



# Managing Diabetes in Women of Childbearing Age

Joy A. Dugan, MPH, PA-C, Amritha Parthasarathy, OMS II

There were 13.4 million women (ages 20 and older) with either type 1 or type 2 diabetes in the United States in 2012, according to the CDC.<sup>1</sup> By 2050, overall prevalence of diabetes is expected to double or triple.<sup>2</sup> Since the number of women with diabetes will continue to increase, it is important for clinicians to familiarize themselves with management of the condition in those of childbearing age—particularly with regard to medication selection.

Diabetes management in women of childbearing age presents multiple complexities. First, strict glucose control from preconception through pregnancy is necessary to reduce the risk for complications in mother and fetus. The American Diabetes Association (ADA) recommends an A1C of less than 7% during the preconception period, if achievable without hypoglycemia.<sup>3</sup> Full glycemic targets for women are outlined in Table 1.

Second, many medications used to manage diabetes and pregnancy-associated comorbidities can be fetotoxic. The FDA assigns all drugs to a pregnancy category, the definitions of which are available at <http://chemm.nlm.nih.gov/pregnancycategories.htm>.<sup>4</sup> The ADA recommends that sexually active women of childbearing age avoid any potentially

Joy A. Dugan is faculty in the MSPAS/MPH program at Touro University California, where Amritha Parthasarathy is an osteopathic medical student.

**TABLE 1**  
**Glycemic Targets for Women of Childbearing Age**

Women with gestational diabetes*	Preprandial ≤ 95 mg/dL One-hour postmeal ≤ 140 mg/dL Two-hours postmeal ≤ 120 mg/dL
Women with preexisting type 1 or type 2 diabetes*	<b>Preconception</b> Premeal, bedtime, and overnight glucose 60-99 mg/dL Peak postprandial glucose 100-129 mg/dL A1C < 7.0%  <b>During pregnancy</b> Fasting < 90 mg/dL Preprandial < 105 mg/dL One-hour postprandial < 130-140 mg/dL Two-hours postprandial < 120 mg/dL A1C < 6.0%
Women for whom above targets are not achievable without excessive hypoglycemia	Fasting < 90 mg/dL Preprandial < 105 mg/dL One-hour postprandial < 130-140 mg/dL Two-hours postprandial < 120 mg/dL A1C < 6.0%

\* If achievable without excessive hypoglycemia  
Source: American Diabetes Association. 2015.<sup>3</sup>

teratogenic medications (see Table 2, page 52) if they are not using reliable contraception.<sup>3</sup>

Excellent control of diabetes is necessary to decrease risk for birth defects. Infants born to mothers with preconception diabetes have been shown to have higher rates of morbidity and mortality.<sup>5</sup> Infants born to women with diabetes are generally large for gestational age and experience hypoglycemia in the first 24 to 48 hours of life.<sup>6</sup> Large-for-gestational-age babies are at in-

creased risk for trauma at birth, including orthopedic injuries (eg, shoulder dislocation) and brachial plexus injuries. There is also an increased risk for fetal cardiac defects and congenital congestive heart failure.<sup>6</sup>

This article will review four cases of diabetes management in women of childbearing age. The ADA guidelines form the basis for all recommendations.

**Case 1** A 32-year-old obese woman with type 2 diabetes mellitus

**TABLE 2**  
**Medication Classes with Pregnancy Category**

Class/Medication	Pregnancy category
<b>Biguanide</b> Metformin	B
<b>Sulfonylureas</b> Glipizide, glimepiride Glyburide	C B/C*
<b>Thiazolidinediones</b> Pioglitazone, rosiglitazone	C
<b>Meglitinides</b> Repaglinide, nateglinide	C
<b>DPP-4 inhibitors</b> Alogliptin, saxagliptin, sitagliptin, linagliptin	B
<b>GLP-1 agonists</b> Liraglutide, exenatide, dulaglutide, albiglutide	C
<b>Long-acting insulin</b> Insulin glargine [rDNA origin] injection; insulin degludec Insulin detemir [rDNA origin] injection	C B
<b>Intermediate-acting insulin</b> Insulin isophane; insulin, human	B
<b>Rapid-acting insulin</b> Insulin lispro; insulin lispro U200; insulin aspart Insulin glulisine	B C
<b>Combination insulin</b> Insulin aspart/insulin aspart protamine; insulin lispro protamine/insulin lispro	B
<b>Statins</b>	X
<b>Alpha blockers</b> Methyldopa Prazosin	B C
<b>ACE inhibitors</b>	D
<b>Angiotensin II receptor blockers</b>	D
<b>Beta blockers</b> Labetolol, metoprolol, nadolol, propranolol, timolol, esmolol Atenolol	C D
<b>Calcium channel blockers</b> Diltiazem, nifedipine	C

\* Depending on manufacturer.

(T2DM) presents for routine follow-up. Recent lab results reveal an A1C of 6.4%; GFR > 100 mL/min/1.73 m<sup>2</sup>; and microalbuminuria (110 mg/d). She is currently taking lisinopril (2.5 mg once daily), metformin (1,000 mg bid), and glyburide (5 mg bid). She plans to become pregnant in the next six months and wants advice.

**DISCUSSION**

This patient should be counseled on preconception glycemic targets and switched to pregnancy-safe medications. She should also be advised that the recommended weight gain in pregnancy for women with T2DM is 15 to 25 lb in overweight women and 10 to 20 lb in obese women.<sup>3</sup>

The ADA recommends a target A1C < 7%, in the absence of severe hypoglycemia, prior to conception in patients with type 1 diabetes mellitus (T1DM) or T2DM.<sup>3</sup> For women with preconception diabetes who become pregnant, it is recommended that their premeal, bedtime, and overnight glucose be maintained at 60 to 99 mg/dL, their peak postprandial glucose at 100 to 129 mg/dL, and their A1C < 6% during pregnancy (all without excessive hypoglycemia), due to increases in red blood cell turnover.<sup>3</sup> It is also recommended that they avoid statins, ACE inhibitors, angiotensin II receptor blockers (ARBs), certain beta blockers, and most noninsulin therapies.<sup>3</sup>

This patient is currently taking lisinopril, a medication with a pregnancy category of X. The ACE inhibitor class of medications is known to cause oligohydramnios, intrauterine growth retardation, structural malformation, premature birth, fetal renal dysplasia, and other congenital abnormali-

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ties, and use of these drugs should be avoided in women trying to conceive.<sup>7</sup>

Safer options for blood pressure control include clonidine, diltiazam, labetalol, methyldopa, or prazosin.<sup>3</sup> Diuretics can reduce placental blood perfusion and should be avoided.<sup>8</sup> An alternative for management of microalbuminuria in women of childbearing age is nifedipine.<sup>9</sup> In multiple studies, this medication was not only safer in pregnancy, with no major teratogenic risk, but also effectively reduced urine microalbumin levels.<sup>10,11</sup>

For T2DM management, metformin (pregnancy category B) and glyburide (pregnancy category B/C, depending on manufacturer) can be used.<sup>12,13</sup> Glyburide, the most studied sulfonylurea, is recommended as the drug of choice in its class.<sup>14-16</sup> While insulin is the standard for managing diabetes in pregnancy—earlier research supported a switch from oral medications to insulin in women interested in becoming pregnant—recent studies have demonstrated that oral medications can be safely used.<sup>17</sup> In addition, lifestyle changes (eg, carbohydrate counting, limited meal portions, and regular moderate exercise) prior to and during pregnancy can be beneficial for diabetes management.<sup>18,19</sup>

Also remind the patient to take regular prenatal vitamins. The US Preventive Services Task Force recommends that all women planning to become or capable of becoming pregnant take 400 to 800 µg supplements of folic acid daily.<sup>20</sup> For women at high risk for neural tube defects or who have had a previous pregnancy with neural tube defects, 4 mg/d is recommended.<sup>21</sup> In women with dia-

betes who are trying to conceive, a folic acid supplement of 5 mg/d is recommended, beginning three months prior to conception.<sup>22</sup>

Research shows that diabetic women are less likely to take folic acid supplementation during pregnancy. A study of 6,835 obese or overweight women with diabetes showed that only 35% reported daily folic acid supplementation.<sup>23</sup> The study authors recommended all women of childbearing age, especially those who are obese or have diabetes, take folic acid daily.<sup>23</sup> Encourage *all* women intending to become pregnant to start prenatal vitamin supplementation.

**Case 2** A 26-year-old obese patient, 28 weeks primigravida, presents for follow-up on her 3-hour glucose tolerance test. Results indicate a 3-hour glucose level of 148 mg/dL. The patient has a family history of T2DM and gestational diabetes.

## DISCUSSION

Gestational diabetes is defined by the ADA as diabetes diagnosed during the second or third trimester of pregnancy that is not T1DM or T2DM.<sup>3</sup> The ADA recommends lifestyle management of gestational diabetes before medications are introduced. A1C should be maintained at 6% or less without hypoglycemia. In general, insulin is preferred over oral agents for treatment of gestational diabetes.<sup>3</sup>

There tends to be a spike in insulin resistance in the second or third trimester; women with pre-conception diabetes, for example, may require frequent increases in daily insulin dose to maintain glycemic levels, compared to the first trimester.<sup>3</sup> A baseline ophthalmology exam should be per-

formed in the first trimester for patients with preconception diabetes, with additional monitoring as needed.<sup>3</sup>

Following pregnancy, screening should be conducted for diabetes or prediabetes at six to 12 weeks' postpartum and every one to three years afterward.<sup>3</sup> The cumulative incidence of T2DM varies considerably among studies, ranging from 17% to 63% in five to 16 years postpartum.<sup>24,25</sup> Thus, women with gestational diabetes should maintain lifestyle changes, including diet and exercise, to reduce the risk for T2DM later in life.

**Case 3** A 43-year-old woman with T1DM becomes pregnant while taking atorvastatin (20 mg), insulin detemir (18 units qhs), and insulin aspart with meals, as per her calculated insulin-to-carbohydrate ratio (ICR; 1 U aspart for 18 g carbohydrates) and insulin sensitivity factor (ISF; 1 U aspart for every 60 mg/dL above 130 mg/dL). Her biggest concern today is her medication list and potential adverse effects on the fetus. Her most recent A1C, two months ago, was 6.5%. She senses hypoglycemia at glucose levels of about 60 mg/dL and admits to having such measurements about twice per week.

## DISCUSSION

In this case, the patient needs to stop taking her statin and check her blood glucose regularly, as she is at increased risk for hypoglycemia. In their 2013 guidelines, the American College of Cardiology/American Heart Association stated that statins “should not be used in women of childbearing potential unless these women are using effective contraception and are not nursing.”<sup>26</sup> This presents a

major problem for many women of childbearing age with diabetes.

Statins are associated with a variety of congenital abnormalities, including fetal growth restriction and structural abnormalities in the fetus.<sup>27</sup> It is advised that women planning for pregnancy avoid use of statins.<sup>28</sup> If the patient has severe hypertriglyceridemia that puts her at risk for acute pancreatitis, fenofibrate (pregnancy category C) can be considered in the second and third trimesters.<sup>29,30</sup>

With T1DM in pregnancy, there is an increased risk for hypoglycemia in the first trimester.<sup>3</sup> This risk increases as women adapt to more strict blood glucose control. Frequent recalculation of the ICR and ISF may be needed as the pregnancy progresses and weight gain occurs. Most insulin formulations are pregnancy class B, with the exception of glargine, degludec, and glulisine, which are pregnancy category C.<sup>3</sup>

**Case 4** A 21-year-old woman with T1DM wishes to start contraception but has concerns about long-term options. She seeks your advice in making a decision.

**DISCUSSION**

For long-term pregnancy prevention, either the copper or progesterone-containing intrauterine device (IUD) is safe and effective for women with T1DM or T2DM.<sup>31</sup> While the levonorgestrel IUD does not produce metabolic changes in T1DM, it has not yet been adequately studied in T2DM. Demographics suggest that young women with T2DM could become viable candidates

for intrauterine contraception.<sup>31</sup>

The hormone-releasing “ring” has been found to be reliable and safe for women of late reproductive age with T1DM.<sup>32</sup> Combined hormonal contraceptives and the transdermal contraceptive patch are best avoided to reduce risk for complications associated with estrogen-containing contraceptives (eg, venous thromboembolism and myocardial infarction).<sup>33</sup>

**CONCLUSION**

All women with diabetes should be counseled on glucose control prior to pregnancy. Achieving a goal A1C below 6% in the absence of hypoglycemia is recommended by the ADA.<sup>3</sup> Long-term contraception options should be considered in women of childbearing age with diabetes to prevent pregnancy. Clinicians should carefully select medications for management of diabetes and its comorbidities in women planning to become pregnant. Healthy dietary habits and regular exercise should be encouraged in all patients with diabetes, especially prior to pregnancy. **CR**

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