Never Say Never in Medicine

Confessions of an old dog

For over two decades I have religiously clung to the notion that maternal hyperglycemia is the root of all evil in pregnancies complicated by diabetes (1). To this end, I have valiantly waved the flag for universal screening for gestational diabetes (2), intensified glucose monitoring (3,4), and intensified insulin delivery for all women with hyperglycemia in pregnancy (5). In addition, I championed absolute normalization of blood glucose to mimic the levels documented in a normal population of pregnant women, as recently reported by Parretti et al. (6). Despite the fact that I have been a coauthor on articles that suggest that normalization of blood glucose may be associated with an increased risk of small-for-gestational-age infants (7), I have tended to ignore or explain away this finding even when the evidence has been convincing. This old dog became an ostrich. Her head was in the sand despite examples of definitive studies that showed that there is an increased prevalence of small-for-dates (<10th percentile birth weight) infants in programs of "tight control." The landmark article of Langer et al. (8) showed the relationship between optimal levels of glycemic control and perinatal outcome in a prospective study of 334 gestational diabetic women and 334 control subjects matched for obesity, race, and parity. Three groups were identified on the basis of mean blood glucose level throughout pregnancy (low, ≤86; mid, 87–104; and high, ≥105 mg/dl). The low group had a significantly higher prevalence of small-for-gestational-age infants (20%). In contrast, the prevalence of large-for-gestational-age infants was 21-fold higher in the high mean blood glucose category than in the low mean blood glucose category (24 vs. 1.4%, $P < 0.0001$). In the control group, the overall prevalence was only 11% for small-for-gestational-age infants and only 12% for large-for-gestational-age infants. They concluded that a relationship exists between level of glycemic control and neonatal weight. "Too tight control," defined as a mean capillary glucose <87 mg/dl, is associated with a higher risk of intrauterine growth retardation in offspring of gestational diabetic women.

If one did not have an emotional attachment to this debate, then when the first report by Buchanan et al. (9) was published, which compared management based on maternal glycemic criteria with management based on fetal abdominal circumference measurements by ultrasound to select gestational diabetic women for insulin treatment, the obvious interpretation would have been that using ultrasound may be the ideal means to identify the women who would benefit from an intensive insulin protocol. Instead, I interpreted the results with caution (10). Buchanan et al. (9) showed in 98 gestational diabetic women with fasting plasma glucose concentrations of 105–120 mg/dl that the women randomized to begin insulin when self-monitored capillary glucose levels were elevated fared no better than the women randomized to receive insulin only when the abdominal circumference, measured monthly, was ≥70th percentile. Birth weights (3,271 ± 458 vs. 3,369 ± 461 g), frequencies of birth weights >90th percentile (6.3 vs. 8.3%), and neonatal morbidity (25 vs. 25%) did not differ significantly between the standard and experimental groups, respectively. However, the cesarean delivery rate was significantly lower (14.6 vs. 33.3%, $P = 0.03$) in the group that was managed by blood glucose monitoring and initiation of insulin when blood glucose became elevated (the standard group) when compared with the group managed by ultrasound abdominal circumference measured monthly. This difference in cesarean delivery rate was not explained by birth weights. They concluded that in women with gestational diabetes, fetal abdominal circumference measurements identified pregnancies at low risk for macrosomia and resulted in the avoidance of insulin therapy in 38% of patients without increasing rates of neonatal morbidity.

My argument against the use of ultrasound as the sole guide for insulin therapy rather than relying on the maternal glucose concentrations was that we may be missing the opportunity to prevent fetal macrosomia (10–13). In our Latino population in California, which has such a high risk of macrosomia if hyperglycemia is left untreated, I became an even stronger advocate for intensified insulin delivery for all documented hyperglycemia in pregnancy (14). However, the study by Schaefer-Graf et al. (15), in this issue *Diabetes Care*, on German women with gestational diabetes confirms the original report. This study may have changed my mind. They showed that when the approach to insulin therapy was determined by monthly fetal growth patterns as evidenced by ultrasound, the outcome improved with a lower cesarean section rate and no increase in macrosomia fetal morbidity as compared with a group of gestational diabetic women treated with insulin based solely on maternal glycemia. They also showed that, much like the study from California (9), this approach reduced the number of women with mild gestational diabetes who required self-monitoring of glucose and/or exogenous insulin therapy, thereby providing the potential to improve the cost-effectiveness of antepartum management of gestational diabetes.

Before this present study, I felt that saving treatment for only those mothers whose babies were already big and sick seemed to go against the notion that fetal macrosomia is the origin of adult type 2 diabetes (16–18). It was not rational, but despite the evidence, I did not believe that we could ignore women who had documented hyperglycemia. In all fairness, I was ignoring the other end of the fetal growth curve.

The "Barker Hypothesis" (19) suggests that low birth weight predicts subsequent physiological disturbances in adult life. Small-for-gestational-age infants and/or intrauterine growth–retarded fetuses have been reported (20–

24) to be at risk for subsequent hypertension, type 2 diabetes, impaired glucose tolerance, and insulin resistance. On the high end of birth weight, the "Pedersen Hypothesis" (25) suggests that large-for-gestational-age infants are also at increased risk. An analysis of all of these reports would generate the theory that there is a U-shaped curve for the relationship between birth weight and these metabolic abnormalities in adult life (26). Thus, an optimal birth weight that would predict the lowest risk for these metabolic defects in adult life would be between 3,000 and 4,000 g. A correlate to this U-shaped curve theory would suggest that treatment during pregnancy should optimize birth weight to decrease the prevalence of these physiological disturbances in adult life. Factors that are assumed to be causative for intrauterine growth retardation include maternal hypertension, smoking, intrauterine infection, prematurity, placental insufficiency, and protein malnutrition. The suggested explanation for the association of low birth weight to adult obesity and type 2 diabetes is that the fetus does not have sufficient substrate during organogenesis to promote β-cell growth and normal insulin secretory responses (16). Factors that are assumed to be causative for large-for-gestational-age infants include maternal obesity and maternal hyperglycemia. The suggested explanation for the association of macrosomia to adult obesity and type 2 diabetes is that maternal hyperglycemia is excess nutrition for the fetus, which in turn promotes fetal hyperinsulinemia, excess adipose tissue, and the insulin resistance syndrome. The old controversy as to what causes type 2 diabetes, i.e., insulin resistance or β-cell defects, may prove that both play a role in the etiology. It just depends on the fetal conditions. The optimal treatment strategy during pregnancy would therefore be a treatment program that prevents both high and low birth weight neonates. High birth weight prevention programs would require treatment of all hyperglycemia in pregnancy. Low birth weight prevention programs would require treating maternal hypertension, promoting smoking cessation, surveillance for infection, and instituting adequate medical nutritional therapy. I never imagined that the strategy to ignore maternal glucose in women who are carrying fetuses predisposed to intrauterine growth retardation and thus allow maternal hyperglycemia to remain untreated in order to encourage more accelerated fetal growth would be added to this list.

In 2001, Spyer et al. (27) reported the cases of two insulin-treated pregnancies in a mother with hyperglycemia resulting from a glucokinase gene mutation. The inheritance of a glucokinase mutation in one child reduced his intrauterine growth (birth weight <1st percentile) by reducing fetal insulin secretion. They suggested for the first time that the fetal inheritance of a glucokinase mutation resulted in decreased fetal insulin secretion. In this case, maternal hyperglycemia may have ameliorated the decreased fetal insulin secretion. Then, Frayling and Hattersley (28) suggested that altered fetal growth and type 2 diabetes may be two phenotypes of the same genotype; in other words, the "thrifty phenotype" is the result of a "thrifty genotype." Supporting this theory is strong evidence that paternal genes influence fetal growth and that these paternal genes may also alter diabetes risk. Further study is needed to determine whether common gene variants can explain the association between reduced birth weight and increased risk of type 2 diabetes. If the genetic hypothesis is true, common diabetes genes are likely to have subtle effects on insulin secretion and/or action and, therefore, subtle effects on fetal growth.

Of course, if we are to use fetal ultrasound clinically, we must be assured that it can accurately estimate fetal weight despite maternal obesity. Field et al. (29) designed a study to answer this question. In a year-long study, 998 singleton pregnancies of 26–43 weeks' gestation underwent both clinical and sonographic fetal weight estimation within 5 days of delivery (within 10% of actual birth weight). Patients were stratified into four different groups based on increasing maternal BMI: underweight (<19.8), normal weight (19.8–26.0), overweight (26.1–29.0), and obese (>29.0 kg/m^2). The different estimations of fetal weight were compared with actual birth weight, and the mean absolute percent error was calculated for each specific method and analyzed among the four BMI groups. For each method of weight estimation, there was no difference (specifically, no increase) in the magnitude of the absolute percent error with increasing maternal obesity. Regardless of maternal size, almost half of the weight predictions were within 5% of the actual birth weight. They concluded that increasing maternal obesity does not alter or decrease the accuracy of either clinical or sonographic fetal weight estimations. Therefore, fetal weight predictions provide equally accurate and valid guidelines for determining management decisions in women, regardless of body size.

On one last note, as this old dog rolls over and pulls her head out of the sand (allow me to mix metaphors if I am to change my spots. . .), the new report by Schaefer-Graf et al. (15) used different glucose targets for the insulin treatment in their two groups. In the standard group, insulin was initiated if the fasting capillary glucose was repeatedly >90 mg/dl or the 2-h capillary glucose was repeatedly >120 mg/dl. In contrast, in the ultrasound group, the thresholds were 130 and 200 mg/dl, respectively. Once insulin was started, however, the goals for insulin titration were higher in the glucose-monitored group (90 mg/dl for fasting and/or 120 mg/dl for 2-h postprandial capillary glucose), whereas the ultrasound group (who monitored pre- and postprandial glucose levels once insulin was started) had their insulin doses increased when the fasting capillary glucose determination was >80 mg/dl and/or the 2-h postprandial glucose level was >110 mg/dl. No wonder the ultrasound group fared so well. The ultrasound group was pushed to lower glucose levels to make up for lost time. Perhaps there may still be a place for old dogs that are set in their ways. But at least I learned a new trick: to "never say never" again.

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