Type 2, Gestational Diabetes Genetically Linked

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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," Dr. Shuldiner added.

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.

'Screening [the mother, father, and fetus] for GCK mutations could potentially be useful in guiding therapy so that the baby has a normal birth weight.'

"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-carbohydrate 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, he said.

Research on the genetics of diabetes is "still in its early days," said Dr. Shuldiner. The genetic loci associated with type 2 diabetes – and often gestational diabetes – are believed to be responsible for no more than 10% of total genetic susceptibility.

"There may be many rare variants [not detected through the association studies performed thus far] involved, and it's certainly possible that the genetic variants already identified may interact in important ways with lifestyle factors and ultimately with diabetes risk," he noted.

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

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'The FRAX algorithm does not currently include type 2 diabetes as a risk factor for fracture, and ... use of the FRAX score in patients with diabetes will likely underestimate risk.'

Dr. Anne V. Schwartz, p. 25