

# Individualize Glucose Control During Pregnancy

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LOS ANGELES — Pregnancies complicated by type 1 or type 2 diabetes mellitus can have good outcomes with new strategies for glucose control, Steven G. Gabbe, M.D., said at the annual meeting of the Society for Gynecologic Investigation.

At less than 5%, the perinatal mortality of children whose mothers have diabetes is comparable with the rate in children of women without diabetes, according to Dr. Gabbe, dean of Vanderbilt University School of Medicine in Nashville, Tenn.

Nonetheless, preventing congenital malformations and overly large babies remains a challenge. "We have to develop individualized programs of insulin for our patients," he said, offering strategies for patient education and self-management.

Glucose control goals change with pregnancy, said Dr. Gabbe. Physicians should counsel diabetic women before conception to bring their glycosylated hemoglobin (HbA<sub>1c</sub>) levels to no more than 1% above the normal range. Targeted plasma glucose levels should be 80-110 mg/dL before meals and less than 155 mg/dL after meals.

During pregnancy, target plasma glucose levels should be 60-90 mg/dL before breakfast; 60-105 mg/dL before lunch, supper, or a bedtime snack; less than 120 mg/dL 2 hours after meals; and above 60 mg/dL between 2 a.m. and 6 a.m. The mean capillary glucose level should be maintained below 100 mg/dL.

To help patients use HbA<sub>1c</sub> levels to approximate mean glucose levels, he suggested teaching them "the rule of eights": An HbA<sub>1c</sub> of 8% equals 180 mg/dL, and each 1% change equals  $\pm 30$  mg/dL.

Pregnant patients need to understand that there is a "lag time" between an injection of insulin and a meal (N. Engl. J. Med. 2005;352:174-83), he continued. Physicians should also warn them against "insulin stacking" in which a correction dose of insulin is given before the prior dose of prandial insulin has reached its peak effect (JAMA 2003;289:2254-64).

Insulin stacking leads to hypoglycemia, he warned. "You have to remember and remind patients about overcorrecting with too much insulin too soon before the insulin they have taken has played out."

Dr. Gabbe said insulin levels increase in pregnancy, but changes can vary for each woman. To help with the adjustment, he advised teaching the patient that:

► One unit of short-acting insulin will lower her blood glucose level by approximately 30 mg/dL.

► Ten grams of carbohydrate will elevate her blood glucose by about 30 mg/dL.

► One unit of short-acting insulin will cover approximately 10 g of carbohydrates.

He recommended the short-acting insulins lispro and aspart for pregnant patients; these can be injected or used with an insulin pump. He said there are concerns but not much experience with the long-acting insulin glargine in pregnancy.

Insulin pumps offer many advantages. Along with eliminating the need for multiple injections, they provide a continuous basal rate, which reduces the risk of mean glucose excursions and hypoglycemia. They also allow a more flexible lifestyle.

But the pumps also have disadvantages. They require excellent compliance, intensive glucose monitoring, and can produce hypo- or hyperglycemia if mechanical problems occur. Pump failure increases the risk of ketoacidosis, and there is the potential for infection at the insertion site. It also "costs \$140 more per month to use a pump vs. multiple injections," he said.

Whatever method is used, Dr. Gabbe said diet is critical as well. Patients should have three meals and three snacks each day.

Another concern is hypoglycemia unawareness, which could be exacerbated by intensive insulin therapy during pregnancy. Determine if the patient has hypoglycemia unawareness; review and adjust her diet, insulin, and exercise; and teach family members to treat hypoglycemia, Dr. Gabbe said.

"Does all of this really make a difference?" he asked rhetorically. "Yes, it does—in having a baby that grows normally and behaves normally in the nursery." ■

## DRUGS, PREGNANCY, AND LACTATION

### Atypical Antipsychotics

The reproductive safety of the older typical antipsychotics, such as haloperidol, is supported by extensive data that have accumulated over the past 40 years, at least with respect to teratogenic risk. Much of the data come from their use in treating nausea, particularly with prochlorperazine (Compazine). While long-term neurobehavioral data have been somewhat sparse, no particular indications of risk have been raised in more than 4 decades of use.

We have far less reproductive safety data on the newer "atypical" class of antipsychotics that have become widely used over the past decade because they lack some long-term side effects associated with the typical antipsychotics. These drugs—olanzapine (Zyprexa), risperidone (Risperdal), quetiapine (Seroquel), aripiprazole (Abilify), ziprasidone (Geodon), and clozapine (Clozaril)—are approved for schizophrenia; several are approved for acute mania indications as well.

But they are also being used widely across psychiatric disease states, including anxiety, agitation in the elderly, generalized anxiety disorder, and obsessive-compulsive disorder, and as adjunctive treatment of depression.

What data are available on the atypicals have been largely limited to manufacturers' accumulated case series or spontaneous reports, which have their inherent biases with respect to overreporting of adverse outcomes.

To date, such information has not suggested any "signals" with respect to concerns regarding their use in pregnancy, but we can make limited conclusions based on such information. Clinicians have been in a bind with respect to use of atypicals in pregnancy.

A study published in April, the first prospective study of the reproductive safety of the atypicals in the literature, provides some reassuring data regarding the risk of malformations, albeit in a relatively small sample of 151 patients. Investigators from the Motherisk Program in Toronto prospectively followed these women who took olanzapine, risperidone, quetiapine, or clozapine during pregnancy. All of the women had taken one of these agents during the first trimester, and 48 were exposed throughout pregnancy. A total of 151 pregnant women who had taken a non-teratogenic drug also were followed.

In the atypical-exposed group, one child was born with a major malformation (0.9%), a rate lower than the 1%-3% background rate in the general population, versus two (1.5%) in the control group, an insignificant difference.

Differences between groups in the rate of spontaneous abortions, still-

births, or gestational age at birth were not statistically significant. Women taking atypical antipsychotics did have significantly higher rates of low-birth-weight babies (10% vs. 2%) and therapeutic abortions (10% vs. 1%) (J. Clin. Psychiatry 2005;66:444-9).

The sample was relatively small, the study was statistically underpowered, and long-term neurobehavioral outcomes were not evaluated. Still, this is the first prospective study that complements spontaneous reports from the manufacturers.

The authors noted the number of spontaneous reports of pregnancy exposures to atypicals, provided by the respective makers, with the exception of newer atypicals. Of 242 reports of olanzapine-exposed pregnancies, there was no increase of major malformations or other abnormal outcomes above baseline. Of 523 clozapine exposed pregnancies, there were 22 "unspecified malformations."

Of the 446 quetiapine-exposed pregnancies, 151 outcomes were reported, of which 8 were different congenital anomalies. Eight malformations were reported among the approximately 250 reports of pregnancies and lactation exposed to risperidone, but no pattern of abnormalities was noted.

If a patient can do without the medication, it is appropriate to discontinue it. In other cases, these decisions have to be made on a case-by-case basis.

For a patient planning a pregnancy who has a severe psychiatric illness and who is maintained on an atypical antipsychotic to sustain functioning, switching to a typical antipsychotic may be prudent. However, we often see women who present when they are already pregnant and on an atypical agent. At this point, a switch may not be wise if the patient is at a risk of relapse. In that case, the Motherisk data are not a guarantee of safety but do provide information that is moderately reassuring. Although this study is encouraging, given the prevalence of reproductive-age women on these agents, it would be ideal if the industry did postmarketing studies to provide the amount of cases we need to reliably estimate risks. Such studies may soon be mandated by the Food and Drug Administration in this post-Vioxx era, with increased emphasis on the safety of marketed drugs.

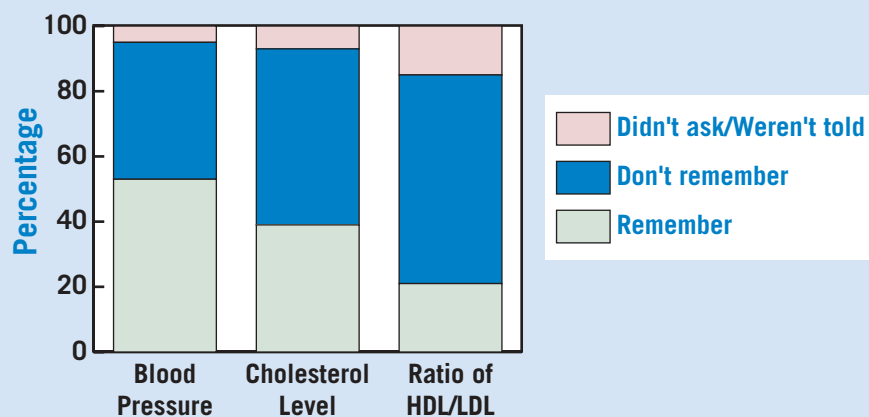
DR. COHEN directs the perinatal psychiatry program at Massachusetts General Hospital, Boston, which offers information on pregnancy and mental health at [www.womensmentalhealth.org](http://www.womensmentalhealth.org). He is a consultant to AstraZeneca, Eli Lilly, and Janssen, manufacturer of atypical antipsychotics.



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## DATA WATCH

### Many Americans Don't Remember Results of BP, Cholesterol Tests



Note: Based on a nationwide survey of 2,288 adults conducted April 22-26, 2004.  
Sources: Harris Interactive, Wall Street Journal Online