Fasting Glucose Levels Tied to Preeclampsia

BY SARA FREEMAN
Contributing Writer

Glasgow, Scotland — Fasting plasma glucose levels in pregnant women are associated with the development of preeclampsia, according to the latest data to be released from the Hyperglycemia and Adverse Pregnancy Outcome study.

Principal investigator Dr. Boyd L. Metzger gave a sneak preview of the latest results from the 7-year multinational trial, known as HAPO, during the annual professional conference of Diabetes U.K.

The new findings were on the secondary outcomes of the study. All three measures of glucose control—FPG at 1 hour and at 2 hours and the oral glucose tolerance test—were associated with preeclampsia. After adjusting for potentially confounding factors, the data showed that the odds of developing preeclampsia were 1.2-1.28 times higher for every 1-point standard deviation increase in maternal glucose concentration.

The key findings are the same as those previously released "in that outcomes are very strongly related to the mother's blood sugar level during her pregnancy and that the effects seem to occur at levels that are lower than we've been diagnosing and treating gestational diabetes at in the past," Dr. Metzger of Northwestern University, Chicago, said in an interview.

But the new data show how the effects of maternal glucose during pregnancy appear to extend beyond an increased chance of having a high-birth-weight baby, fetal hyperinsulinemia, and delivery by cesarean section, and into outcomes such as preeclampsia. However, there was no specific number at which the risk of these adverse outcomes started to increase, he said. Although adverse outcomes appeared to occur at fasting plasma glucose (FPG) levels as low as 4.0-4.9 mg/dL, the data did not seem to agree as far as what level was needed to experience one adverse outcome over another.

Four outcomes were designated as "primary" at the start of the study, and were reported last June. These included the frequency of having a high-birth-weight baby, a first cesarean section, neonatal hypoglycemia, and fetal hyperinsulinemia. The last was assessed by measuring the level of C-peptide in the cord blood; a high level was defined as greater than the 90th percentile of what would be expected. Of these, Dr. Metzger said that there were strong associations between maternal glucose levels and both birthweight and fetal hyperinsulinemia; there were milder associations with having a first cesarean section and neonatal hypoglycemia.

"The relationship between maternal blood glucose and the outcome of [a woman's] pregnancy appears to be continuous across the whole spectrum of adverse outcomes, so how much risk is too much risk?" commented Dr. Metzger. This highlighted just one of the problems of applying the HAPO data as they stand to clinical practice. "If the clinical assessment of this information is that we should be intervening to prevent these risks, then we are going to have to lower the values that we have traditionally been using" to diagnose women with gestational diabetes—which will mean that a lot more women will be diagnosed with the disorder, he said.

The effects from blood sugar occur at levels that are lower than have been treated in the past.

DR. METZGER

This was the first time the HAPO findings have been discussed at a professional diabetes meeting outside the United States since their presentation at the American Diabetes Association 67th Annual Scientific Sessions last June.

The investigators are just starting to decipher all the data gathered from the more than 23,000 women who participated in the observational study, and it could be some time before there is an agreement on what these results mean for the diagnosis and management of gestational diabetes. There are also further analyses to be performed, such as the effect of maternal glucose on insulin sensitivity and triglyceride levels.

The first steps toward achieving a consensus on the clinical significance of the HAPO data will be made during a stand-alone meeting to be held in Pasadena, Calif. in a few months. The International Workshop Conference on Gestational Diabetes: Diagnosis and Classification (www.iadpsg.org) will be held directly after the American Diabetes Association 68th Annual Scientific Sessions. The first 2 days of the meeting, to be held June 11 and 12, will involve further presentations of the data followed by a 1-day consensus meeting to try to hash out some of practicalities of the results. A full publication of the HAPO data also is likely to emerge before the end of the year, and Dr. Metzger is hopeful that this may even be available before the consensus conference.

"We are now faced with a lot of information," said Dr. Metzger. "What change will occur is going to be determined by consensus, and by weighing up all the clinical implications." ■

Drugs, Pregnancy, and Lactation

Patient Perception of Teratogenic Risk

BY GIDEON KOREN, M.D.

Ever since the thalidomide disaster almost 50 years ago, people have been fearful of the possible teratogenic effects of medications, and many pregnant women believe almost any drug is teratogenic.

The way in which they and their families perceive the teratogenic risks of medications—even in medications with no such known risks—can result in unnecessary anxiety and sometimes even the unnecessary termination of a pregnancy.

But when women are provided with the available evidence and accurate information, those concerns can be put into the proper perspective, particularly these days, when more information about the reproductive safety of drugs is becoming available.

A striking example of the effects of an exaggerated perception of risk is provided by a 1987 report from Greece that estimated that in May 1986, the month after the Chernobyl nuclear accident in Ukraine, 23% of early pregnancies in Athens were terminated because of concerns about the radiation risk from the fallout of the accident (Br. Med. J. Clin. Res. Ed. 1987;295:1100).

When the Motherisk program, a teratogen information service, was started in 1985, the primary focus for me and my colleagues was to prevent malformations in cases in which women were exposed to genuine teratogens. But it soon became apparent to us that our work would also include preventing unnecessary terminations of pregnancies.

We received many calls from pregnant women who had been exposed to nonteratogenic drugs in early pregnancy and who were concerned nevertheless that there was a risk of having a baby with a malformation. They were considering terminating their pregnancies. Today, we continue to receive such calls, including some from women whose physicians have advised them to terminate pregnancy because of such an exposure.

Because of this experience, we have conducted studies for more than 20 years on how women perceive the teratogenic risk of medications and other exposures, such as dental x-rays, and we have shown how providing them with the available, accurate information has a significant impact on their misperceptions, swaying them away from choosing to terminate the pregnancy.

In our first study of 80 women who consulted Motherisk about drug, chemical, and radiation exposures, we used a visual analog scale measuring a woman's perception of risk during pregnancy, with a range of 0%-100%.

We were surprised to find that women exposed to nonteratogenic drugs such as acetaminophen, or to dental x-rays, which have no known fetal risk, considered themselves to be at about a 24% risk of having a major malformation, similar to the magnitude of risk associated with thalidomide. But after the women were provided with relevant information, this percentage dropped to about 14.5%, and there was a significant reduction in the tendency toward choosing to terminate the pregnancy (Am. J. Obstet. Gynecol. 1989;160:1190-4).

Since that time, we have conducted similar studies on the perceptions of risk associated with other exposures, including mild maternal drinking, x-rays, recreational cocaine use, and treatments for nausea and vomiting, with similar results. In a 1999 study, we found that evidence-based counseling of women with unfounded fears of the teratogenic risks of drug treatment for nausea and vomiting reduced the proportion of women in the study who mistakenly believed that antiemetic drug therapy increased the risk of major malformations (Reprod. Toxicol 1999;13:313-9).

Radiation exposure elicits huge anxieties, as does mild alcohol consumption and use of drugs that are teratogenic at high doses in animals, but have not been shown to be teratogenic in humans.

Because of the fear of fetal-alcohol syndrome, some women consider terminating pregnancy because of a few drinks they had before they knew they were pregnant—yet another example where misinformation and misperception unnecessarily lead to terminations of otherwise wanted pregnancies.

The lack of information in the product labeling of drugs contributes dramatically to these misperceptions of risk. The current pregnancy category letter labeling system in the United States remains unchanged, despite plans to revise the system.

Although more information about safety during pregnancy has been added to some drug labels, in most cases, labels suggest there are not enough data—even if relevant data exist. A physician who reads the fluoxetine label, for example, may not find adequate information to counsel a patient, despite evidence in the literature that the drug is safe in terms of morphology, as well as IQ and learning.

By providing evidence-based counseling, clinicians can address a patient's unrealistically high perception of risk and make a difference. Providers can obtain more information about the reproductive risks of drugs from the Organization of Teratology Information Specialists (866-626-6847 or www.otispregnancy.org). Other resources include Motherisk (www.motherisk.org), and the MGH Center for Women's Mental Health (www.womensmentalhealth.org). There is also my book, "Medication Safety in Pregnancy and Breastfeeding," (McGraw-Hill, 2007), which summarizes information from the Motherisk database.

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