Type 2 diabetes in women of reproductive age

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Intended audience: This continuing education (CE) activity has been designed to meet the educational needs of nurse practitioners and other healthcare providers who provide primary care for women.

CE approval period: Now through April 30, 2023

Estimated time to complete this activity: 1 hour

CE approval hours: 1.0 contact hour of CE credit including 0.25 contact hours of pharmacology content

Goal statement: Nurse practitioners and other healthcare providers who provide primary care for women will increase their knowledge about screening, diagnosis, lifestyle and pharmacologic management, and prevention of complications for type 2 diabetes and prediabetes in reproductive-age women.

Needs assessment: Approximately 12% of women in the United States older than age 18 years have diabetes. Additionally, an approximate 47 million women older than 18 years have prediabetes. The prevalence of type 2 diabetes mellitus in women of reproductive age has been reported to be from 3% to 7%. Type 2 diabetes occurs in 1% to 2% of all pregnancies, conferring a significantly greater maternal and fetal risk than gestational diabetes mellitus. Knowledge about screening recommendations, diagnostic criteria, and management of type 2 diabetes and prediabetes is needed to prevent complications and to help reproductive-age women with these conditions to develop a healthy reproductive plan.

Educational objectives: At the conclusion of this educational activity, participants should be able to:

- 1. Identify screening recommendations and diagnostic criteria for type 2 diabetes and prediabetes.
- 2. Describe the components of lifestyle management for type 2 diabetes and prediabetes.

3. Discuss indications, mechanism of action, efficacy, adverse effects, and contraindications for pharmacologic options in treating type 2 diabetes and prediabetes.

Accreditation statement: This activity has been evaluated and approved by the Continuing Education Approval Program of the National Association of Nurse Practitioners in Women's Health (NPWH) and has been approved for 1 contact hour of CE credit, including 0.25 hours of pharmacology credit.

Faculty disclosures: NPWH policy requires all faculty to disclose any affiliation or relationship with a commercial interest that may cause potential, real, or apparent conflict of interest with the content of a CE program. NPWH does not imply that affiliation or relationship will affect the content of the CE program. Disclosure provides participants with information that may be important to their evaluation of an activity.

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Successful completion of the activity: Successful completion of this activity, J-21-02, requires participants to do the following:

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- 2. Read the learning objectives, disclosures, and disclaimers on the next page and then click on the "Continue" button.
- 3. Study the material in the learning activity during the approval period (now through April 30, 2023).
- 4. Complete the post-test and evaluation. You must earn a score of 70% or higher on the post-test to receive CE credit.

5. Print out the CE certificate after you have successfully passed the post-test and completed the evaluation.

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he prevalence of type 2 diabetes in women of reproductive age ranges from 3% to 7%. Due to the common nature of this condition, it is imperative for nurse practitioners who care for women to understand evidence-based methods of diabetes management. The aim of this article is to describe current screening and diagnostic criteria for type 2 diabetes, discuss current evidencebased management and patient education necessary to prevent longterm complications, and provide the tools for a healthy reproductive plan in women with type 2 diabetes from puberty until menopause. Diabetes management extends well beyond glucose control, and nurse practitioners should be attuned to all factors that can impact cardiovascular risk and quality of life.

Key words: type 2 diabetes, prepregnancy counseling, reproductive plan, pregestational diabetes, prediabetes

Type 2 diabetes is an endocrine condition, strongly linked to visceral adiposity and physical inactivity, in which a progressive loss of adequate beta-cell insulin secretion related to insulin resistance occurs.¹ Insulin resistance results in a compensatory rise in insulin with progressive loss of beta-cell function. Over time, the loss of beta-cell function typically requires medication intensification and may lead to total reliance on self-administered insulin.

Approximately 12% of women in the United States older than age 18

years have diabetes.² Additionally, an approximate 47 million women older than 18 years have prediabetes.² The prevalence of diabetes mellitus in women of reproductive age has been reported to be from 3% to 7%.³ Type 2 diabetes affects 1% to 2% of all pregnancies, conferring a significantly greater maternal and fetal risk than gestational diabetes mellitus (GDM).³

Nurse practitioners (NPs) who provide care for women of all ages should be equipped to provide patient education that may prevent type 2 diabetes as well as reduce the risks for long-term complications. NPs who provide care for reproductive-age women have the additional opportunity to provide prepregnancy education to promote reproductive plans that can improve pregnancy outcomes.

Risk factors and screening

The American Diabetes Association (ADA) recommends screening for prediabetes and type 2 diabetes for all adults age 18 years and older who are overweight (body mass index [BMI] ≥ 25 kg/m³) or in Asian Americans with BMI 23 kg/m³ or more, with one additional risk factor (Table 1).¹ The ADA also recommends risk-based screening for adolescents (after onset of puberty or after age 10 years, whichever occurs earlier) who are overweight or obese with one or more additional risk factors based on the strength of their association with diabetes (Table 2).1

Diagnosis

Overall, approximately one-quarter of those with diabetes in the United States and nearly half of Asian and Hispanic Americans with diabetes are undiagnosed.¹ NPs can help to

Table 1. Criteria for testing for diabetes or prediabetes in asymptomatic adults¹

Testing should be considered in adults with overweight or obesity (BMI \ge 25 kg/m² or \ge 23 kg/m² in Asian Americans) who have one or more of the following risk factors:

- First-degree relative with diabetes
- High-risk race/ethnicity (eg, African American, Latino, Native American, Asian American, Pacific Islander)
- History of CVD
- Hypertension (140/90 mm Hg or on therapy for hypertension)
- HDL cholesterol level < 35 mg/dL and/or triglyceride level > 250 mg/dL
- Women with polycystic ovary syndrome
- Physical inactivity
- Other clinical conditions associated with insulin resistance (eg, severe obesity, acanthosis nigricans)

Patients with prediabetes (A1c \ge 5.7%, IGT, or IFG) should be tested yearly. Women who were diagnosed with GDM should have lifelong testing at least every 3 years.

For all other patients, testing should begin at age 45 years.

If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

Human immunodeficiency virus

CVD, cardiovascular disease: HDL, high-density lipoprotein; GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Table 2. Risk-based screening for type 2 diabetes or prediabetes in asymptomatic adolescents in a clinical setting¹

Testing should be considered in youth* who have overweight (> 85th percentile) or obesity

(> 95th percentile) and who have one or more additional risk factors based on strength of their association with diabetes:

- Maternal history of diabetes or GDM during the child's gestation
- Family history of type 2 diabetes in first- or second-degree relative
- Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander)
- · Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome, or small-for-gestational age birth weight)

GDM, gestational diabetes mellitus

* After onset of puberty or after age 10 years, whichever occurs earlier. If tests are normal, repeat testing at minimum of 3-year intervals (or more frequently if BMI is increasing or risk factor profile deteriorating) is recommended. Reports of type 2 diabetes before age 10 years exist, and this can be considered with numerous risk factors.

reduce these numbers by following screening guidelines as well as recognizing symptoms in reproductive-age women that may indicate the need for diabetes testing. Clinical presentations of recurrent vulvovaginal yeast infections or urinary tract infections, urinary frequency, nocturia, vulvar pruritus, and fatigue that persists over time could have an underlying type 2 diabetes etiology and should be further investigated.

A variety of laboratory tests can be used to diagnose type 2 diabetes. The easiest test to perform is the HgA1c (A1c) because no fasting is required. An A1c of 6.5% or higher is indicative of diabetes. Other tests

include a fasting plasma glucose of higher than 126 mg/dL (fasting at least 8 hours), a random plasma glucose higher than 200 mg/dL in the presence of symptoms of hyperglycemia, or a 2-hour plasma glucose higher than 200 mg/dL after an oral glucose tolerance test (OGTT) with 75-g glucose. NPs should be aware that there are multiple factors that can affect the accuracy of the A1c test including common conditions such as pregnancy and anemia, and the results should be interpreted with caution if there is a condition that impacts the lifespan of the red blood cell.⁴ A diagnosis of diabetes must be confirmed with a second

test that can be performed on the same sample.¹

Prediabetes in which glucose levels are abnormal but do not meet the criteria for a diagnosis of diabetes is a risk factor for cardiovascular disease as well as for future diabetes. Prediabetes diagnostic criteria include a fasting plasma glucose of 100 to 125 mg/dL or an A1c of 5.7% to 6.4%.¹

Management

Priorities for management of diabetes include optimizing A1c according to individual targets, cardiovascular risk reduction (CRR), avoiding hypoglycemia, promoting a healthy lifestyle, avoiding diabetes complications, and enhancing quality of life. Evidence is consistent for reduction of conversion of prediabetes to type 2 diabetes when utilization of lifestyle changes in diet and physical activity are optimal.⁵ Diabetes self-management education and support and engagement with a multidisciplinary diabetes care team can enhance outcomes and achievement of optimal health goals. Pharmacologic treatment may be required and should be individualized and monitored. Women with prediabetes should be referred to a National Diabetes Prevention Program that emphasizes delaying or preventing type 2 diabetes.⁶

Glycemic targets

The most important component in preventing diabetes complications is to maintain a normal A1c. Self-monitoring of glucose levels is key for achieving glycemic targets.¹ Glucose monitoring allows women to evaluate individual response to therapy and assess whether glycemic targets are being safely achieved.¹

The ADA recommends A1c targets for most women with diabetes at 7% or lower (correlating to an average blood glucose ~ 154 mg/dL), but these targets may be tighter (< 6.5%) if the individual is able to achieve it without hypoglycemia (< 70 mg/dL) or undue treatment burden. Women who have significant comorbidities, shorter life expectancy, or who are not able to achieve lower glucose levels without hypoglycemia or excessive burden may have less strict treatment targets such as less than 8%. All individuals should avoid hypoglycemia. Women with type 2 diabetes who are planning a pregnancy require stricter A1c goals with targets less than 6.5% offering the lowest risk of fetal abnormalities.¹

Lifestyle management

The cornerstones of lifestyle management for prediabetes and type 2 diabetes are a healthy, well-rounded diet, physical activity, and mental/ emotional well-being. There is not one recommended diet for women with diabetes, although reducing carbohydrate intake has proven to have the most impact on glycemic management.¹ Reducing and eliminating high-fructose drinks and food should be a primary consideration. Alcohol should be limited to no more than one drink per day in nonpregnant women. Alcohol is associated with hypoglycemia (particularly for those on insulin or sulfonylureas) and should be consumed with caution. Tobacco use should always be avoided. A major nutrition goal is the achievement and maintenance of a healthy weight. A 5% reduction in body weight for individuals who are overweight or obese can confer improvements in blood pressure, lipids, and glycemic control.¹ A referral to a registered dietician for individualized diet planning is recommended.

The current physical activity recommendations for most adults with diabetes are 150 minutes per week of moderate or vigorous exercise, along with 2 to 3 sessions per week of strength training.¹ In general, reducing the amount of time in sedentary behavior is a good starting point for many women with diabetes. Insulin resistance is decreased through a steady exercise routine.¹

NPs should be attuned to the potential for mental health comorbidities that impact overall health and can impair self-care behaviors. Depression, anxiety, and eating disorders are all commonly associated with type 2 diabetes. Diabetes distress, distinct from other psychological disorders, refers to significant negative psychological reactions related to emotional burdens and worries specific to having to manage a complicated chronic condition with constant behavioral demands. It is reported in up to 45% of individuals with type 2 diabetes.¹ Screening for these conditions should be incorporated into care with a system in place for referral to behavioral health providers.¹

Digital health technology through approved online platforms may be helpful in the management of type 2 diabetes for some individuals. Online programs/apps must be compliant with the US Health Insurance Portability and Accountability Act of 1996 and ensure data safety.¹ Technology selection must be appropriate for the individual and consider cost, access, and patient motivation.¹ There are a variety of apps available, some that allow for increasing social networks for patients with diabetes or for sharing health information between patient and provider or health team. Rigorous clinical trial data on these digital programs is not currently available.

Pharmacologic management

Medication therapy for type 2 diabetes should always be individualized and patient centered. Considerations prior to medication selection should include pregnancy status (or plans for pregnancy), cost, comorbidities (renal insufficiency, heart failure, cardiovascular disease), risk of hypoglycemia, route (oral or injection), medication efficacy, and potential side effects. Guidelines are available from the ADA Standards of Medical Care in Diabetes (2021) and the American Association of Clinical Endocrinologists (AACE) (2020) describing the most updated, evidence-based pharmacologic approaches to diabetes management.^{1,7}

Pharmacologic treatment for women with diabetes of reproduc-

Table 3. Metformin (biguanide) prescribing¹

- · Mechanism of action: decreases hepatic glucose production; increases peripheral glucose uptake (increases insulin sensitivity)
- Expected HgA1c reduction of 1.5% at maximum doses
- · Weight neutral or slight weight loss anticipated
- Does not cause hypoglycemia
- Can be obtained for as little as \$4 per month or free with some pharmacy programs

Prescribing considerations

- Obtain GFR prior to initiating therapy
- Monitor GFR annually or more often if < 60 mL/min
- Start with low dose (500 mg) and titrate every 7 days as tolerated
- · Switch to extended-release (once daily) version if GI symptoms are significant with immediate release
- · Periodically monitor B12 levels due to risk of B12 deficiency
- Use a maximum dose of 2,000 mg per day (2,500 mg is available but typically increases the risk of GI effects without significant benefit)
- Hold metformin before iodinated contrast dye procedure if GFR < 60 or if significant hepatic impairment, heart failure, or excessive alcohol use. Recheck GFR 48 hours after procedure before restarting

Types of metformin Immediate release (500–2,000 mg daily in 2 divided doses) Extended release (500–2,000 mg once daily)	Renal function parameters	Black box warning
	GFR > 60: No adjustment; monitor annually	Lactic acidosis is rare but serious.
	GFR 45–60: No adjustment; monitor every 6 months GFR: 30–45: Discuss risks and benefits of continuing, consider lower dose; do not start metformin if GFR < 45; monitor GFR every 3 months GFR < 30: Contraindicated	Severe renal impairment Severe hepatic impairment Excessive alcohol consumption Age > 65 years Radiology study with contrast dye

GFR, glomerular filtration rate; GI, gastrointestinal.

tive age should be approached with careful consideration. NPs should always be aware of current pregnancy status and conception plans. Oral diabetes medications are not approved for women who are pregnant.¹

For women who are not pregnant, there are a wide variety of options for medications that can optimize glucose levels. The ADA recommends metformin as firstline treatment for most people with type 2 diabetes (*Table 3*).¹ Metformin works by suppressing hepatic glucose production. First approved in 1995, metformin has long-term safety and efficacy data in nonpregnant adults and has the benefit of being inexpensive and well-tolerated with no independent risk for hypoglycemia. For women with prediabetes, metformin has shown benefit especially for those who have BMIs 35 kg/m² or higher, those younger than age 60 years, and women with a prior history of GDM.¹ The AACE's prediabetes algorithm emphasizes the need to treat any atherosclerotic cardiovascular disease (ACSVD) risk factors alongside hyperglycemia.⁷

The criteria for initiating or continuing metformin requires monitoring estimated glomerular filtration rate (eGFR). The AACE provides an algorithm for the initiation of dual therapy after a 3-month follow-up on monotherapy.⁷ If A1c targets are not met with metformin, second-line treatment should be added. Preferred second-line treatments in the nonpregnant woman include sodium glucose co-transporter 2 (SGLT-2) inhibitors, glucagon-like peptide 1 receptor agonists (GLP-1 RA), dipeptidyl peptidase 4 inhibitors (DPP-IV), or basal insulin. Sulfonylureas (SU) and thiazolidinediones (TZD) are not preferred due to risk of hypoglycemia (SU) and risk for fluid volume overload (TZD).

The two newest classes of medications for diabetes are the SGLT-2 inhibitors and GLP-1 RAs. SGLT-2 inhibitors work by blocking reabsorption of glucose in the proximal tubule of the kidney. This allows for increased glucose release in the urine, thereby lowering serum glucose levels. These medications have also been shown to reduce weight and lower blood pressure.⁸ Additionally, multiple clinical trials have shown that several of the SGLT-2 inhibitors reduce cardiovascular risk. The SGLT-2 inhibitors can cause increased urination and may lead to urinary tract or genital yeast infections. Due to their diuretic effect, attention should be paid to volume status and blood pressure. Although SGLT-2 inhibitors are being studied heavily for use in individuals with chronic kidney disease, they must be dose-adjusted for decreased eGFR less than 45 mL/min.

GLP-1 RAs work by slowing gastric emptying, stimulating glucosedependent insulin secretion, and suppressing glucagon release, among other mechanisms of action that benefit individuals with diabetes.⁸ Similar to the SGLT-2 inhibitors, many GLP-1 RAs have proven to be effective in CRR. Notably, none of the CRR studies for either SGLT-2 inhibitors or GLP-1 RAs were conducted in women of reproductive age, so the translation to this population should be interpreted with caution. GLP-1 RAs should not be used in patients with a family or personal history of medullary thyroid cancer or multiple endocrine neoplasia and should be used with caution in patients with significant gastrointestinal issues. This class of medication can cause decreased gastric emptying along with the possibility of bloating, diarrhea, or constipation.

When considering management options regarding second-line pharmacologic treatment for diabetes, the NP should consider whether the patient has comorbidities such as heart failure, chronic kidney disease, or ASCVD. If heart failure or chronic kidney disease exist, an SGLT-2 inhibitor should be considered as these have been shown to reduce new-onset heart failure and hospitalization for heart failure, along with reducing the progression of chronic kidney disease.⁸ If ASCVD predominates, the woman should be preComplications are not confined to Older adults and have the potential to affect WOMEN at ANY Stage in life. Patients should be assessed regularly for the most COMMON diabetes COMPLICATIONS including retinopathy (annual eye exams), Neuropathy, nephropathy, Nonalcoholic fatty liver disease, and certain Cancers including endometrial, breast, and bladder.

scribed either a GLP-1 RA or a SGLT-2 because both have proven CRR.¹ A recent consensus statement from the American College of Cardiology provides a comprehensive overview of diabetes medication management and CRR implications.⁸

Metformin, SGLT-2 inhibitors, and GLP-1 RAs have no risk of hypoglycemia (unless in combination with an agent that does). All three of these medications may precipitate weight loss.

If patients fail to achieve glycemic targets with two agents, further medications should be added with consideration to the items mentioned previously. Lifestyle (physical activity and diet) should always be discussed as a foundational treatment for diabetes. Patient preferences and goals should be taken into consideration. A positive pregnancy test should prompt a quick conversion to insulin injections.

Prevention of complications

Throughout a woman's lifespan, it is essential for the NP to initiate measures to prevent complications that

can ensue from type 2 diabetes. It is important to remember the number one way to prevent complications is to maintain a normal A1c. Cardiovascular disease is the number one cause of death for individuals with diabetes and prevention should be a priority.¹ Common coexisting conditions are hypertension and dyslipidemia, both clear risk factors for ASCVD.¹ Current blood pressure recommendations include maintaining a blood pressure lower than 140/90 mm Hg for low atherosclerotic risk individuals (ASCVD risk score < 15%) and lower than 130/80 mm Hg for high atherosclerotic risk women (> 15% ASCVD risk score).¹ Currently, statin medications are not routinely recommended for women younger than age 40 years with diabetes but may be considered if they have additional risk factors for ASCVD.9 Women older than age 40 years with diabetes should be on a moderate-intensity statin for primary prevention. High-intensity statins with or without additional low-density-lipoprotein lowering therapy



(eg, ezetimibe) should be used for women who require secondary prevention.⁹ Statin therapy, along with certain blood pressure medications including angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, are contraindicated in pregnancy. These should be discontinued when women are actively seeking pregnancy and used with caution or avoided in reproductive-age women who are not using reliable contraception.

Complications are not confined to older adults and have the potential to affect women at any stage in life. Patients should be assessed reqularly for the most common diabetes complications including retinopathy (annual eye exams), neuropathy, nephropathy, nonalcoholic fatty liver disease, and certain cancers including endometrial, breast, and bladder. Women with new-onset diabetes (< 5 years) have a twofold increased odds of developing endometrial cancer.¹⁰ There is also a positive association between diabetes and increased bladder cancer.¹⁰

Special considerations

Reproductive-age women with prediabetes or type 2 diabetes can benefit from education that allows them to develop a reproductive life plan that will optimize future pregnancy outcomes. In accordance with the ADA, beginning at puberty, prepregnancy counseling should be incorporated into routine diabetes care for all women with reproductive potential.¹ Prepregnancy counseling can begin with the question: "Do you plan to become pregnant in the next year?"¹¹ This is an opportunity to counsel about wellness and healthy habits that may improve reproductive and obstetric outcomes.¹¹

Counseling reproductive-age, sexually active women with prediabetes or type 2 diabetes not currently desiring a pregnancy should include providing information to facilitate shared decision making about contraception. Most contraceptive methods are safe for women with diabetes of less than 20 years' duration and without nephropathy, retinopathy, neuropathy, or vascular disease. The US Medical Eligibility Criteria for Contraceptive Use should be consulted.¹²

Women with diabetes who are seeking pregnancy should receive information about potential fetal complications of hyperglycemia including spontaneous abortion, fetal anomalies, fetal macrosomia, and stillbirth. Potential maternal complications should also be discussed including increased risk for worsening of diabetic retinopathy and nephropathy, hypertensive disorders of pregnancy, and the increased incidence of preterm birth and cesarean delivery.³ Stricter A1c goals of lower than 6.5% with lower than 6% being ideal when possible are recommended.¹ An evaluation for baseline complications including hypertension, nephropathy, retinopathy, and cardiovascular disease should be conducted.³ Folic acid of at least 400 µg per day should be initiated prior to becoming pregnant to reduce the risk for neural tube defects.³

Care for women who were diagnosed with GDM should include screening at 4 to 12 weeks postpartum using an OGGT.¹³ Significantly, 15% to 70% of women with GDM go on to develop type 2 diabetes later in life.¹³ Women with GDM should have lifelong screening for type 2 diabetes or prediabetes every 1 to 3 years.¹ They should be advised to seek screening for diabetes as part of future prepregnancy care.

Polycystic ovary syndrome (PCOS) is the most common endocrine disturbance in women of reproductive age. Women with PCOS have a twofold to fivefold increased risk of diabetes and up to 33% increased risk if also diagnosed with metabolic syndrome.¹⁴ Although different organizations hold varying cutoffs for the diagnosis of metabolic syndrome, NPs should be attuned to waist circumferences greater than 80 cm, triglyceride levels higher than 150 mg/dL, high-density-lipoprotein cholesterol lower than 50 mg/dL, blood pressure higher than 130/85 mm Hg (or on treatment), and elevated fasting plasma glucose higher than 100 mg/dL (or on treatment).¹⁵ Insulin resistance is a hallmark of both PCOS and metabolic syndrome as well as type 2 diabetes. Fasting glucose levels are poor predictors of glucose intolerance risk in women with PCOS, thus an OGTT is recommended.¹⁶ Lifestyle modifications such as exercise and diet modifications for weight loss are first-line interventions for women with PCOS.¹⁷ Combined oral contraceptives are considered firstline pharmacologic treatment for PCOS for reproductive-age women who are also wanting to prevent pregnancy but are ineffective in increasing insulin sensitivity.¹⁷ Although not approved by the US Food and Drug Administration for the treatment of PCOS, metformin is commonly prescribed to increase peripheral insulin sensitivity. The AACE prediabetes algorithm addresses the timeline for initiation of metformin in metabolic syndrome.⁷

Conclusion

NPs should be vigilant with screening, diagnosis, and effective management of prediabetes and type 2 diabetes in women of reproductive age. Attention should be given to prepregnancy counseling, promoting healthy diet, physical activity, optimal glycemic control, reduction of cardiovascular risk, and enhancing quality of life. With appropriate self-management and effective provider recommendations, women with diabetes can reduce the risk of complications and enjoy a long and healthy life.

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Web resource

A. npwh.org/courses/home/details/1625