MASTER CLASS

The Diabetes Pandemic

BY E. ALBERT REECE, M.D., PH.D., M.B.A.

The world is experiencing a diabetes pandemic, with the incidence projected to double worldwide over current levels by 2030. This extraordinary rise in the rate of diabetes worldwide has been paralleled by a similarly rapid rate of increase in the incidence of obesity. Most of the rise in diabetes rate is occurring in the type 2 category.

As a result of this pandemic in the general population, pregnant women also have a high rate of diabetes. Indeed, some clinics report that as many as 20% or more of their pregnant patients have diabetes. This presents an increasing challenge to the practitioner, especially because these patients present not only with diabetes but its associated complications for the mother and for fetal development and fetal outcome.

If there was ever a time when educating practitioners regarding contemporary methods of managing pregnant patients with diabetes is needed, it is now. Thus, we have decided to dedicate two issues of our Master Class series to the management of diabetes in pregnancy. The first installment, below, addresses how diabetes affects perinatal outcomes and how we can work to detect diabetes early and provide intensive treatment. The second installment, scheduled for the December issue, will delve into the use of oral antidiabetic agents in pregnancy.

Between the two parts of this series will be another Master Class that addresses another very challenging public health problem: the novel influenza A(H1N1) pandemic.

Both topics—diabetes in pregnancy, and influenza in pregnancy—are extremely high priority and highly contemporary, and are worthy of significant attention.

For this Master Class, I have invited Oded Langer, M.D, Ph.D., an internationally recognized expert on diabetes in pregnancy who has written and lectured extensively on this subject. Dr. Langer is the Babcock Professor and chairman of the department of obstetrics and gynecology at St. Luke's–Roosevelt Hospital Center, a university hospital of Columbia University in New York. ■

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How Type 2 Diabetes Complicates Pregnancy

With the incidence of obesity rising in the United States and Europe, the rate of type 2 diabetes is increasing significantly as well. In 2000, investigators reported a 33% increase from 1990 to 1998 in the prevalence of type 2 diabetes, and a 76% prevalence increase in individuals aged 30-39 years (Diab. Care 2000:23:1278-83). Others have estimated that the majority of pregestational pregnant diabetic women (80%-90%) are type 2.

BY ODED LANGER, M.D.

The rates of obesity and type 2 diabetes have risen further since 2000, so much so that the current pandemic—now often referred to "diabesity"—has implications that are more urgent than ever for obstetrics and for our goal of optimizing outcomes for women and their newborns. Today it is estimated that 8%-15% of pregnant women have type 2 diabetes, and if current trends continue, it will soon be higher.

Unless we take a more aggressive and intensive approach to identification and management—unless we aim for primary prevention of hyperglycemia-related complications to the greatest degree possible—a significant number of our pregnant patients will face complications and adverse perinatal outcomes associated with type 2 diabetes.

We have to focus on the care of these women with the same diligence that has been applied to pregnant and nonpregnant women with type 1 diabetes. For one, we must be more proactive in promoting preconception care, and in cases in which that doesn't happen, we must act early to identify potentially harmful levels of glycemia.

We must then strive for as much glycemic control as possible, because various levels of improvement can prevent different anomalies and complications.

Perinatal Outcomes

Compared with type 1 diabetes, there are relatively few data on the effects of type 2 diabetes on pregnancy outcome. Still, evidence is mounting that the abnormal maternal glycemic profiles characterizing type 2 diabetes are associated with adverse perinatal outcome, and that improvement in glycemic control results in better perinatal outcomes.

Investigators have consistently reported significantly higher rates of perinatal morbidity and mortality in women with type 2 diabetes than in the general population, and most studies report a prevalence of congenital anomalies in the offspring of women with type 2 diabetes that is several times higher than the rate found in the general population and similar to the prevalence of congenital anomalies associated with type 1 diabetes. (The rate of congenital abnormalities contributes significantly, of course, to overall perinatal mortality.) Other studies suggest that the rate of congenital anomalies in the children of women with type 2 diabetes is twice as high as the rate reported with type 1 diabetes.

Fetal macrosomia is another major problem. Most studies report fourfold to fivefold higher rates of macrosomia in infants of mothers with type 2 diabetes. Metabolic and respiratory complications also occur. More specifically, the perinatal mortality in women with type 2 diabetes has varied from approximately 3.7% in a study done in New Zealand to 18% in research conducted in Canada, with an overall mean of 7.6% in the 14 studies conducted since 2000.

The rate of major anomalies in type 2 diabetic women has ranged from 3% in South Africa to 12.3% in the United Kingdom with an overall mean of 8% in the 17 studies conducted since 2000. The rate of anomalies in the general population, as reported in only 6 of the 17 studies, has ranged from 1.6% to 3.1%.

The rate of large-for-gestational-age (LGA) infants in studies addressing type 2 diabetes and published between 1970 and 1980 was 33% (a range of 28%-40%). The rate reported since 2000 in published studies is 39% (a range of 30%-45%). The rate of cesarean section since 2000 is 62% (J. Mater. Fetal Med. 2008:21;181-9).

Unfortunately, in the past 4-5 decades, we have not improved the care of pregnant patients with type 2 diabetes. There has been no significant change in perinatal outcomes. Analyses of anomaly rates, for instance, show no real change since the 1970s. We have to ask, therefore, what are we really doing for these patients?

Part of the problem is that patients are diagnosed too late. The majority of women with type 2 diabetes is seen for the first prenatal visit during or after organogenesis occurs. We talk with patients about organogenesis occurring during the first trimester, but most anomalies actually occur in the first 4-5 weeks of pregnancy.

Only a small percentage of type 2 patients (5%-24%) receive preconception care, a shortcoming driven partly by the fact that 50%-60% of pregnancies are unplanned and partly by our own failures in the public health and preventive arena. Moreover, testing for gestational diabetes, which often uncovers type 2 diabetes, does not occur until about midpregnancy.

The other part of the problem could well be that we are not treating these patients intensively enough.

Early Detection, Intensive Treatment

We must intensify efforts to educate patients and physicians about the risks of type 2 diabetes in pregnancy and the need to control glucose levels before pregnancy occurs.

The benefits of preconception care in reducing congenital malformations in the context of diabetes are clear. In a meta-analysis of studies on preconception care in women with diabetes published from 1970 to 2000, the pooled rate for major malformations among a total of approximately 2,600 offspring was 2.1% in the group that received preconception care compared with 6.5% in the group that did not receive the care.

Another look at major and minor anomalies together showed a pooled rate of 2.4% in the preconception care groups compared with 7.7% in the women who did not receive this care. Early first trimester mean glycosylated hemoglobin values also were significantly lower in the women who received preconception care (QJM 2001:94;435-44).

Stepping up our promotion of preconception care is a first step toward primary prevention of diabetes-associated complications, but we also ought to set new criteria in our practices that stipulate that patients who are obese or have a previous history of gestational diabetes will have fasting plasma glucose tests performed in conjunction with the first prenatal office visit or immediately afterward.

A deliberate methodology for identifying patients early on who are at risk for type 2 diabetes and testing them promptly—and not waiting for standard gestational diabetes testing—will enable us to impact pregnancy outcomes.

Neither the American Diabetes Association nor other medical groups have yet issued guidelines on fasting plasma glucose testing in early pregnancy, but this does not mean we shouldn't pursue such testing. Currently, for adults younger than 45 years, the ADA recommends testing to detect prediabetes and type 2 diabetes in individuals who are overweight or obese and who have one more risk factor. Giving birth to a baby weighing more than 9 pounds or being diagnosed with gestational diabetes is considered a risk factor.

Given the stakes for the child as well as the mother, I do not believe, however, that we should require *both* overweight/obesity and previous macrosomia or gestational diabetes as criteria for testing.

Similarly, I believe that we should lower our diagnostic threshold for type 2 diabetes in patients who are pregnant. More than 60% of patients with gestational diabetes fall into the category of impaired glucose tolerance (fasting plasma glucose of 100-125 mg/dL). Today we are calling these patients gestational

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diabetics when they really should be called type 2 diabetics.

The recently completed National Institutes of Health–sponsored Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study and the study on gestational diabetes by the Maternal-Fetal Medicine Units Network (MFMU) used fasting plasma glucose levels of 105 mg/dL and 95 mg/dL, respectively, as thresholds for the exclusion of patients from the studies.

The HAPO study linked adverse pregnancy outcomes with glycemia levels that have traditionally been considered normal, and the MFMU study is yielding similar findings. However, given the studies' exclusion thresholds (which were set with ethical considerations in mind), we have disallowed ourselves the opportunity to firmly establish whether patients with impaired glucose tolerance should be considered type 2 diabetics.

Current diagnostic criteria for the population in general—by which a fasting blood glucose level (FBG) of 126 mg/dL indicates diabetes and an FBG of 100-125 mg/dL indicates impaired fasting glucose or prediabetes—were set several years ago when it became apparent that the previous diagnostic threshold of 140 mg/dL was too high. Studies showed clearly that complications relating to hyperglycemia—from retinopathy to nephropathy, neuropathy, and various micro- and macrovascular complications—occur in patients with FBG levels much lower than 140 mg/dL.

Recent research has shown, moreover, that long-term damage to the body may occur even in patients diagnosed with prediabetes. Investigators have reported, for instance, that approximately 10% of these patients have neuropathy and/or retinopathy.

When I see an FBG level of 100-125 mg/dL in a pregnant patient, even though this is by current standards considered "prediabetes" in the nonpregnant state, I consider this to be diabetes. This approach takes into account the fact that fasting plasma glucose levels during pregnancy are lower than actual values post pregnancy. It also takes into consideration something I have found in my discussions with patients: the observation that psychologically, these women are significantly more receptive to a serious approach to glycemic control if we're talking about diabetes rather than prediabetes or gestational diabetes.

With respect to the glucose threshold that will minimize adverse perinatal outcome, studies have shown that glucose levels of pre- and postprandial and fasting blood glucose under 140 mg/dL will be sufficient to achieve rates of congenital anomalies, spontaneous abortion, and perinatal mortality comparable with those seen in nondiabetic populations.

The target glucose threshold for the prevention of macrosomia and its accompanying complications, however, is significantly lower. Studies suggest that we need to achieve mean blood glucose levels of less than 100 mg/dL to prevent macrosomia (J. Matern. Fetal Neonatal Med. 2000:9;35-41). Fortunately, we have a bit more time to impact the rates of macrosomia since this complication develops later in pregnancy, in contrast to the development of congenital anomalies so early.

We still have much to learn about the exact levels of glycemia that are necessary to reduce complications, but our current knowledge that different glucose thresholds exist for different types of complications enables us to keep patients motivated to improve glycemic control.

Even when it's not possible to achieve optimal glycemic control, any improvement should be beneficial because it will reduce the rate of complications for a given glucose threshold.

As obstetricians work together to improve care for pregnant patients with type 2 diabetes, it is also important that we develop criteria for blood glucose measurement and monitoring. Should we all measure fasting blood glucose? Postprandial blood glucose? Right now, our approaches vary. We need consistency and clear definitions if we are to compare outcomes effectively.

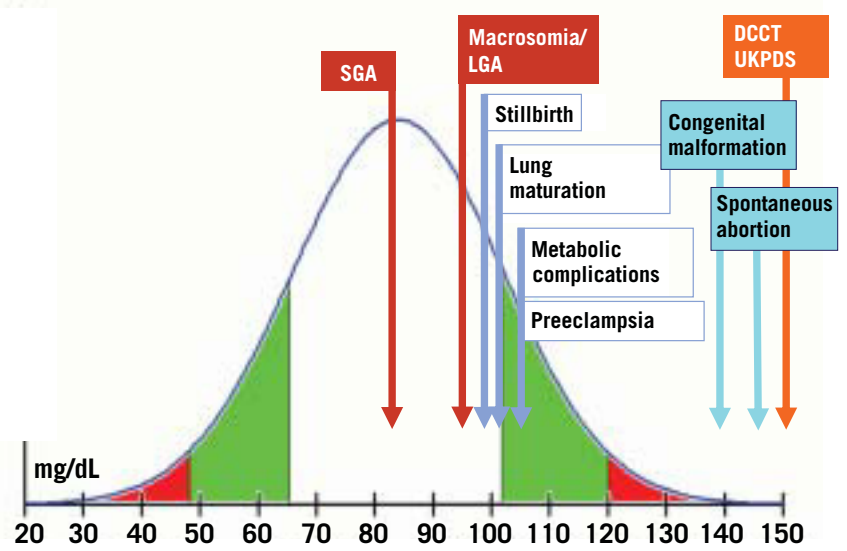
I always tell patients that if we work together, we will be able to improve outcomes, and I tell them never to give up. In the preconception phase, we aim for an FBG of less than 140 mg/dL, then we work on continuously lowering this level until, at around 20 weeks' gestation, we tighten glycemic control to prevent stillbirth, macrosomia, and metabolic complications.

We need to remember that diabetes in pregnancy is a chronic disease that is extremely demanding, requiring frequent blood glucose tests throughout the day, insulin injections or ingestion of oral hypoglycemic agents, frequent fetal testing, and adherence to a diet protocol. This all requires patient-physician cooperation.

Compliance in these patients should comprise all the above demands so that if a patient fails to adhere to the diabetic protocol, we can ask whether her failure to comply is based on her needs and expectations, or her physician's needs and expectations. In the end, we as obstetricians treat two patients whose needs sometimes coincide and sometimes collide. Our goal is to develop management protocols that maximize the mutual needs of both. ■

Dr. Langer said he has no disclosures relevant to this article.

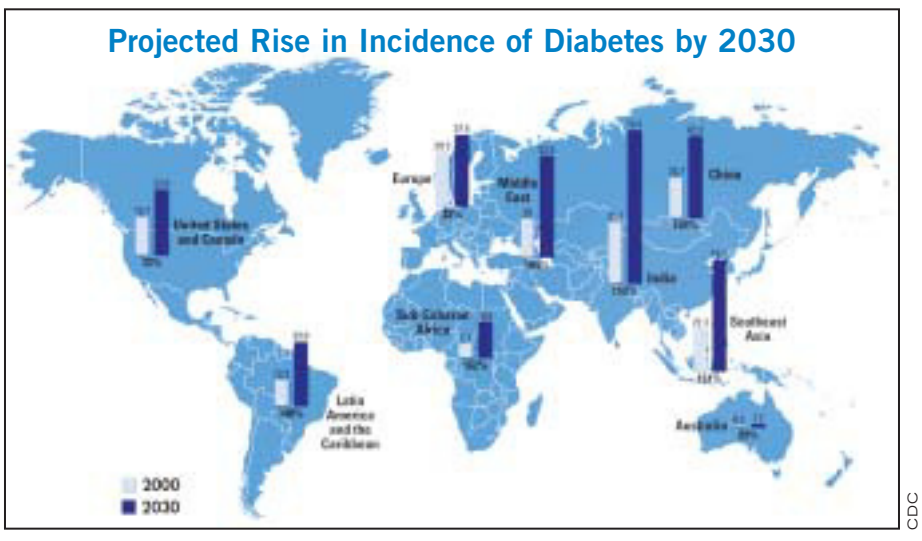
Spectrum of Mean Blood Glucose Thresholds Associated With Complications in the Pregnant Diabetic Patient



Note: The Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) box represents the mean blood glucose threshold that these two major studies found for the prevention of complications of diabetes in nonpregnant subjects, and is part of this figure to demonstrate that the threshold for complications in pregnancy is much lower.

Source: Dr. Langer

Projected Rise in Incidence of Diabetes by 2030



CDC

Study: Metoclopramide May Not Raise Risks to Fetus

BY MARY ANN MOON

The use of metoclopramide to control nausea and vomiting in the first trimester does not increase the risk for congenital malformations, low birth weight, or perinatal death, according to a report in the New England Journal of Medicine.

These findings from a large retrospective cohort study "provide reassurance about the safety of metoclopramide," which has not been convincingly established until now, wrote Ilan Matok of Ben-Gurion University of the Negev, Beer-Sheva, Israel, and associates.

"Despite its extensive use, only a few studies have assessed the safety to the fetus of maternal exposure to metoclopramide during the first trimester, and the relatively small sizes of these studies limited their power to detect adverse effects of the drug," they noted.

The researchers assessed singleton deliveries between 1998 and 2007 at the largest HMO in Israel, where metoclopramide is the antiemetic drug of choice during pregnancy. Approximately half of the 81,703 infants in the study were born to Jewish parents and half to Bedouin Muslim parents.

A total of 3,458 (4%) of these infants were exposed to metoclopramide during the first trimester. The mean duration of exposure was 1 week.

The rate of major congenital malformations was 5.3% among exposed infants, compared with 4.9% among unexposed infants, a nonsignificant difference. This difference remained nonsignificant when data from pregnancies that were terminated were included in the analysis.

The rates of minor congenital malformations (3.8% vs. 3.5%) and of multiple malformations (2.5% vs. 2.3%) also were similar between exposed and nonexposed infants. There also were no significant associations between subclasses of congenital malformations and metoclopramide exposure, nor was there any clustering of anomalies among exposed infants.

When the data were analyzed according to subjects' ethnic backgrounds, the drug did not raise risks to infants of either Jewish or Bedouin Muslim parents (N. Engl. J. Med. 2009;360:2528-35).

Metoclopramide also was not associated with an increased risk of preterm birth, low Apgar scores, perinatal death, or low birth weight.

A subgroup of 758 mothers who took metoclopramide refilled their prescriptions at least once. No dose-response effect of exposure to the drug was found.

The researchers reported having no relevant conflicts of interest. ■