Pregnancy is associated with relative carbohydrate intolerance and insulin resistance. Gestational diabetes mellitus (carbohydrate intolerance first diagnosed during pregnancy) has long been recognized as a risk factor for a number of adverse outcomes during pregnancy, including excessive fetal growth, an increased incidence of birth trauma and cesarean delivery, and neonatal metabolic abnormalities such as polycythemia, hyperbilirubinemia, and hypoglycemia. This recognition has led to recommendations to screen all pregnant women for gestational diabetes mellitus and to treat those whose glucose-tolerance tests exceed threshold criteria.

The threshold criteria for diagnosing gestational diabetes were initially specified rather arbitrarily as values greater than 2 SD above the mean for the original study population. There are now alternative expert recommendations for the test and thresholds that should be used to diagnose gestational diabetes mellitus, but regardless of the definition chosen, there is evidence that lesser degrees of carbohydrate intolerance might increase risks for perinatal complications. The Toronto Tri-Hospitals Study, for example, showed that values on glucose-tolerance testing higher than the normal range, but not high enough to warrant the diagnosis of gestational diabetes mellitus, are associated with outcomes similar to those in women with gestational diabetes mellitus (e.g., having larger babies). Similarly, others have found that even a single abnormal value on a 100-g, 3-hour oral glucose-tolerance test, rather than the two abnormal values needed to diagnose gestational diabetes mellitus, is associated with an increased risk of excessive fetal growth. Critics have argued, however, that observational studies have not appropriately accounted for varying diagnostic criteria for gestational diabetes mellitus, provider expectations and biases, and confounding variables such as the patient’s age and body-mass index (BMI) and other medical complications.

The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study reported in this issue of the Journal is an elegantly designed, very large, international study that answers previous questions by clearly demonstrating that there is a continuum of risk, without clear thresholds, between carbohydrate intolerance in pregnancy and adverse pregnancy outcomes. The HAPO study investigators assessed the pregnancy outcomes of more than 23,000 women with glucose values of less than 200 mg per deciliter 2 hours after a 75-g glucose load. Some, but not all, of these women (those with values of 140 to 200 mg per deciliter) would meet World Health Organization criteria for the diagnosis of gestational diabetes mellitus but, because hyperglycemia was considered to be mild and because at the time the study was organized the merits of treating such mild abnormalities were uncertain, it was considered ethical to observe these women without treatment. The subjects’ care providers were unaware of the results of the glucose-tolerance tests, but they could not be blinded to variables such as BMI or previous gestational diabetes, which are known to correlate with higher glucose values and thus might conceivably have affected provider behavior. Women whose glucose values were measured for other clinical purposes (and whose providers might have altered their treatment of the patients on the basis of the results) were excluded from the study.

The HAPO study showed that outcomes such as birth weight, umbilical cord-blood C-peptide level (a proxy for fetal insulin levels), incidence
of cesarean delivery, and incidence of neonatal hypoglycemic episodes all changed in direct proportion to maternal glucose levels, after an overnight fast and 1 hour and 2 hours after a 75-g glucose load. These associations held in analyses adjusted for potential confounders, including maternal BMI, previous macrosomia, and previous gestational diabetes.

Given the results of the HAPO study, should we lower our threshold for the diagnosis and treatment of gestational diabetes? This is a testable hypothesis, but it will be very difficult to show that treating lesser degrees of carbohydrate intolerance will provide meaningful improvements in clinical outcomes. For many, the debate about whether to screen for or treat gestational diabetes mellitus was settled by the results of the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS), which demonstrated moderate improvement in neonatal outcomes after treating women with glucose values of 140 to 200 mg per deciliter 2 hours after a 75-g glucose load. The number needed to treat to avoid one adverse outcome was 43. It is likely that any advantage to treating lesser degrees of hyperglycemia is even smaller. Furthermore, in the HAPO study the outcome measure that showed the strongest association with maternal carbohydrate intolerance was the cord-blood C-peptide level, a surrogate marker that itself would generally not be considered of clinical concern. In contrast, the HAPO outcome of potentially greatest concern, cesarean delivery, was only moderately increased with increased maternal glucose levels (adjusted odds ratio, 1.07 to 1.10 per standard deviation, depending on which element of glucose-tolerance testing was studied).

Echoing these findings, the ACHOIS trial did not show any reduction in the rate of cesarean delivery with treatment of maternal hyperglycemia. In addition, in the HAPO study, women with higher glucose levels had higher rates of delivering large infants but lower rates of delivering infants who were small for gestational age. Whether treating mild degrees of hyperglycemia would increase the risk for poor fetal growth and attendant complications should be carefully determined before such treatment is implemented at lower glucose thresholds. Finally, there is the possibility that the associations of mild carbohydrate intolerance with adverse outcomes during pregnancy are just that—associations that are not causally mediated. Until trials show clinical benefits from expanding the diagnostic criteria for “gestational diabetes,” we would not favor any change.

Also in this issue of the Journal are the results of the Metformin in Gestational Diabetes Trial, which compared metformin with insulin as initial medical therapy when diet and exercise alone fail to bring blood sugars into an acceptable range for women with gestational diabetes. This non-inferiority trial of 751 women showed that infants of mothers in the metformin group fared no worse than those in the insulin group. Unfortunately, maternal outcomes such as cesarean delivery were not reported, but birth weights were similar in the two groups.

Not surprisingly, patients preferred pills to shots. The main question now is whether metformin is better or worse than glyburide, an acceptable alternative pill. On the basis of a previous trial in which 404 women with gestational diabetes achieved equivalent metabolic control using either glyburide supplemented as necessary with insulin or insulin alone, glyburide has replaced insulin as the first-line pharmacologic treatment of gestational diabetes in many practices. Although the two oral agents have not been directly compared in trials, it is notable that in the Metformin in Gestational Diabetes Trial, 46% of subjects in the metformin group required supplemental insulin, whereas in the previous trial, only 4% of women treated with glyburide needed insulin. These differences could be the result of varying populations and protocols but deserve further evaluation.

Although both the HAPO study and the Metformin in Gestational Diabetes Trial address adverse outcomes associated with maternal hyperglycemia, gestational diabetes first received attention as a predictor of future diabetes in women. Identifying women at risk for diabetes offers the possibility of intervention to reduce risk, yet frequently these women do not receive recommended follow-up and surveillance. This failure results, perhaps, from a breakdown in communication between obstetricians who diagnose gestational diabetes mellitus and primary care providers who subsequently treat these patients. Recognizing the continuum of risk between hyperglycemia in pregnancy and associated outcomes, we should recommit ourselves to sharing this information so that it can meaningfully affect a woman’s health long after she has completed childbearing.
No potential conflict of interest relevant to this article was reported.

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Early Repolarization Revisited
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For more than 60 years, physicians have been fascinated by a peculiar electrocardiographic pattern called “early repolarization.” When Google is queried, more than 1 million hits turn up on this subject. Although Boineau recently described the electrocardiographic features of early repolarization as being quite diverse, such features have one factor in common: slurring or notching that produces a positive hump, called a J wave, is found at the junction at the end of the QRS complex and the beginning of the ST segment. However, the location of the electrocardiographic leads showing the J wave may vary among patients, and dynamic changes may occur in the width and height of the wave. The J wave may show circular changes, may not always be present, and usually disappears during exercise. The lead with the J wave commonly shows ST-segment elevation. The T wave can be negative, and the QRS width and QT time may be shorter than normal.

From an epidemiologic perspective, electrocardiographic features of early repolarization are commonly present in 2 to 5% of the population and are found mostly in men, young adults, athletes, and dark-skinned persons. Usually such changes, which can be easily differentiated from those caused by cardiac ischemia, have been considered to be benign, although isolated case reports, mostly from Asia, have mentioned such changes in the QRS–ST junction in men with idiopathic ventricular fibrillation.3-8

In this issue of the Journal, two groups of investigators focus attention on junctional changes in a large group of patients with otherwise normal hearts who were resuscitated after life-threatening ventricular arrhythmia. In a study involving 22 tertiary care arrhythmia centers, Haïssaguerre et al.9 found junctional changes on electrocardiography in 64 of 206 patients (31%) who were resuscitated after idiopathic ventricular fibrillation. These junctional changes consisted of slurring or notching at the end of the QRS complex and were confined to inferolateral leads. In a letter to the editor, Nam et al.10 describe similar junctional changes in 9 of 15 Korean patients (60%) with idiopathic ventricular fibrillation, but the authors do not state in which leads the changes were seen. Although Nam et al. do not provide information regarding the age and sex of their patients, in the study by Haïssaguerre et al., the mean (±SD) age of patients with idiopathic ventricular fibrillation was 35±13 years, and 46 of the 64 patients with this condition (72%) were male. All the patients who were described in the cited case reports3-8 were male, and 12-lead electrocardiography, when reported, showed the junctional changes in the inferolateral leads.

One question that arises is whether the described abnormality at the end of the QRS complex is indeed early repolarization or, rather, delayed activation of the inferolateral area. A late potential coincident with the terminal QRS abnormality was found on signal averaging in the patient described by Garg et al.3 However, in the study by Haïssaguerre et al. late potentials were found in only 5 of 44 patients (11%) in whom