Gestational Diabetes Therapies and Fetal Risk

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

WASHINGTON – Insulins and oral hypoglycemics used during pregnancy can theoretically cause harm to the fetus, but evidence of harm is lacking, said Dr. Barak M. Rosenn.

"Is there any evidence that pharmacologic agents used in the treatment of gestational diabetes can indeed and do indeed cause harm? Not really," said Dr. Rosenn, director of the division of obstetrics and maternal-fetal medicine at St. Luke's-Roosevelt Hospital in New York.

On the other hand, there have been "no long-term follow-up studies of infants whose mothers were treated with metformin, glyburide, or any of the insulin analogs," he noted, and past experience with thalidomide has shown that "what may seem safe in the present may prove to be unsafe in the future."

"Like anything in medicine, we have to be aware of potential risks and weigh the potential risks and benefits," he said at the meeting. "We can't ignore the fact that diabetes in pregnancy has to be treated."

Transplacental passage of insulin, insulin analogs, and metformin has indeed been demonstrated, he said.

In 1990, for instance, investigators reported that antibody-bound animal insulin was transferred from mother to fetus, and that the extent of transfer correlated with the maternal concentration of anti-insulin antibody (N. Engl. J. Med. 1990;323:309-15).

Another study published in 2007 reported a similar insulin antibody response – and placental passage – in women with gestational diabetes mellitus (GDM) who were receiving human insulin (Diabetes Care 1997;20:1172-5).

In vitro studies on term placentas have demonstrated the transfer of lispro, and aspart has been detected in the cord blood at delivery (Diabet. Med. 2007;24:1129-35). A transplacental passage study of glargine "again showed small amounts crossing into the fetal circulation," but with higher doses, Dr. Rosenn said (Diabetes Care 2010;33:29-33). "We don't know what this small amount [of transfer] means for the fetus," he noted.

In vitro studies have shown metformin to cross the placenta "almost freely," and clinical studies measuring metformin concentrations in the maternal and cord blood have shown at least comparable maternal-fetal levels of the antihyperglycemic agent. "There's some suggestion that [metformin concentrations] may even be higher in [the fetus]," he said. "But again, the question is, 'What does it do to the fetus apart from the fact that it controls glucose in the mother?' "

With glyburide, the degree of transplacental passage is less clear. Investigators of a recent Obstetric-Fetal Pharmacology Research Unit Network study on glyburide in 40 women with GDM reported that the average ratio of umbilical cord/maternal plasma glyburide concentration was 0.7 at the time of delivery (Clin. Pharmacol. Ther. 2009;85:607-14).

"I do have an argument with the validity of this declaration ... because it's pretty obvious that, based on concentrations in the mothers ... it [had been] a long time after the last dose [in most mothers]," he said.

The fetal concentration "may be low, but it's not normal," noted Dr. Rosenn, also professor of obstetrics and gynecology at Columbia University, New York.

Theoretically, it's possible that small quantities of insulin, insulin analogs, or oral hypoglycemics could affect "in-utero fetal programming with respect to sensitivity to insulin or insulin resistance" or could cause undetected fetal hypoglycemia in utero," he said.

Concern has been expressed, moreover, about IGF-I receptor affinity and increased mitogenic potency of some of the insulin analogues.

"Concern has been raised with respect to the mom, but if indeed these cross the placenta, we have [to consider] the fetus as well," Dr. Rosenn said.

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