

Diabetes prevention: Reproductive age women affected by insulin resistance

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Shadi Reza¹, Stephen LoBue² and Cassandra E Henderson¹

Abstract

In the United States, 29.1 million people are affected by diabetes, of which 95% have type 2 diabetes. There has been a fivefold increase in type 2 diabetes in the latter half of the 20th century, an increase strongly linked to the obesity epidemic in the United States. In addition, insulin resistance affects 86 million Americans, or more than one-third of the adult population, as manifested by impaired fasting glucose tolerance with random glucose values ranging from ≥ 100 to < 126 mg/dL. In all, 90% of those affected by impaired fasting glucose tolerance or pre-diabetes are unaware of their metabolic derangement. Although impaired fasting glucose tolerance increases one's risk of developing type 2 diabetes, once identified, application of lifestyle changes by affected individuals may avoid or delay the onset of type 2 diabetes. For reproductive age women who are found to have impaired fasting glucose tolerance, lifestyle changes may be an effective tool to diminish the reproductive health consequences of insulin resistance related diseases.

Keywords

Lifestyle changes, diabetes prevention, medical nutrition therapy, type 2 diabetes mellitus, gestational diabetes, insulin resistance, preconception counseling, pregnancy, reproductive age women

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Introduction and background

In the United States, approximately 9.3% of the population or 29.1 million people have diabetes mellitus, of which 95% have type 2 diabetes (T2D).¹ In total, 86 million or more than one-third of American adults have impaired fasting glucose tolerance (IFGT) with random glucose values ranging from ≥ 100 to < 126 mg/dL.² However, 90% of those affected by IFGT or pre-diabetes are unaware of this diagnosis or the related increased risk of developing T2D. A disease risk can be diminished with the adoption of lifestyle changes (LSCs) as outlined in self-management education protocols.³

A recent Centers for Disease Control (CDC) report indicates the prevalence of gestational diabetes mellitus (GDM) may be as high as 9.2%.⁴ Although this transient glucose intolerance usually resolves after delivery, the diagnosis identifies a group of reproductive age women affected by insulin resistance or pre-diabetes who are at increased risk of developing T2D within 5 years of the index delivery. This cohort of women has the opportunity to ameliorate or reduce this metabolic risk by electing to make LSCs as outlined as a component of diabetes self-management education (DSME).

GDM

GDM, defined as any degree of glucose intolerance with its onset or initial recognition documented during pregnancy, places the parturient and her offspring at an increased risk of developing T2D.⁵ In addition to GDM, some conditions that increase the risk that a reproductive age woman will be affected by T2D are having a body mass index (BMI) greater than 30 kg/m², a history of unexplained fetal demise, having delivered an infant weighing more than 9 lbs, family history of diabetes, polycystic ovarian syndrome, or being a member of an ethnic minority, Black Caribbean, Pacific Islander, Native American, Mexican American, or of Middle Eastern origin.⁶

¹Department of Obstetrics and Gynecology, Lincoln Medical and Mental Health Center, Weill Cornell Medical College, New York, NY, USA

²School of Medicine, St. George's University, Grenada, West Indies

Corresponding author:

Cassandra E Henderson, Department of Obstetrics and Gynecology, Lincoln Medical and Mental Health Center, Weill Cornell Medical College, 234 East 149th Street, Bronx, New York, NY 10451, USA.
Email: Cassandra.henderson@nychhc.org

Table 1. Screening and diagnosing GDM and pre-GDM.

Pregnant women without known prior diabetes	Screen at 24–28 weeks
Pregnant women with risk factors	Screen for undiagnosed T2D at first prenatal visit and at 24–28 weeks
Women with GDM history	Screen for diabetes or pre-diabetes every ≥ 3 years
Women with GDM	Screen for persistent diabetes 6–12 weeks postpartum using OGTT and non-pregnancy diagnostic criteria

GDM: gestational diabetes mellitus; T2D: type 2 diabetes; OGTT: oral glucose tolerance test.

Table 2. Glycemic guidelines during pregnancy.

Pre-prandial, bedtime, and overnight glucose range from 60–99 mg/dL
Peak postprandial glucose 100–129 mg/dL
A1C < 6.0%

First-line treatment for after diagnosis of GDM is the adoption of LSCs described in DSME that incorporates medical nutrition therapy (MNT) and recommended physical activity (Table 1). MNT is a specific diet designed to achieve predetermined glycemic targets (Table 2). Hypoglycemic agents may be combined with MNT, if glycemic targets are not achieved. The majority of women with GDM will be able to meet their glycemic targets with the application of the MNT principles that emphasize food choices and portion control.⁷ Mild to moderate exercise of up to 30 min a day is recommended.⁸ To begin MNT, referral to a nutritionist or certified diabetes educator is recommended. However, to reinforce the MNT principles, it is important that the responsible healthcare practitioners are aware of the important concepts of this meal-planning tool.

Pregnancy increases the daily calories that women require. The parturient usually requires an extra 300 calories a day, which may vary slightly depending on the level of physical activity.⁸ The application of the principles of MNT and LSC during pregnancy would lead to recommended modification of diet such that consumption of high sugary foods such as most desserts, candy, soft drinks, and fruit juice would be limited. Fruit should also be limited to one small serving on any given occasion with no more than three servings a day. Meals should be smaller and more frequent resulting in lower glycemic loads and decreased endogenous insulin requirement.⁸ The quantity and glycemic index of carbohydrates consumed should not only be limited but should be combined with concurrent ingestion of water and a protein choice. Carbohydrates are found in breads, potatoes, cereals, rice, pasta, beans, fruits, milk, yogurt, and some vegetables. Certain carbohydrates have a lower glycemic index, thus have less of an effect on raising

blood glucose.⁹ Low glycemic carbohydrate starches that are high in fiber include wholegrain bread, Quinoa, buckwheat, amaranth, black beans or kidney beans, potatoes, or corn.⁹

Diabetes and pregnancy

Persistent hyperglycemia during pregnancy can lead to adverse outcome for mother and fetus. Therefore, reproductive age women affected by diabetes should be encouraged to plan all pregnancies. The principles of MNT and LSC should be implemented during the preconception and early prenatal period upon identification of signs or symptoms of insulin resistance.

Insulin is the hypoglycemic agent of choice for any pregnancy complicated by type 1 diabetes (T1D) and T2D.⁷ The use of oral hypoglycemic agents is an additional therapeutic option for gravidas affected by T2D or GDM. Hypoglycemic agent is appropriate when glycemic targets are not met despite the use of MNT in conjunction with LSC. Although overweight gravidas who achieve weight gain as recommended by the Institute of Medicine (BMI: 25–22.9 and >30, 11–25 and 11–20 pounds, respectively) will likely decrease their risk of developing T2D, these recommendations serve merely as clinical guidelines. The lack of supportive evidence leaves gestational weight gain to be determined by individual choice and clinical judgment.

Psychosocial stressors as possible barriers to achieving glycemic goals should be considered if glycemic targets are not met despite appropriate medical and individual management.¹⁰ Psychosocial factors to be evaluated include poverty, diabetes-related distress, health literacy, depression, and family responsibilities that may alter treatment effectiveness. MNT and LSC are effective tools to help individuals reach their glycemic targets, especially when the program is modified according to the individual's abilities, culture, and circumstances.¹⁰ MNT and LSC can lower hemoglobin A1C by as much as 1% for individuals affected by glucose intolerance.^{11,12}

MNT and LSC as components of DSME positively affect psychosocial and behavioral aspects of diabetes. DSME is reported to reduce the presence of diabetes-related distress,¹³ enhance self-efficacy,¹⁴ increase healthy coping,¹⁵ decrease onset and/or advancement of diabetes-associated complications,^{16,17} promote healthy LSCs such as diet and exercise,¹⁸ and improve quality of life.¹⁹ LSC DSME has been shown to increase the knowledge, understanding, and ability required for successful diabetes self-care. This process takes into account the patient's specific requirements, long-term goals, and life experiences within the treatment paradigm. Overall, adoption of DSME principles by individuals affected by pre-diabetes may support informed decision making, problem solving, and effective self-care to improve insulin sensitivity.

A diagnosis of glucose intolerance or pre-diabetes can be a very difficult and challenging scenario for many individuals. To achieve maximum effectiveness, the ideal time to implement MNT and LSC is during the early stages of insulin resistance.²⁰ MNT and LSC education at diagnosis of pre-diabetes should focus on safety concerns and basic instructions that an engaged affected person can easily understand, remember, and implement if they so desire.²⁰ A nutritionist or diabetes educator should be available to answer questions, address initial concerns, and provide support or referrals to any necessary outside resources.²⁰ Once the diagnosis of glucose intolerance is made, an essential component of the diabetes education visit is the discussion of MNT principles with formulation by the educator and patient of the appropriate achievable glycemic targets as well as physical activity goals.²⁰

Improving insulin sensitivity is a goal of MNT and LSC. These insulin sensitivity tools, practiced by the individual affected by insulin resistance with assistance from individual healthcare provider, are lifetime tools to prevent or manage T2D.¹⁰ For individuals with a diagnosis of diabetes, glucose intolerance, or pre-diabetes, the cost of limited diabetes prevention encounters by certified providers may be reimbursed by Medicare, Medicaid, and some private payers. Additional sessions to provide MNT or psychosocial counseling may also be covered by third-party payers when provided by health professionals with appropriate diabetes-related credentials.²⁰

Postpartum treatment to delay onset of T2D

LSCs and use of insulin sensitizers, such as metformin, have been shown to decrease the risk of developing T2D. Research has been conducted to compare these two interventions to prevent or delay the onset of diabetes. A multicenter clinical research study, Diabetes Prevention Program (DPP) compared lifestyle modification versus metformin (Glucophage) to prevent or delay the onset of T2D in study participants.²¹ At the beginning of the DPP, participants were all overweight and had blood glucose levels higher than normal, but not high enough for a diagnosis of diabetes or pre-diabetes.²¹

DPP investigators found that LSCs and treatment with metformin reduced the incidence of diabetes in persons at risk of developing insulin resistance.^{22,23} When outcome for lifestyle versus medication were compared, lifestyle intervention was more effective than metformin. Exercise and weight loss may improve vascular endothelial function, resulting in lower risk of cardiovascular disease.^{22,23} Lifestyle modification consisting of a moderate diet, minimum of 7% weight loss, and 150 min of aerobic exercise each week, lowered the rates of diabetes, cardiovascular disease, and hypertension associated with metabolic syndrome.²¹ Lifestyle modification specifically decreased the onset of T2D by 58% in subjects with impaired glucose

Table 3. Preventing/delaying type 2 diabetes.

Patients with A1C 5.7–6.4%, IGT, or IFG
Refer to dietician or diabetes educator for medical nutrition therapy management
Weight loss of 7% body weight
Increased moderate physical activity >150 min a week
Metformin therapy
BMI > 35
Age <60 years
Women with history of gestational diabetes

IFG: impaired fasting glucose; IGT: impaired glucose tolerance.

tolerance and is effective in all age groups.^{22,23} In contrast, metformin was associated with a 31% decrease in the rate of T2D for the 25–44-year subjects with a BMI >35.^{22,23} Another analysis of DPP data concluded that the presence of high blood pressure in DPP participants was decreased in the lifestyle intervention group, but increased in the metformin and placebo groups. Measures of triglyceride and high-density lipoprotein (HDL) cholesterol levels also improved in the lifestyle intervention group.²¹ A third analysis documented that levels of C-reactive protein and fibrinogen, risk factors for heart disease, were lower in the metformin and lifestyle intervention groups, with a larger reduction in the lifestyle group.²¹

Participants who lost weight through dietary changes and increased physical activity had a greater diabetes risk reduction. Each year only 5% of the lifestyle modification group developed diabetes versus 7.8% each year for those in the metformin group.²¹ However, while metformin was less effective than lifestyle, its use in DPP was associated with cost savings over a 10-year period.²⁴

In contrast, for women who had a history of GDM, metformin and intensive LSCs led to an equivalent 50% reduction in diabetes risk.²⁵ As a result, metformin is a diabetes risk reduction option for high-risk individuals such as those with a BMI >35 and a history of GDM.

The latest American Diabetes Association Guidelines for preventing/delaying the onset of T2D coincides with the above statements and as indicated in Table 3.¹⁰

DSME is a validated diabetes management intervention.¹⁰ This education tool is useful in the postpartum period for women affected by T2D or at risk of developing T2D. These patient-centered education programs reinforce behaviors that can prevent or delay the onset of diabetes.¹⁰

Insulin resistance and infertility

T2D should be included in the differential diagnosis for menstrual abnormalities. Infertility risk factors related to insulin resistance include menstrual abnormalities, shortening of reproductive period (late menarche and premature menopause), and sexual dysfunction.²⁶

Insulin resistance affects reproductive health causing menstrual changes, fertility disorders, vaginal and urinary tract infections, urinary incontinence, depressive disorders, sexual dysfunction, and is directly related to risk of acute myocardial infarction (Box 1).²²

Box 1. Risk factors for insulin resistance in reproductive age women.

1. Greater than 40 years of age
2. Two BMI > 35
3. First-degree relative with a diagnosis of DM
4. Black Caribbean, Pacific Islander, Native American, Mexican American, Latino
5. History of GDM or delivery of an infant weighing >9lbs
6. Sedentary lifestyle
7. Hypertension >140/>90
8. HDL < 35 mg/mg/dL
9. Fasting triglyceride >250 mg/dL
10. Acanthosis nigricans
11. PCOS
12. Depression
13. Obstructive sleep apnea

BMI: body mass index; DM: diabetes mellitus; GDM: gestational diabetes mellitus; HDL: high-density lipoprotein; PCOS: polycystic ovary syndrome.

Insulin resistance and cancer

Hyperinsulinemia may promote mammary carcinogenesis. Insulin resistance, a characteristic of T2D, has been linked to an increased risk of breast cancer.²⁷ In addition, high levels of insulin have been associated with an increased mortality rate after diagnosis of breast cancer.²⁸ Also, the presence of inflammatory markers such as tumor necrosis factor- α , interleukin-6, and fasting serum insulin correlate with worse clinical outcomes in metastatic breast cancer.²⁹ Higher levels of tumor necrosis factor- α , interleukin-6, and fasting serum insulin are associated with a worse prognosis for metastatic breast cancer.²⁹

Studies have shown a direct correlation between development of ovarian cancer with consumption of high glycemic index foods resulting in a high glycemic load. Thus, some hypothesize a possible role for hyperinsulinemia/insulin resistance in development of ovarian cancer.³⁰

Another study linked high glycemic index and high glycemic load diets to moderately increased risk of cancer at several common sites.³¹ Although insulin levels were not measured, normal physiological states require increased levels of insulin to meet requirements to metabolize high glycemic loads. High glycemic load diets may increase the risk of colorectal cancer in women.³² The association of colorectal cancer with hyperinsulinemia and insulin resistance suggests that a diet resulting in hyperglycemia may contribute to a metabolic environment conducive to tumor growth.³² Hyperinsulinemia is also associated with precancerous lesions such as adenomas. Elevated insulin is significantly associated with increased colorectal adenoma

risk and low apoptosis in the normal mucosa.³³ A proposed mechanism is that insulin increases adenoma risk through downregulation of apoptosis.³³ Patients with elevated serum insulin may benefit from frequent screening for polyps/colon cancer.³³

Insulin resistance and depression

Depression is thought to be linked with increased risk factors for chronic disease. Depression with one concurrent chronic disease risk factor affects 12.8% of reproductive-aged women.³⁴

Women with a past or current diagnosis of depression have a higher prevalence of diabetes, smoking, alcohol abuse, obesity, and physical inactivity ($p < 0.001$ for all).³⁴ Depressed women of reproductive age are at increased risk of chronic disease that may affect their overall health and future pregnancies.³⁴

Future perspective

Prospective study of LSCs as a tool to improve the reproductive health of women affected by insulin resistance.

Executive summary

- Gestational diabetes
 - The prevalence of GDM may be as high as 9.2%
 - First-line treatment is referral to dietician or diabetes educator to begin MNT and DSME
- Diabetes in pregnancy
 - Glycemic targets should be agreed by the pregnant woman and her dietary counselor
 - DSME is associated with improved diabetes knowledge, self-care behavior, quality of life, healthy coping techniques, and lower A1C and self-reported weight
- Preventing/delaying T2D
 - Lifestyle modification/change is most effective in reducing the incidence of T2D for individuals with impaired fasting glucose or pre-diabetes
 - Lifestyle modification includes dietary modification, physical activity >150 min a week, and losing 7% of the individual's body weight.
 - Metformin is as effective as lifestyle modification in prevention of T2D in women with BMI > 35, age below 60, and a history of GDM
 - DSME is an effective tool to develop behaviors that can prevent and delay of onset of T2D, especially in the presence of aberrant psychosocial conditions
 - To be most effective, education provided by DSME needs to be modified to take into

consideration the individual's age, culture, and psychosocial needs

- Diabetes and infertility
 - Insulin resistance is associated with menstrual changes and fertility disorders
 - Menstrual disorders related to insulin sensitivity may be resolved with adoption of recommended lifestyle modification/change
- Insulin, diabetes, and cancer
 - Hyperinsulinemia may promote mammary, ovarian, and colorectal carcinogenesis
 - DSME may be a tool to lower serum glucose levels with a resultant decrease in serum insulin concentrations
- Diabetes and depression
 - Women affected by or with a history of depression have a higher prevalence of diabetes
 - Early identification of insulin resistance with adoption of lifestyle modification/change may delay or prevent T2D

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