

Preconception Care for Women With Preexisting Type 2 Diabetes

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In 2000, the World Health Organization (WHO) estimated that 171 million people worldwide had type 2 diabetes. Even more startling, WHO estimates that 366 million people worldwide will be diagnosed with type 2 diabetes by 2030.¹

Unfortunately, many of these individuals will be younger women who have not entered or completed their childbearing years. Hotu et al.² studied the rise in type 2 diabetes in adolescents and reported a sixfold increase in visits for type 2 diabetes at an adolescent diabetes clinic between 1996 and 2002. Type 2 diabetes referrals accounted for almost 25% of all new referrals from 1997 to 2001. In Britain, Hsia et al.³ showed a doubled prevalence of insulin use from 1998 to 2005 in children and adolescents and an eightfold increase in oral antihyperglycemic medications in the same population, suggesting a rapid increase in the prevalence of type 1 and type 2 diabetes, especially in adolescents. The female adolescents in this rapidly expanding group will have type 2 diabetes as they enter young adulthood, typically the beginning of their gestational years.

With the onset of type 2 diabetes occurring at a younger age, there is a greater responsibility on the part of health care providers to provide optimum care to women considering pregnancy and especially to their unborn fetuses. This responsibility will fall mostly to primary care providers (PCPs). Now more than ever,

PCPs will need to assume the important role of preconception counselor to women with type 2 diabetes who want to become pregnant.

PCPs may be the only health care providers these women see on a regular basis before pregnancy, at the time of conception, and during their pregnancies. With more limitations on health care spending and fewer resources, PCPs—not obstetricians (OBs) or gynecologists (GYNs), may be the ones providing preventive care (i.e., PAP smears and breast exams) and education to these women. These women may not be referred to OB/GYNs until after conception.

Therefore, the unique role and knowledge base of PCPs must expand yet again to include providing proactive preconception counseling. This counseling includes knowledge of appropriate A1C and blood glucose values before conception, risks of high A1C and blood glucose levels to the fetus, pre- and post-delivery care, medication regimens that are safe and appropri-

ate for women with type 2 diabetes wishing to conceive, and appropriate screening for and monitoring of diabetes-related complications. It is also important for women to know the risk of type 2 diabetes in their child's lifetime. Providing this information to patients and striving to achieve these treatment goals before they conceive will improve outcomes for both mothers and babies.

Preconception care worldwide is poor in women with type 2 diabetes. In one study,⁴ only 5% of 61 pregnancies in the women with type 2 diabetes were planned. Also, the first visit to an OB occurred after the first trimester in > 50% of the women in the study.⁴ In a French study of 146 pregnant women with type 2 diabetes, only 24% had preconception care.⁵ Roland et al.⁶ showed a similar, significant, prepregnancy counseling rate of 29% in women with type 2 diabetes. Numerous studies demonstrate poor perinatal outcomes (i.e., perinatal mortality, major congenital malformations, and preterm labor) associated with poorly controlled diabetes and some, more specifically, in uncontrolled type 2 diabetes compared to the general population and compared to pregnancies of women with type 1 diabetes.^{4,5,7-10}

Controlling blood glucose levels early is key to improving perinatal outcomes in women with type 2 diabetes. The American Diabetes Association (ADA) and the American Association of Clinical

IN BRIEF

With the onset of type 2 diabetes occurring at younger ages, there is a greater responsibility on the part of health care providers to provide optimum care to women with diabetes who are considering pregnancy. Controlling blood glucose levels early is key to improving perinatal outcomes in women with type 2 diabetes.

Endocrinologists (AACE) differ slightly in A1C goals for those with type 2 diabetes: < 7.0% for ADA and ≤ 6.5% for AACE to reduce microvascular complications, including retinopathy, nephropathy, and neuropathy.¹¹ However, for pregnant women with type 2 diabetes, A1C goals are tighter. ADA recommends < 6.3% before and during early pregnancy.¹² For the second and third trimesters, the A1C goal is < 6.0%. Striving for these targets often requires a more intense and involved regimen, with patients playing an active role in their own diabetes care, including diet, exercise, self-monitoring of blood glucose (SMBG), and adherence to prescribed medication regimens.

SMBG is frequent, and levels are strict. SMBG during pregnancy is recommended to be carried out fasting, 1 hour after each meal, and at bedtime. Fasting and bedtime blood glucose goals are 60–99 mg/dl.¹² One-hour postprandial blood glucose goals are 100–129 mg/dl, with average daily glucose values of < 110 mg/dl.¹² An A1C of 5–6% translates to an average glucose of 90–120 mg/dl.¹³

High A1C values before pregnancy and at the time of conception can affect early fetal development, the crucial period of major organ development and also the period when women may not yet know they are pregnant. Pregestational diabetes mellitus (PGDM), type 1 or type 2 diabetes diagnosed prior to pregnancy, is associated with a plethora of congenital defects. Correa et al.¹⁴ analyzed 26 defects and found preexisting diabetes to be associated with 50% of categories of birth defects, including isolated noncardiac defects, isolated cardiac defects, multiple noncardiac defects, and multiple cardiac defects. Correa et al. estimate that ~ 70% of isolated birth defects can be linked to moth-

ers' preexisting diabetes and an even higher percentage—90%—of multiple defects. Women with PGDM are at greater risk of having babies with multiple defects than with single or isolated defects. The defects most closely linked with preexisting diabetes include central nervous system defects, limb deficiencies, renal agenesis, hypospadias, orofacial clefts, and heart defects.¹⁴

Compared to pregnant women with type 1 diabetes, pregnant women with type 2 diabetes are at greater risk for adverse outcomes.⁶ Fewer women with type 2 diabetes have documented prepregnancy counseling. These women have more congenital malformations, small-for-gestational-age babies, and macrosomia.⁶

There is a high risk of fetal mortality and morbidity associated with type 2 diabetes.¹⁵ Clausen et al.⁴ found a fourfold increase in perinatal mortality in women with type 2 diabetes compared to women with type 1 diabetes and a ninefold increase in perinatal mortality compared to the background population. Compared to those of women with type 1 diabetes and to the background population, pregnancies in women with type 2 diabetes had a more than doubled rate of major congenital malformations. These researchers also found A1C levels of type 2 diabetic women to be elevated throughout pregnancy (5.9–6.8%).⁴ High A1C levels are associated with higher rates of spontaneous abortion or miscarriage. A study by Dunne et al.¹⁰ of 182 pregnancies of women with type 2 diabetes throughout 12 years found a miscarriage rate of 8.8%, nearly doubling to 15.7% in those with poor glycemic control.

For the latter part of pregnancy and delivery, diabetes is a risk factor for preterm labor^{9,16} and perinatal morbidity and mortality. In the previously mentioned study by Dunne

et al.,¹⁰ results indicated a twofold greater risk of stillbirth, a 2.5-fold greater risk or perinatal mortality, a 3.5-fold greater risk of death within the first month, and a sixfold greater risk of death up to 1 year compared to general population rates in Britain. The study also found the risk of congenital malformation to be 11 times greater than in the general population and to be associated with poor glycemic control.¹⁰

In the postpartum period, newborns are at risk for a number of poor outcomes. Gonzalez-Quintero et al.¹⁷ looked at outcomes of infants born to > 3,000 mothers with gestational diabetes mellitus (GDM) placed into an optimally controlled blood glucose group (fasting < 95 mg/dl, 1-hour postprandial < 140 mg/dl, 2-hour postprandial < 120 mg/dl) compared to a suboptimally controlled group. The infants born to the mothers in the suboptimal group had higher rates of macrosomia, jaundice, stillbirth, and neonatal hypoglycemia. There were also higher incidences of cesarean section delivery and need for higher-level nursery care. Overall, the composite outcome for one or more of the above outcomes was 33% in the suboptimally controlled group compared to 24% in the optimally controlled group.

Infants in the postpartum period are also at risk for other complications. As mentioned above, infants of mothers with diabetes are at risk for hypoglycemia. The goal is to prevent neonatal hypoglycemia by tightly controlling maternal blood glucose during pregnancies.¹⁸ Other risks include hypocalcemia, hypomagnesemia, polycythemia, iron deficiency, and hyperbilirubinemia. These infants are also at risk for respiratory complications secondary either to surfactant deficiency or remaining fetal lung fluid because of cesarean section delivery.¹⁸

Higher A1C levels are associated with poorer pregnancy outcomes. There is a 3.4% incidence of congenital complications when A1C values are < 8.5%, but this incidence increases to 22.4% with A1C values > 8.5%.¹⁹

Guerin et al.²⁰ reviewed cohort studies to determine the absolute risk of developing a congenital anomaly in pregnant women with preexisting diabetes based on periconceptional glycated hemoglobin (GHb), which was then converted to A1C. The main anomalies included cardiac, central nervous system, and urogenital system defects. The researchers concluded that, when periconception GHb was in the normal range, the risk of developing a congenital anomaly was the same as in general population—about 2%. As GHb increases, so does the absolute risk of developing a congenital anomaly, to 3% when GHb is 2 SDs above normal and to 10% when GHb is 8 SDs above normal (Figure 1).

There are many more data available on poor pregnancy outcomes for women with type 1 diabetes than for those with type 2 diabetes. De Valk et al.²¹ reviewed data on pregnancies in women with preexisting type 2 diabetes from 1992 and 2006, including A1C level during pregnancy, in relation to adverse outcomes. They studied 66 pregnancies in 48 women, the majority being planned, and all women treated with insulin during pregnancy. The mean A1C value was 6.9% before pregnancy, 6.0% during the second trimester, and 6.2% in the third trimester.

These researchers reviewed both maternal pregnancy outcomes and infant outcomes. Compared to the normal population, there were higher incidences of spontaneous abortion, preeclampsia, preterm delivery, and cesarean section delivery. Regarding infant outcomes,

compared to the normal population, there were higher incidences of macrosomia, severe hypoglycemia, and major congenital malformation. The researchers concluded that, despite reasonable glucose control and pregnancy planning, type 2 diabetes before pregnancy continues to be linked to a higher incidence of poor pregnancy outcomes. Despite the limitations of this study—namely, that it was retrospective and included a small sample size—it highlights the need for early referral to a specialist and for more research on pregnancy in women with type 2 diabetes.²¹

There is also a higher risk to babies of type 2 diabetic women for developing type 2 diabetes later in life. Lindsay et al.²² looked at the weight, BMI, and incidence of diabetes in childhood and early adulthood of children born to mothers with type 2 diabetes that was diagnosed either before or during pregnancy. This large study showed that the children of mothers with diabetes were heavier at birth, had

higher BMIs at all ages throughout childhood, and had an increased incidence rate (7- to 20-fold) of diabetes in childhood and early adulthood.²²

Pettitt et al.²³ looked at participants in the SEARCH for Diabetes in Youth study to compare the age of type 2 diabetes diagnosis in children < 20 years of age born to mothers with type 2 diabetes diagnosed before pregnancy compared to mothers diagnosed after the children's birth or at an undetermined time. The SEARCH study is a large trial looking at diagnosis of type 1 and type 2 diabetes in youth < 20 years of age. The researchers found that children born to mothers with diabetes in pregnancy had a younger age of diagnosis of their own type 2 diabetes than those born to mothers whose diabetes was diagnosed after the pregnancy. These results suggest that exposure to hyperglycemia in utero predisposes children to an earlier age of diagnosis with type 2 diabetes.²³

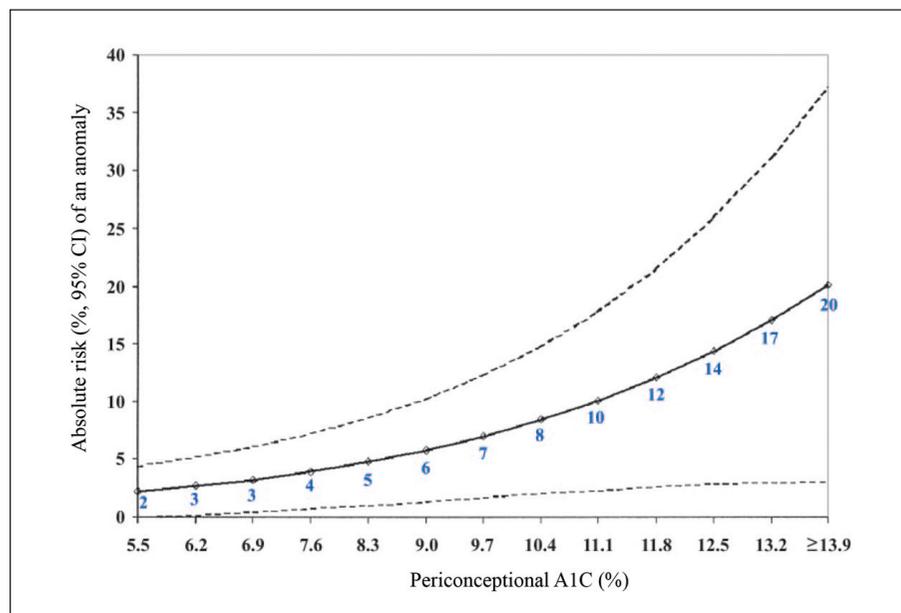


Figure 1. Risk of a major or minor anomaly according to periconceptional A1C. Data are presented as absolute risk (solid line and blue values) ± 95% CIs (dashed lines). Reprinted with permission from Ref. 20.

Hillier et al.²⁴ studied the incidence of obesity (defined as > the 85th and > the 95th percentiles for weight) in nearly 10,000 5- to 7-year-old children of mothers who were screened for GDM during their pregnancies. The researchers found that an increasing hyperglycemia level in pregnant women is associated with an increased future risk of obesity in their children at age 5–7 years.²⁴ Multivariate analysis to adjust for the patients with GDM who were appropriately treated indicated that this risk is modifiable. The study found that the most important indicator of childhood obesity is the mother's fasting hyperglycemia during pregnancy.²⁴

A basal/bolus insulin regimen remains the best treatment option to manage blood glucose and decrease A1C levels to the target range. NPH insulin and rapid-acting analog insulins are the best options. Rapid-acting analog insulins allow for better postprandial glucose-lowering with less risk of hypoglycemia than regular human insulin.^{12,25} NPH is recommended two to four times daily as basal insulin, with rapid-acting insulin analogs given as premeal bolus doses with consideration to carbohydrate intake and activity level.¹² NPH remains the long-acting insulin of choice in the absence of clinical trials supporting the safety and efficacy of the long-acting insulin analogs glargine or detemir for these patients.¹²

Although retrospective and prospective reviews of glargine use during pregnancy in women with type 1 diabetes have shown no difference in maternal and fetal outcomes compared to traditional NPH treatment, there remains a lack of randomized, controlled trials (RCTs) to confirm these results.^{26,27} A recent transplacental transfer study by Pollex et al.²⁸ used a “human perfused placental lobule”

technique to determine whether glargine crosses the placenta. In this laboratory-controlled setting, minus the circumstances surrounding labor, the researchers determined that glargine most likely does not cross the placenta.

This topic is of great concern because of glargine's capacity to bind to insulin-like growth factor-1 receptors, which may influence fetal growth.^{26,27} ADA currently does not recommend glargine use in pregnancy.¹² Glargine is also not currently approved by the U.S. Food and Drug Administration for use in pregnancy and carries a category C rating. This rating indicates that adverse effects have been seen in animal studies with no adequate human studies but that the benefits of use may outweigh the risks in some cases.²⁹ The decision to continue or start glargine should be made by patients only after consultation with an endocrinologist.

With patient education regarding the benefits of tight glucose control, women wishing to become pregnant are usually willing to start an insulin regimen. Most often, women want to improve and optimize the probability of having a healthy baby by improving their glycemic control.¹³ Starting an insulin regimen before pregnancy allows time for patients to become familiar and comfortable with insulin therapy and administration. However, there is room for improvement in transitioning women to insulin before conception. Roland et al.⁶ found that, at the time of conception, treatment for type 2 diabetes in 28.8% of 146 type 2 diabetic women was diet alone; 44.5% were treated with oral hypoglycemic agents; and only 29.7% were treated with insulin. The researchers concluded that oral hypoglycemic medications are not a direct cause of congenital malformations, but rather

poor prepregnancy preparation in women with diabetes.

Sulfonylureas (preferably glimepiride)^{30,31} and metformin³² may effectively manage blood glucose during pregnancy and may not be teratogenic.^{33,32} Metformin, compared to insulin, does not appear to be associated with increased perinatal complications.³² However, ADA recommends discontinuing oral medications, including sulfonylureas and metformin, and initiating insulin before conception.¹² Oral antidiabetic agents and incretins are not recommended during pregnancy.¹²

Polycystic ovary syndrome (PCOS) is a condition featuring polycystic ovaries, ovulatory dysfunction, and androgen excess.³⁴ Hyperinsulinemia is a key finding in PCOS, as well as insulin resistance and obesity; thus, having PCOS places women at high risk for developing type 2 diabetes. The prevalence of type 2 diabetes in women with PCOS is five to 10 times higher than in those without PCOS.³⁴ Infertility is common in this group, which has placed metformin at the forefront in PCOS management.

Reviews of metformin use in women with PCOS suggest that this agent may induce ovulation, reduce miscarriages, improve pregnancy outcomes, and reduce cardiovascular disease (CVD) markers, which decreases the risk of type 2 diabetes.^{34,35} Although the results of the studies included in these reviews show promise, both reviews conclude that more data, including from RCTs, are needed before clear recommendations can be made regarding metformin use in pregnancy. However, in a prospective observational study, Glueck et al.³⁶ found that metformin use during pregnancy in nondiabetic women with PCOS decreased preconception weight and resulted in less weight

gain during pregnancy. Also, it decreased insulin resistance and the risk of developing GDM.

Both reviews cited above^{34,35} also conclude that metformin should be stopped after a positive pregnancy test.^{34,36} This is in agreement with current ADA recommendations to halt oral diabetes therapies during pregnancy. Again, insulin is the treatment of choice during pregnancy.¹²

Metformin is not only under investigation for use during pregnancy in women with PCOS; it is also being studied for use in pregnant women with type 2 diabetes. Hughes and Rowan³⁷ reviewed pregnancy cases in women with type 2 diabetes from 1998 to 2003. They compared a control group comprising 121 pregnant women not treated with metformin to an intervention group of 93 pregnant women taking metformin at some point during their pregnancy, including 32 who remained on metformin throughout their pregnancy. They found no difference between the groups in preeclampsia, perinatal loss, neonatal morbidities (including prematurity), neonatal unit admission, infant respiratory distress, or treatment of infant hypoglycemia with intravenous dextrose. Interestingly, the metformin group started with increased A1C levels, increased BMI, and more chronic hypertension than the control group.

RCTs are needed to evaluate metformin use in pregnant women with type 2 diabetes. Long-term data are also needed on the effects of metformin on infants. An RCT is now underway comparing metformin to insulin in pregnant women with type 2 diabetes, with study completion in June 2011.³⁸ Data are now being assessed regarding the effect of metformin on the 2-year-old offspring from the Metformin in Gestational Diabetes (MiG) trial studying

metformin use in GDM.³² A decision to remain on metformin during pregnancy should be discussed with patients in conjunction with specialists, including the OB/GYN, a maternal fetal medicine specialist, and an endocrinologist.

PCPs also must be aware of the use of ACE inhibitors and angiotensin II receptor blockers (ARBs) for hypertension and HMG-COA reductase inhibitors (statins) for hyperlipidemia in type 2 diabetic women who want to become pregnant because of teratogenicity. ACE inhibitors and ARBs are pregnancy category C drugs in the first trimester and category D in the second and third trimesters.²⁹ Category D indicates positive evidence of human fetal risk but notes that the benefits of use may outweigh the risks.²⁹ Ideally, these agents should be discontinued before conception. Antihypertensive agents commonly used in pregnancy include methyldopa, nondihydropyridine calcium channel blockers, and certain β -adrenergic blockers such as labetalol and carvedilol.¹² Statins carry the category X rating, indicating that animal or human studies have shown fetal abnormalities or toxicity and that the risk of using these agents outweighs the benefits.²⁹ Statins should ideally be discontinued a few months before conception.

Because statins, ACE inhibitors, and ARBs are mainstay therapies for those with type 2 diabetes, women must be counseled that these medications are not safe in pregnancy, that they should use contraception while on these therapies, and that these medications need to be discontinued before conception. Just as these women must be educated about the need for good glucose control as part of effective family planning, so too must they be made aware of the potential safety issues related to these medications.

As part of the prepregnancy care and counseling, providers must also address complications related to diabetes, including diabetic nephropathy, neuropathy, and retinopathy. ADA also recommends addressing CVD, hypertension, dyslipidemia, depression, and thyroid disease. These recommendations are discussed briefly below and are based on ADA technical reviews and consensus recommendations for managing preexisting diabetes for pregnancy.¹² These sources should be consulted for complete guidelines, which are beyond the scope of this article.

To assess diabetic nephropathy, patients' serum creatinine, glomerular filtration rate, and degree of albuminuria should be measured before pregnancy. Controlling blood pressure and blood glucose levels is the best way to control or prevent the progression of nephropathy to improve pregnancy outcomes. As discussed in the section above regarding blood pressure medications, patients planning pregnancy should discontinue ACE inhibitors and ARBs and switch to antihypertensive agents that are considered safe during pregnancy.

Women with type 2 diabetes should have a comprehensive eye exam with dilation before conception. If retinopathy is present, the women should be educated about the risk of progression of retinopathy, which is double that in the nonpregnant state. ADA recommends the slow lowering of blood glucose levels to almost normal over 6 months before pregnancy in women with type 2 diabetes who have either proliferative or severe nonproliferative diabetic retinopathy. Referral to an ophthalmologist is necessary, and frequent eye exams will be necessary dependent on the degree of retinopathy present. For women who do not have retinopathy before pregnancy,

the risk of developing it during pregnancy is low.

PCPs should screen for distal polyneuropathy and autonomic neuropathy annually, at a minimum, and provide patients with foot care education. Women wanting to become pregnant should be educated that pregnancy does not appear to increase the risk for development or progression of distal sensorimotor or diabetic autonomic neuropathies except for transient but possible severe effect on gastroparesis.¹² There is increased risk of poor perinatal outcomes and morbidity with gastroparesis, which should be treated based on pregnancy guidelines.

Women with type 2 diabetes tend to have higher rates of hypothyroidism and therefore should be screened and treated, if hypothyroidism is present, in the prepregnancy period, bearing in mind that the dose of replacement thyroxine may need to be increased in early pregnancy. ADA recommends measuring thyroid-stimulating hormone and thyroid peroxidase antibody levels for screening purposes.

CVD and diabetes share numerous risk factors. Therefore, recommendations include screening for family history, hypertension, smoking, albuminuria, and dyslipidemia. CVD screening should include physical examination of carotid, abdominal, and femoral bruits; aortic ejection murmur; and foot pulses. Treatment of CVD risk factors, including smoking, hypertension, hyperglycemia, and dyslipidemia, should be tailored to pregnancy. An electrocardiogram (ECG) should be performed on diabetic women ≥ 35 years of age before pregnancy. For women who have had type 2 diabetes for > 10 years and have high CVD risk, stress ECG or stress echocardiogram also should be considered. Those with suspicion of active

coronary heart disease warrant a cardiology consultation and further testing.

Hypertension management with appropriate medications for pregnancy was discussed earlier. High blood pressure during the prepregnancy period should be treated to a systolic blood pressure of < 130 mmHg and a diastolic blood pressure of < 80 mmHg. A lipid panel also should be completed before pregnancy. Nutrition and lifestyle modifications are the priority treatment for dyslipidemia, both before and throughout pregnancy, because statins are contraindicated during pregnancy.

Finally, psychological assessment of and treatment for depression, eating disorders, and anxiety and stress disorders should be completed as part of routine care because these conditions can affect blood glucose and overall diabetes control.

Because of the complexity of managing pregnant women with type 2 diabetes and the numerous risks to the fetuses of such women, referral should be made to an endocrinologist who practices as part of a diabetes care team, including a nurse practitioner or physician's assistant, a certified diabetes educator, and a registered dietitian. This team must be in frequent contact with the patient's OB/GYN. PCPs are in an integral position to prepare women with type 2 diabetes for pregnancy. However, the intensive medication regimens, blood glucose monitoring needs, and tight glycemic goals required for pregnancy in diabetes make specialty referrals necessary. Such referrals should occur before conception.²¹

Crucial topics for PCPs to cover in preconception education and counseling include appropriate A1C and blood glucose values before conception, the risks posed to fetuses by high maternal A1C and blood

glucose levels, appropriate pre- and post-delivery care, safe medication regimens, the risk to offspring of developing type 2 diabetes in their lifetime, and screening guidelines for diabetes-related complications. Many OBs provide their patients with diabetes with education on these topics, but often patients first learn about these crucial issues at their initial consultation appointment with an endocrinologist, which can be well into their first trimester of pregnancy.

The importance of achieving optimal glucose control before conception cannot be overemphasized. If we, as a health care community, are to improve outcomes for these women with type 2 diabetes and, even more importantly, for their future children, we must stress this point. PCPs play a vital role in providing this knowledge and assisting their patients with type 2 diabetes who want to become pregnant in reaching these very strict goals.

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