffirms the importance of taking family histories in obstetrical practice, Dr. Alan R. Shuldiner said.

Hundreds of candidate genes for type 2 diabetes have been analyzed in association studies over the past several years, and more recently, whole genome approaches have identified close to 40 genes with variations that increase the risk of type 2 diabetes, he explained at the meeting. Moreover, "most of these genetic variants that have also been looked at in [studies of] gestational diabetes all seem to increase risk there as well."

While the utility of genetic screening in obstetrics needs to be investigated, it's clear that "people who have a family history of type 2 diabetes are probably at increased risk for gestational diabetes," he said in an interview.

"From a genetic point of view, recent research reaffirms the importance of clinicians asking about family history," said Dr. Shuldiner, who directs the program in personalized medicine and chairs the division of endocrinology, diabetes, and nutrition at the University of Maryland, Baltimore.

"Until recently, we really didn't know [about this interface]," he said. "It was possible that the genetic factors contributing to gestational diabetes would be very different and distinct from those contributing to type 2 diabetes. So far, that appears not to be the case."

Most recently, an analysis of more than 5,500 pregnant women participating in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study demonstrated that a common maternal variant of the TCF7L2 gene is associated with a higher risk of gestational diabetes, as defined by the new International Association of Diabetes and Pregnancy Study Groups and thus a higher risk of adverse pregnancy outcomes, he told meeting participants.

The risk-conferring variants of the TCF7L2 gene appear to be associated with impaired beta-cell function rather than insulin resistance, he noted.

An earlier report on TCF7L2 polymorphisms and progression to diabetes from the Diabetes Prevention Program Research Group showed that patients with the TCF7L2 variant are at increased risk of developing diabetes but "may be superresponders to lifestyle interventions," Dr. Shuldiner said.

It is findings like these that may, with further research, lead to future recommendations for genetic screening.

Growing evidence on the effects of mutations in the glucokinase (GCK) gene, which appear to account for approximately 5% of gestational diabetes cases in white mothers, may similarly drive screening efforts in the future, he said. (Glucokinase is an enzyme present in pancreatic beta cells required for proper glucose sensing and insulin secretion.)

In a small study conducted in the United Kingdom, maternal hyperglycemia due to a GCK mutation – with no GCK mutation in the fetus – has been shown to result in higher birth weights, while inheritance by the fetus of a paternal GCK mutation appears to result in significant reductions in birth weight. "Screening for GCK mutations could potentially be useful in guiding therapy so that the baby has a normal birth weight," said Dr. Shuldiner, also John L. Whitehurst Professor of Medicine and professor of physiology. "The data so far suggest that if both mom and the fetus have a GCK mutation, you may want to forego treatment [with oral hypoglycemic agents or insulin], and even put mom on a high-carb diet, because the baby needs a high glucose level."

Glucokinase mutations are also associated with maturity-onset diabetes of the young (MODY), which begins before the age of 25 and which we "now know is a heterogeneous group of disorders" resulting in mutations in any of at least eight different genes, he said.

In fact, many experts refer to MODY as being either "glucokinase diabetes" (resulting from mutations in the gene that encodes the glycolytic enzyme glucokinase) or "transcription factor diabetes" (resulting from mutations in genes that encode various transcription factors). Unlike GCK MODY, transcription factor MODY is characterized by hyperglycemia that progressively worsens and often requires treatment with oral hypoglycemic agents or insulin.

Dr. Shuldiner reported that he had no relevant financial disclosures. ■