EDITORIAL (SEE HARMON ET AL., P. 2198)

Aiming at New Targets to Achieve Normoglycemia During Pregnancy

In a recent issue of *Diabetes Care*, Hernandez et al. (1) from the University of Colorado presented a comprehensive review of the 24-h glucose profile during pregnancy in women without diabetes. In the current issue, Harmon et al. (2) from the same institution present new observations on the glycemic profile of pregnant nondiabetic women, examining differences between obese and normal-weight mothers and between different trimesters of pregnancy. Why are articles about women without diabetes being published in a journal whose very title declares that it is about the care of diabetes? The answer is that these two reports give us an idea of what is truly "normal" glucose during pregnancy, and this has important implications for the way we all manage diabetes during pregnancy. The articles are startling in that they both show that normal glucose values are substantially lower than the target values currently recommended for treatment of diabetes during pregnancy. Hernandez et al. (1) propose that we ought to change these targets to more closely approximate nondiabetic norms.

Contemporary management of diabetes during pregnancy is guided by the Pedersen Hypothesis, which holds that diabetic fetal macrosomia and various newborn metabolic sequelae are caused by endogenous fetal hyperinsulinemia, which is a response to fetal hyperglycemia. This, in turn, is a direct reflection of maternal hyperglycemia because glucose readily traverses the placenta whereas insulin does not (3). The corollary is that diabetic fetopathy should largely be preventable by preventing maternal hyperglycemia. The cornerstone of diabetes management in pregnancy, then, is to attempt to keep maternal glucose as close to normal as possible. But what exactly is a "normal" glucose during pregnancy? The articles by Hernandez et al. (1) and Harmon et al. (2) help us to answer this question.

The review by Hernandez et al. (1) reported on literature spanning half of a century concerning normoglycemia in nondiabetic women. Surprisingly, our understanding of the normal 24-h glycemic profile is based on a total of 12 studies comprising only 255 nondiabetic subjects, mostly nonobese and mostly in the late third trimester of pregnancy. Some of these women were observed in inpatient settings using whole blood or plasma glucose measurements, others were followed as outpatients using self-monitored capillary glucose measurements, and others with tissue glucose measurements using continuous glucose monitoring systems. Despite the variations in methodology and settings, there was some consistency in the results. Pooling the results, the weighted average glucose values (± 1 SD) were 71 ± 8 mg/dL fasting, 109 ± 13 mg/dL at 1-h postprandial, and 99 ± 10 mg/dL at 2-h postprandial.

These values constitute our best assessment of normoglycemia during pregnancy. But the literature review had a paucity of studies regarding the influence of important cofactors, such as maternal obesity, maternal ethnicity, or trimester of pregnancy. The study by Harmon et al. (2) begins to address some of these, specifically the differences between obese and nonobese nondiabetic women, studied in the early second trimester and again during the early third trimester. They report that glucose averaged about 5–10 mg/dL higher in obese women than in normal-weight women throughout the day, including both the fasting and the fed states, regardless of whether the women were on a strictly regulated diet or an ad libitum intake. Newborn adiposity (percent body fat) was correlated with average daytime glucose. The authors introduce the term "occult hyperglycemia" to describe the higher average glucose values among obese women. They speculate that this subtle degree of hyperglycemia may partially explain the increased adiposity and the high rates of macrosomia and large-for-gestational age (LGA) among newborns of obese mothers.

Does such a subtle elevation of glucose really matter that much? Recent evidence suggests that it does. The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study (4) found that there is a continuous linear relationship between maternal glucose and cord blood C-peptide (a measure of fetal hyperinsulinism), LGA and newborn adiposity. Treatment trials such as the Australian Carbohydrate Intolerance Study (ACHOIS) (5) and the American Maternal-Fetal Medicine Units (MFMU) Network trial (6) demonstrated that the risk of LGA and other adverse outcomes can be reduced with diet and medication designed to lower glucose, even when it is only mildly elevated.

Various national and international professional organizations and consensus groups have recommended target glucose values for management of gestational diabetes mellitus (GDM) (7–9) or overt diabetes during pregnancy (10–12). The recommended targets are to keep typical fasting glucose <95–99 mg/dL, 1-h postprandial glucose 130–144 mg/dL, and 2-h postprandial glucose <120 mg/dL. These targets are all 20–35 mg/dL higher than the weighted average normal values in nondiabetic women reported by Hernandez et al. (1). Even compared with the obese nondiabetic women in the Harmon study (2), they are 5–30 mg/dL higher. Hernandez et al. (1) speculated that the wide gulf between normal glucose and the treatment targets may explain why many caregivers find an excess rate of fetal macrosomia among offspring of diabetic mothers, even when glucose control is maintained within target. In their review, they proposed new, lower target glucose values for pregnancy based on 1 SD above the mean values from nondiabetic pregnant women. Specifically, they proposed targets of 81 mg/dL for fasting glucose, 122 mg/dL for 1-h postprandial glucose, and 110 mg/dL for 2-h postprandial glucose.

There is some indirect evidence to support the hypothesis that striving for lower glucose targets ought to reduce the rate of fetal macrosomia. One line of evidence comes from the HAPO Study (4), which found the lowest rates of LGA among those with the lowest glucose levels, whether measured fasting or after a glucose challenge. But these results are simply correlations from an observational study based on measurement of glucose at a single time-point in the early third trimester. It is not necessarily valid to extrapolate from these observations to a treatment regimen continued for several

weeks or months. Another line of evidence comes from the two recent GDM treatment trials. The ACHOIS trial (5) aimed for target fasting glucose values of <99 mg/dL (5.5 mmol/L) and 1-h postprandial values <144 mg/dL (8.0 mmol/L), whereas the MFMU (6) trial had slightly lower targets, <95 mg/dL and <140 mg/dL, respectively. The rates of LGA in the two studies were 13 and 7% respectively. It is tempting to speculate that the lower rate of LGA in the MFMU trial was a result of the lower targets used in that study, but other factors may well have been involved, including differences in patient populations and enrollment criteria.

Controlled clinical trials are needed to test whether lower glucose targets will give improved pregnancy outcomes. To date, there have not been any treatment trials testing whether one particular set of target values is superior to another. Indeed, there have not even been trials addressing whether it is better to base treatment on 1-h or 2-h postprandial glucose measurements. All the standard recommendations (7–12) are based on level III evidence (i.e., expert opinion and consensus).

Glycemic control during pregnancy is often a balancing act. If control is not strict enough, LGA and metabolic complications may result, but if control is too strict, the frequency of significant maternal hypoglycemia and small-for-gestational-age (SGA) infants may increase (13,14). These competing factors leave us in a state of equipoise regarding the level of glycemia to target during pregnancy. That equipoise, that uncertain balance of competing factors, is necessary and sufficient justification to call for a clinical trial. Investigators will need to debate whether such a trial should test new targets based on 1 SD above the normal mean nondiabetic values as proposed by Hernandez et al. (1), or targets based upon 2 SDs above the mean, or other possible values. The selection of targets for a trial will involve a weighing of anticipated benefits (such as less LGA and neonatal hypoglycemia) against potential risks (such as more SGA and maternal hypoglycemia), with consideration given to the practical challenges of motivating subjects to achieve stricter targets.

The new International Association of Diabetes in Pregnancy Study Groups criteria for diagnosis of GDM (15) are expected to substantially increase the percentage of women diagnosed with GDM. This is probably appropriate, given the current worldwide epidemic of obesity. More obesity means more fetuses at risk. More women diagnosed with GDM means more opportunities to reduce that risk. But how do we accomplish the reduction? The American Diabetes Association suggests that much of the increase in GDM will be attributable to women with mild degrees of hyperglycemia who may not need intensive therapy (16). But the evidence reviewed here suggests that all women with GDM may need more intensive therapy than we have previously recommended. The time is right for controlled trials to determine what our glucose targets ought to be.

C. Andrew Combs, md, phd[1]
Robert G. Moses, md[2]

From the [1]Obstetrix Medical Group, San Jose, California; and the [2]Diabetes Services, Wollongong Hospital, Wollongong, New South Wales, Australia.
Corresponding author: Robert G. Moses, robert.moses@sesiahs.health.nsw.gov.au.
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