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*JAMA*. 2008;299(21):2550-2557 (doi:10.1001/jama.299.17.jrr80003)

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# A 40-Year-Old Woman With Diabetes Contemplating Pregnancy After Gastric Bypass Surgery

Donald R. Coustan, MD, Discussant

**DR BURNS:** Mrs T is a 40-year-old gravida 2, para 1 woman with type 2 diabetes and hypertension who is trying to conceive. In July 2003, Mrs T had a clomiphene-conceived pregnancy. She was treated with insulin during her pregnancy and was treated with nifedipine for her hypertension after developing a warm antibody response to methyldopa. Her pregnancy was otherwise uncomplicated and she delivered a healthy boy at 40 weeks by low transverse cesarean delivery because of a herpes simplex virus outbreak at the time of delivery. Her gynecologic history is significant for herpes simplex virus. She had a normal Papanicolaou test result in November 2005. She has a distant history of polycystic ovary syndrome but has been menstruating regularly since losing weight following a gastric bypass procedure.

Her medical history is significant for type 2 diabetes, diagnosed in 1999, for which she is currently taking metformin, and for hypertension, diagnosed in 1996, which has been well controlled with valsartan, though her gynecologist is planning to switch her back to nifedipine in anticipation of a pregnancy. She has a history of anticardiolipin antibodies and was treated with enoxaparin during her previous pregnancy. The antibodies were detected during routine screening; her sister has anticardiolipin antibodies and there is a strong family history of thromboses, although Mrs T has never had any.

Her surgical history is significant for a Roux-en-Y gastric bypass operation in 2004. She subsequently lost 45 kg (100 lb) over the course of a year, though she has now developed iron-deficiency anemia. She is intolerant of oral iron and will shortly undergo a course of intravenous iron.

At an office visit in September 2006, her blood pressure was 122/70 mm Hg and her body mass index was 30. Her examination was otherwise unremarkable. Laboratory studies revealed a glucose level of 70 mg/dL and a hemoglobin A<sub>1c</sub> level of 5.4%. Her hemoglobin level was 8.8

**Mrs T is a 40-year-old woman with type 2 diabetes and chronic hypertension who has had a gastric bypass procedure and is planning to conceive. She would like to know whether she can continue using metformin during the pregnancy and also is concerned about the effect of the gastric bypass surgery. This article discusses the management of diabetes prior to and during pregnancy, including appropriate preconception evaluation and the use of insulin and oral antidiabetic agents. The implications of gastric bypass surgery for pregnancy are also outlined. Important aspects include the need to optimize metabolic control prior to conception, to evaluate and treat vascular complications of diabetes prior to conception, and to provide the services of a health care team to gravid women with diabetes. Gastric bypass surgery with subsequent weight loss is likely to ameliorate type 2 diabetes, and special attention must be paid to nutrition when women who have undergone such procedures become pregnant.**

JAMA. 2008;299(21):2550-2557

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g/dL, with an iron level of 19 µg/dL and a ferritin level of 1.8 ng/mL.

Her current medications include valsartan, 160 mg/d, and slow-release metformin, 500 mg/d. She is allergic to labetalol with development of lichen planus, codeine with development of hives, and latex; angiotensin-converting enzyme inhibitor therapy was complicated by

**This conference took place** at the Obstetrics and Gynecology Grand Rounds at the Beth Israel Deaconess Medical Center, Boston, Massachusetts, on April 25, 2007.

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**Clinical Crossroads Section Editor:** Margaret A. Winker, MD, Deputy Editor.

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a cough, and methyl dopa was associated with warm antibody production.

She is married and lives with her husband and son. She works as a midwife. She has no history of tobacco, alcohol, or drug use.

### MRS T: HER VIEW

With my first pregnancy, I knew that I was at high risk, not only because of the diabetes but I also had high blood pressure. My hemoglobin A<sub>1c</sub> was in the 7 range. So they decided to bring my sugar down quickly and started me on insulin. They also switched me from glipizide to metformin. The metformin was stopped in the early first trimester and then I continued with the insulin shots, which were about 6 times a day. There were no complications in the pregnancy from the diabetes; it was well controlled by medication and diet.

A year after I had my son, I decided to really do something about my health. So I ended up having gastric bypass, as was recommended by my endocrinologist and my internist, which helped me lose 100 lb. I went off the insulin and now I'm only taking 500 mg of metformin.

I understand that the next pregnancy is going to be a lot of work. I have reduced a lot of my high-risk symptoms, but I have added another risk, because I had the gastric bypass and now I'm severely anemic. As far as diabetes, I know that my hemoglobin A<sub>1c</sub> being in the normal range puts my risk at about the same as the rest of the population. I know that probably during the pregnancy I will need insulin again, as my blood glucose will probably get higher and my blood pressure is still an issue.

I do have concerns with a future pregnancy. For me, the first pregnancy was really tedious because I had to be on the insulin. I was on it for the 10 months of the pregnancy, and then a year after that because I was breastfeeding. But I knew about the benefits for the baby of breastfeeding, including for diabetes, and I just thought it was worth it.

I don't understand why infertility patients can take the metformin until 15 or 16 weeks but if you're diabetic, as soon as you get a positive pregnancy test you have to stop the metformin and continue with the insulin. I'm not so sure the insulin is completely necessary, even through the pregnancy, because you could also give oral medication during the pregnancy.

### AT THE CROSSROADS: QUESTIONS FOR DR COUSTAN

How should the case of a woman with type 2 diabetes be managed preconception, what are the goals of therapy, and what are the preferred agents? What evaluation, if any, should a woman with type 2 diabetes undergo before trying to conceive? What risks and benefits do gastric bypass surgery have for an obese woman with type 2 diabetes preconception? What is the evidence that intensive antidiabetic therapy im-

proves pregnancy outcome? What do you suggest for Mrs T? What does the future hold?

**DR COUSTAN:** Mrs T is a 40-year-old gravida 2, para 1 woman who has had type 2 diabetes for the past 8 years, currently treated with metformin, and who is planning to conceive. She also has chronic hypertension currently being treated with an angiotensin receptor blocker. She has undergone a gastric bypass procedure since her last pregnancy, with a resultant 45-kg weight loss. She has previously given birth by cesarean delivery.

In the past, most pregnant patients with diabetes had type 1 diabetes, but since the onset of the epidemic of diabetes and obesity,<sup>1</sup> type 2 diabetes now predominates over type 1 diabetes in most pregnant populations. Among individuals younger than 44 years, the combined prevalence of both types of diabetes doubled between 1980 and 2005, from 6 per 1000 to 14 per 1000, with rates in that age group similar for men and women.<sup>2</sup> So Mrs T's questions are relevant to an increasing number of women.

### Management of Type 2 Diabetes Prior to Conception

Management of diabetes prior to or during conception is not informed by clinical trial evidence. However, case series, comparisons of outcomes with those of historical controls, and other nonrandomized studies<sup>3</sup> have demonstrated that a number of adverse outcomes occur more frequently in diabetic pregnancies and less commonly when strict metabolic control can be achieved. These include perinatal mortality (approximately 20% in the 1940s and now near normal<sup>3</sup>), macrosomia (20%-30% vs 10% with good control<sup>4</sup>), and congenital malformations (10-fold reduction with good control).<sup>5</sup> The level of hemoglobin A<sub>1c</sub> in early pregnancy is strongly associated with the malformation rate as well as with spontaneous abortion.<sup>5</sup> Adding the most recent study<sup>6</sup> to the review by Kitzmiller et al,<sup>5</sup> the rates of malformation overall were 2% for normal hemoglobin A<sub>1c</sub>, 7% for hemoglobin A<sub>1c</sub> up to 30% above the normal range, and 25% for hemoglobin A<sub>1c</sub> more than 30% above the normal range. Therefore, the standard of care is to maintain near-euglycemia throughout gestation, starting if possible prior to the time of conception.<sup>7</sup>

Any medical encounter with a woman with diabetes who is or will soon be capable of bearing children should be considered a preconception visit. The patient should be counseled that any pregnancy in a woman with diabetes should be planned, and if pregnancy is not desired then safe and effective contraception should be made available. In 1 meta-analysis, major anomalies were found in 2.1% of offspring of women with diabetes who received preconception care compared with 6.5% of offspring of those not receiving preconception care.<sup>8</sup>

Based on observational studies, the American Diabetes Association recommends that before conception is attempted, hemoglobin A<sub>1c</sub> level should be no more than 1% above the upper limit of normal.<sup>9</sup> Goals for glucose control

during the preconception period are somewhat less strict than those typically recommended during pregnancy: premeal levels of 80 to 110 mg/dL and 2-hour postmeal levels of less than 155 mg/dL.<sup>10</sup> (To convert glucose to millimoles per liter, multiply by 0.0555.) To help patients be informed about the importance of these interventions, women in the preconception period should be counseled about the importance of excellent control and the apparent relationship between suboptimal metabolic control during the preconceptional period and congenital malformations. The preconception period also is an excellent time to reinforce good lifestyle habits for diet and exercise. In addition, as with all women planning to conceive, women with diabetes should take supplementary folic acid in a dose of at least 0.4 mg/d to lower the risk of neural tube defects in offspring,<sup>11</sup> and women who have previously had a child with a neural tube defect should take 4 mg/d.<sup>11</sup> Mrs T has maintained excellent control using metformin, with her most recent hemoglobin A<sub>1c</sub> measurement at 5.4%, so she may be advised to go ahead with her plans to become pregnant.

The team approach to diabetes care prior to and during pregnancy, including a maternal-fetal medicine specialist, diabetologist, internist, and obstetrician or other clinician with experience and expertise in management of diabetic pregnancies, plus a dietitian, diabetes nurse educator, social worker, and pediatrician or neonatologist, has been shown to be both practical and cost-effective in observational studies and a cost-benefit analysis.<sup>12,13</sup> The central and most important member of the team is the patient. In my experience, when the patient is educated and involved, understands the rationale for all that is asked of her, and owns the goal of good diabetes control to enable the healthiest pregnancy outcome possible, then the team is most likely to accomplish its mission. When the patient is engaged in a struggle with the caregivers, the mission is more likely to fail.

### **Evaluation of a Patient With Type 2 Diabetes Prior to Conception**

In the past, in women of childbearing age, diabetic vascular disease generally was limited to individuals with type 1 diabetes.<sup>14</sup> However, a major factor determining development of diabetic nephropathy and retinopathy is the duration of diabetes, and with the onset of type 2 diabetes occurring at younger ages, potentially years prior to diagnosis,<sup>9</sup> patients with type 2 diabetes should be evaluated for end-organ damage as well.<sup>9</sup> Examination should include evaluation for cardiovascular disease (blood pressure measurement and electrocardiogram plus additional evaluation if needed), retinopathy (examination with dilation plus laser therapy if indicated), nephropathy (serum creatinine, creatinine clearance, and protein excretion measurement), and neuropathy (neurologic examination), as well as an assessment of glycemic control (hemoglobin A<sub>1c</sub> measurement plus self-monitoring).<sup>10</sup>

Angiotensin-converting enzyme inhibitors, otherwise indicated for patients with diabetes to reduce the likelihood of nephropathy, have been associated with fetal renal malformations and dysfunction<sup>15</sup> when taken during the second and third trimesters, and, therefore, should be discontinued once a woman has become pregnant. Evidence that they may also be associated with malformations when taken in the first trimester, during organogenesis,<sup>16</sup> supports the practice of treating women planning a pregnancy with other agents prior to conception. Whether these findings extend to angiotensin receptor antagonists is unknown. Methyldopa and  $\beta$ -blockers generally are the first-line agents for treating chronic hypertension in pregnancy should treatment be necessary,<sup>17</sup> but Mrs T was unable to take either. While nifedipine is commonly used in pregnancy, both as a tocolytic agent and as treatment for hypertensive disorders in the second half of pregnancy, the American Diabetes Association recommends using a nondihydropyridine calcium channel blocker such as diltiazem for hypertensive gravidas with diabetes because of its potential benefit of reducing urinary albumin excretion.<sup>18</sup> In Mrs T's case, her treatment with a calcium channel blocker was appropriate given her adverse reaction to methyldopa and a skin condition temporally related to a  $\beta$ -blocker in the past.

As discussed above, the goal of glycemic control prior to conception should be established. Any medications that might have an adverse effect in early pregnancy should be discontinued and safer drugs substituted. Medical treatment of diabetic complications generally should be optimized during the preconception period, although laser photocoagulation is not contraindicated by pregnancy.<sup>19</sup> The patient's knowledge base and diabetes management skills should be assessed and the patient educated about meal planning, glucose self-monitoring, insulin administration, and sick day management. The family's social support system should be assessed and family members educated about issues such as response to a hypoglycemic episode.

### **Preconception Gastric Bypass for an Obese Woman With Type 2 Diabetes**

Randomized controlled trials have shown that weight loss, even less than the loss that typically occurs after gastric bypass, can ameliorate or eliminate type 2 diabetes or impaired glucose tolerance<sup>20</sup> and improve lifelong prognosis for those with marked obesity. In 1 study, gastric banding was more effective than lifestyle intervention in inducing remission of type 2 diabetes in obese patients.<sup>21</sup> Theoretically, such interventions may reduce the risk of adverse pregnancy outcomes associated with diabetes, hypertension, and obesity. However, gastric bypass carries risks<sup>22</sup> including nutritional deficiencies because of decreased nutrient intake as well as decreased fat absorption. With a Roux-en-Y bypass, iron-deficiency anemia is particularly prone to occur because of the lack of acid in the gastric pouch, which slows

the absorption of iron,<sup>23,24</sup> as Mrs T experienced. Intestinal herniation and obstruction have occurred during pregnancy after gastric bypass,<sup>25,26</sup> including 1 case of maternal and fetal death.<sup>27</sup> In Mrs T's case, her diabetes and hypertension persisted despite a 45-kg weight loss. Her iron stores should be replenished prior to conception as planned, and her nutritional status should be improved by taking the prescribed supplements, particularly fat-soluble vitamins. Mrs T and her caregivers should be aware of the remote possibility of bowel herniation during pregnancy and promptly evaluate symptoms such as abdominal pain and vomiting if they occur.

### Effects of Type 2 Diabetes on Pregnancy

Untreated or undertreated diabetes, whether type 1 or type 2, has many effects on pregnancy. Congenital malformations are inversely proportional to the adequacy of glucose control. Spontaneous abortions and stillbirths are more likely; macrosomia may lead to a greater likelihood of shoulder dystocia, operative vaginal delivery, or cesarean delivery.<sup>28</sup> Fetal growth restriction is more likely in the presence of significant diabetic vascular disease.<sup>29</sup> Respiratory distress syndrome is more likely at a given gestational age, and neonatal hypoglycemia, plethoria, hyperbilirubinemia, and hypocalcemia occur more frequently.<sup>30</sup> Observational studies in Pima Indian populations have found that exposure to hyperglycemia in utero is associated with an increased likelihood of childhood and adult obesity as well as impaired glucose tolerance and diabetes.<sup>31-33</sup> From the perspective of the mother, the likelihood of premature delivery is increased, possibly iatrogenic but possibly spontaneous, and hypertensive complications, worsening of nephropathy and retinopathy, and other problems are more likely.<sup>28</sup>

According to the hypothesis of Pedersen,<sup>34</sup> diabetes affects the offspring when the fetus is exposed to maternal hyperglycemia and has a brisk insulin response, leading to fetal hyperinsulinemia and its resulting problems. In observational studies, these adverse outcomes are reduced to near normal levels when a program of tight metabolic control is instituted.<sup>3</sup> One randomized trial demonstrated that identifying and treating gestational diabetes led to a reduction in serious adverse perinatal outcomes including death, shoulder dystocia, bone fracture, and nerve palsy.<sup>35</sup> However, no randomized trials have tested the efficacy of more intensive treatment of preexisting diabetes, despite its widespread acceptance.

In general, diabetes is no longer considered a contraindication to pregnancy, but individuals with type 2 diabetes should make an informed decision, after being provided accurate and appropriate counseling, whether to undertake a pregnancy. The presence of retinopathy,<sup>19</sup> nephropathy,<sup>36</sup> or coronary heart disease<sup>37</sup> increases the risks associated with pregnancy. Since diabetic vasculopathy is more likely to occur the longer one has diabetes, there is an advantage to plan-

ning to have a family earlier rather than later in life, all other factors being equal.

### Management of Type 2 Diabetes During Pregnancy

In type 1 diabetes during early pregnancy, the goal of near euglycemia must be balanced with avoidance of hypoglycemia and may limit the ability to achieve strict metabolic control. However, individuals with type 2 diabetes, which is characterized by insulin resistance more than insulinopenia, are typically not prone to hypoglycemia except under unusual circumstances, such as taking insulin then missing a meal. In addition, as in nondiabetic pregnant women, the insulin resistance of type 2 diabetes tends to increase as pregnancy progresses.<sup>38</sup> Typical goals for glucose control in diabetic pregnancy recommended by the American College of Obstetricians and Gynecologists<sup>7</sup> include fasting glucose values of 95 mg/dL or lower, 1-hour postprandial values of 130 to 140 mg/dL or lower, and 2-hour postprandial values of 120 mg/dL or lower.

Diet and exercise are important cornerstones in the management of diabetes, whether during pregnancy or at other times. The American Diabetes Association<sup>18</sup> recommends that medical nutrition therapy in pregnancy include the targeting of individual weight gain based on body mass index, physical activity level, fetal growth pattern, and the desire to prevent excess maternal weight gain and postpartum weight retention. Exercise is beneficial in pregnancy in general and may improve diabetic control in a pregnant woman with type 2 diabetes, particularly with exercise training. However, in patients with vascular disease or neuropathy, exercise training may exacerbate these conditions and in patients with neuroglycopenia, glucose may be affected unpredictably. However, most patients with type 2 diabetes tolerate regular exercise well.<sup>39</sup> Specific recommendations for exercise and other interventions are provided in the American Diabetes Association position statement.<sup>18</sup>

Mrs T wondered whether it was truly necessary to switch from metformin, an oral agent, to insulin, which must be given by injection. She also noted some apparent disagreement among her care providers as to when in the pregnancy the change needs to be made. Her questions as to why frequent injections are necessary rather than convenient tablets are apt. A number of oral agents are used to treat diabetes.<sup>40</sup> Of these, the thiazolidinediones, such as pioglitazone, decrease insulin resistance, but little is known about their safety or efficacy in pregnancy, and 1 study noted that fetal levels as early as 12 weeks of gestation were approximately half of maternal levels.<sup>41</sup> A general principle of medication use in pregnancy is not to use medications that cross the placenta unless there is benefit to the fetus or at least unless it has been demonstrated that there is little likelihood of harm.<sup>40</sup>

The biguanide class of drugs are insulin sensitizers, and metformin, which Mrs T takes, is the only biguanide drug available in the United States. Metformin is widely used for

both type 2 diabetes and for polycystic ovary syndrome, and in 2 randomized trials, metformin appeared to reduce the spontaneous abortion rate among women with polycystic ovary syndrome.<sup>42,43</sup> However, in a more recent, larger randomized trial of metformin and clomiphene for ovulation induction in polycystic ovary syndrome patients,<sup>44</sup> not only was metformin inferior to clomiphene for the main outcome of live birth rate (22.5% for clomiphene, 7.2% for metformin, and 26.8% for both;  $P < .001$ ), but the spontaneous abortion rates in the 3 groups did not differ significantly (22.6% for clomiphene, 40% for metformin, and 25% for both;  $P = .15$ ). Regardless, in response to Mrs T's question, in all 3 of these trials, the metformin was discontinued once pregnancy was confirmed, providing no support for continuing metformin beyond the time of conception. Metformin crosses the placenta from mother to fetus<sup>45</sup> and may even be actively transported, since cord blood levels were considerably higher than maternal levels in 1 study.<sup>44</sup> Metformin acts to increase insulin sensitivity in both the liver and the periphery, which could benefit the fetus if insulin secretion in response to hyperglycemia were decreased, or it could harm the fetus if the effects of elevated insulin levels on the fetus were augmented by increased insulin sensitivity. These potential effects have not been delineated, making it safest to avoid using metformin once pregnancy has been established. Metformin is a pregnancy category B drug, meaning there is no evidence to date of teratogenicity, but other adverse effects on the fetus cannot be ruled out at this time. Finally, metformin may not be sufficient to maintain euglycemia in the face of increasing insulin resistance as seen in type 2 diabetic pregnancy.

Other oral agents include the insulin secretagogues, particularly sulfonylureas, which increase insulin secretion in patients with type 2 diabetes. While early agents crossed the placenta and had the potential to cause fetal effects, the second-generation agent glyburide was shown in 2 studies not to cross the placenta appreciably,<sup>46,47</sup> and a randomized trial has demonstrated similar efficacy to insulin in patients with gestational diabetes.<sup>47</sup> Glyburide is becoming more commonly used to treat gestational diabetes and may be effective in maintaining desired levels of euglycemia in up to 80% of patients.<sup>48</sup> However, its safety during organogenesis has not been examined, and a recent report,<sup>49</sup> as yet available only in abstract form, reported that glyburide was detectable in the cord blood of exposed neonates at about half the maternal blood concentrations. This finding contradicts previous reports, so the use of glyburide in gestational diabetes has become more controversial. Finally, because of the greater severity of preexisting type 2 diabetes, it is not clear whether glyburide would be sufficiently effective for such patients during pregnancy.

This leaves insulin, currently given by multiple injections throughout the day, as the standard of care for diabetes in pregnancy, mainly because insulin is a large molecule that has been demonstrated not to cross the placenta

except, perhaps, in an antibody-bound state.<sup>50,51</sup> A number of different types of insulin are available, each with a slightly different onset and duration of action. Most may be used in pregnant women, but the newer, longer-acting analogs have not been systematically evaluated in pregnancy, which is necessary to establish that they do not cross the placenta. Some, like lispro insulin, have been undetectable in the cord blood of infants whose mothers were taking the drug, providing reassurance of their applicability in pregnancy.<sup>52</sup> However, in vitro studies of perfused human placentas showed some transplacental passage at maternal levels that were similar to peak levels found in pregnant women taking 50 units of lispro insulin.<sup>53</sup> Similar results have been reported for insulin aspart,<sup>54</sup> and a randomized trial of aspart vs human insulin in 322 pregnant women with type 1 diabetes demonstrated similar safety and efficacy.<sup>55</sup> Others, such as insulin detemir and glargine, have not been tested, particularly with respect to placental transfer. Theoretical questions have also been raised regarding other potential adverse effects of these insulin analogs, such as the possibility of unanticipated interactions with insulinlike growth factor 1 receptors,<sup>56</sup> and much research remains to be done.

No particular regimen of insulin has been demonstrated to be more effective than others in treating diabetes during pregnancy. In my clinical practice, I start with the simplest regimen and advance to more complex regimens when simpler ones are not successful. If a woman becomes pregnant while using a particular insulin regimen and her diabetic control is optimal, there is no reason to change her insulin regimen; changes should be made only in response to circulating glucose levels outside of the target range. One size does not fit all, and arbitrary shifting of the insulin regimen in response to a change in clinicians is likely to engender mistrust and threaten adherence in patients who are comfortable with their current status. However, patients who conceive while using one of the newer insulin analogs that has not been systematically evaluated in pregnancy should be made aware of the theoretical concerns and should be involved in deciding whether to continue that form of insulin. In the case of Mrs T, I would suggest that she continue taking metformin until pregnancy is achieved, at which point she should switch to insulin injections using intermediate-acting (NPH [neutral protamine Hagedorn]) and short-acting (lispro or regular) insulin.

Evaluation of the effectiveness of therapy is based on frequent glucose self-monitoring. A randomized trial in patients with gestational diabetes requiring treatment demonstrated that adjusting insulin dosage on the basis of postmeal hyperglycemia (target 1-hour levels  $< 140$  mg/dL) or fasting hyperglycemia (target,  $< 100$  mg/dL) is more effective at preventing macrosomia and other pregnancy complications than is adjustment based on premeal values (target, 60-105 mg/dL).<sup>57</sup> Pregnant women with diabetes generally measure their own circulating glucose levels at least 4 times a day (before breakfast and 1 or 2 hours

after each meal) and may do so as many as 7 times a day with the addition of premeal values. This is an arduous schedule and requires a great deal of commitment to the pregnancy but provides information that is helpful in decreasing the various pregnancy risks associated with maternal diabetes.<sup>57</sup>

One of the most critical times appears to be approximately the first 10 weeks of gestation, during organogenesis.<sup>58</sup> While it is not clear that diabetic control needs to be as assiduous as that needed during the later half of pregnancy, patients whose control is particularly erratic and elevated may be offered hospitalization to institute improvements as quickly as possible to minimize fetal exposure to high glucose levels during these critical first 10 weeks. In my experience, in regions of the United States where I have practiced, hospitalization for this indication is covered by insurance companies.

### RECOMMENDATIONS FOR MRS T

For the reasons discussed above, I suggest that Mrs T continue with her current medications of metformin for her diabetes and nifedipine for her hypertension. She should proceed with her iron therapy and, if not already doing so, should consult with a dietitian regarding proper nutrition given her gastric bypass surgery. Mrs T should have a dilated retinal examination by an ophthalmologist to rule out diabetic retinopathy and should have measurement of her creatinine clearance and urinary protein excretion to rule out nephropathy. Diabetes is one of the most significant risk factors for coronary artery disease, and Mrs T is at particular risk given her diabetes and hypertension. I would order a baseline electrocardiogram and, if that is abnormal or there is evidence of other vascular disease, a stress electrocardiogram or stress echocardiogram. The American Diabetes Association now recommends stress testing only for individuals aged at least 35 years with diabetes for at least 10 years and excess cardiovascular risk because of its poor predictive value in individuals with fewer risk factors.<sup>18</sup> Since Mrs T's most recently measured glycohemoglobin level was 5.4%, which is within 1% of the upper limit of normal, I support her wish to conceive. Whether the metformin she is also taking for her diabetes will help the process along is uncertain. If and when she conceives, she should discontinue the metformin and begin insulin therapy once the conception is confirmed. She should be counseled that her chances of conception are reduced because of her age and that the likelihood of spontaneous abortion also increases with advancing maternal age, reaching as high as 74% in those older than 45 years.<sup>59</sup>

Since Mrs T is now having regular menses and has lost considerable weight, she may be ovulatory and clomiphene may not be necessary. If Mrs T is not successful in conceiving on her own or while taking clomiphene and metformin, other options are available but beyond the scope of this discussion. Consultation with a reproductive endocri-

nologist may be helpful. More advanced approaches to reproductive technology are not absolutely contraindicated for patients with medical challenges such as Mrs T, but they are arduous and involved and should be entered into with full understanding of the issues. The presence of anticardiolipin antibody, while beyond the scope of this discussion, should be fully evaluated and taken into consideration in formulating a treatment plan.

During her pregnancy, Mrs T should work closely with her team of caregivers to maintain her glucose levels as close to the target goals as possible. She should have screening to detect neural tube defects and should receive genetic counseling to assess her age-related risks so that she can decide which screening and diagnostic tests are most appropriate for her. Typically, a specialized (targeted) ultrasound examination<sup>60</sup> is offered in the middle trimester to help detect congenital malformations associated with diabetic pregnancy. Periodic ultrasound examinations are then recommended to detect abnormalities of fetal growth.<sup>7</sup> Antepartum fetal monitoring is generally used to look for fetal intolerance of the intrauterine environment and is commenced earlier in the presence of significant vascular, metabolic, or fetal complications and later in less complicated pregnancies with good metabolic control.<sup>7</sup> Mrs T is at risk of developing preeclampsia and she will need to be watched carefully for signs and symptoms of this disorder. In the absence of any complications, her pregnancy can be allowed to proceed to term. The mode of delivery should be determined by Mrs T and her caregivers. She had her first child by cesarean delivery because of a herpes outbreak, which might not recur in a subsequent pregnancy, so she may be a good candidate for a vaginal birth, assuming that this is what she desires and there are no other indications for cesarean delivery. The likelihood of uterine rupture during a trial of labor after a previous low-segment transverse cesarean delivery, assuming labor is not induced, is generally less than 1%.<sup>61</sup>

### QUESTIONS AND DISCUSSION

**QUESTION:** Do oral antidiabetic agents get into breast milk, and which, if any, are safe for breastfeeding mothers to use?

**DR COUSTAN:** Metformin is excreted into human milk, with the milk concentration being about one-third to one-half of that in plasma.<sup>62,63</sup> The calculated average infant dose would be less than 1% of the maternal dose, calculated on the basis of body weight. Furthermore, in 1 of the cited studies,<sup>63</sup> glucose levels were normal in 3 neonates 4 hours after a feeding. Therefore, while the potential effect of metformin on the nursing infant is unknown, mothers who nurse while taking metformin should be reassured that the actual amount reaching their child is minimal. Glyburide, which is sometimes used to treat gestational diabetes, crosses the placenta minimally, as noted above. When breast milk produced by breastfeeding mothers taking glyburide was analyzed, glyburide levels were unde-

tectable.<sup>64</sup> Therefore, glyburide appears safe for use by lactating women.<sup>62-65</sup>

**QUESTION:** Type 2 diabetes is obviously a risk factor for a number of different complications after pregnancy. Do we know whether pregnancy itself accelerates the risk of any of those problems?

**DR COUSTAN:** The complications of type 2 diabetes include vascular diseases such as retinopathy and nephropathy, which are the same as for type 1 diabetes. Once nephropathy is diagnosed, it tends to worsen progressively. A number of case series have failed to demonstrate a permanent effect of pregnancy on the progression of nephropathy, although the definitive answer is not yet available.<sup>36</sup> With regard to retinopathy, when 133 pregnant women with diabetes observed longitudinally were compared with 241 women with diabetes who did not experience a pregnancy during the same interval, the 2 strongest independent predictors of progression of retinopathy were hemoglobin A<sub>1c</sub> at the beginning of the observation period and the fact of pregnancy itself. Pregnancy was associated with an 80% increase in the likelihood of progression of retinopathy.<sup>66</sup> However, the study could not differentiate between the effect of pregnancy as opposed to the known transient worsening of retinopathy associated with the rapid institution of tight control in individuals previously poorly controlled. This sudden improvement of diabetic control is desirable in early pregnancy as outlined above.

**Financial Disclosures:** None reported.

**Funding/Support:** This Clinical Crossroads was made possible in part by a grant from the Sidney R. Rabb Charitable Trust and the Sidney and Esther Rabb Charitable Foundation.

**Role of the Sponsor:** The funding organization did not participate in the collection, analysis, and interpretation of the data or in the preparation, review, or approval of the manuscript.

**Additional Contributions:** We thank the patient for sharing her story and for providing permission to publish it.

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