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## Gestational diabetes mellitus: postpartum opportunities for the diagnosis and prevention of type 2 diabetes mellitus

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### SUMMARY

Gestational diabetes mellitus (GDM) affects approximately 4% of all pregnant women in the US and represents 90% of all cases of diabetes mellitus diagnosed during pregnancy. In addition to the adverse pregnancy outcomes associated with this complication, a history of GDM predisposes women to the future development of type 2 diabetes mellitus (T2DM). Incidence rates of GDM are increasing in the US. As a consequence, a growing number of women are now at increased risk for T2DM. Opportunities to diagnose and prevent T2DM in women with a history of GDM include early diagnosis by postpartum screening and implementation of diabetes prevention measures. In this Review, we discuss current guidelines for postpartum screening, how they might be implemented, and who should take responsibility for screening individuals at risk of T2DM. In addition, we describe measures to prevent the onset of T2DM in women with a history of GDM, focusing on lifestyle modifications, such as diet and breast-feeding.

### Keywords

gestational diabetes mellitus; lactation; postpartum; screening; type 2 diabetes mellitus

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## INTRODUCTION

Gestational diabetes (GDM) is defined by the American Diabetes Association (ADA) as “glucose intolerance of any degree with onset or first recognition during pregnancy.”<sup>1</sup> GDM affects approximately 4% of all pregnant women in the US; however, estimates of prevalence rates vary from 1–14%.<sup>1</sup> Some of this variability relates to differences in the criteria used to diagnose GDM. The original diagnostic criteria for GDM were established by O’Sullivan and Mahan in 1964.<sup>2</sup> Since then, different interpretations of laboratory methods or the implications of GDM for perinatal outcomes have led to the development of several additional diagnostic criteria for GDM (Table 1).<sup>3–6</sup> Differences in the population studied can also contribute to the observed variability in disease prevalence, as higher rates of GDM are reported among racial and ethnic minorities than in non-Hispanic white populations.<sup>7,8</sup> Furthermore, incidence rates of GDM are increasing, which could reflect the increased prevalence of obesity<sup>9</sup> and type 2 diabetes mellitus (T2DM)<sup>10</sup> within the general population. Both obesity and a family history of T2DM represent important risk factors for the development of GDM.<sup>11</sup>

GDM is associated with adverse pregnancy outcomes, which include macrosomia and an increased Cesarean section rate.<sup>12</sup> In addition, a history of GDM is associated with an increased long-term risk for the development of T2DM.<sup>13,14</sup> Women who have experienced GDM have a 17–63% risk of developing T2DM within 5–16 years of the index pregnancy.<sup>15</sup> Furthermore, the Diabetes Prevention Program (DPP)<sup>16</sup> found that women with a self-reported history of GDM and postpartum impaired glucose tolerance had a 74% increased risk of developing T2DM when compared with a cohort of women without a history of GDM, even after adjusting for age. Factors associated with progression to T2DM include the degree of abnormality on glucose tolerance testing during pregnancy, gestational age at diagnosis of GDM, insulin use during pregnancy, and longer periods of postpartum follow-up to test for T2DM.<sup>15</sup> Pregnant women with high glucose levels have an elevated risk of delivering infants of increased birth weight, even when their glucose levels are below those diagnostic of GDM.<sup>17</sup> Glucose tolerance testing during pregnancy might, therefore, predict long-term risk for T2DM, even when the diagnostic criteria for GDM are not met. In addition to an increased risk of T2DM, it should also be noted that a small percentage of women with a history of GDM might develop type 1 diabetes mellitus postpartum, which would be assessed in the setting of symptoms of diabetes mellitus.<sup>18</sup>

Despite the high rates of progression of GDM to T2DM, and the availability of screening protocols, the majority of women with a history of GDM are not currently being screened. In addition, data from a number of studies suggest that it is possible to prevent and/or delay disease progression.<sup>19–21</sup> Nonetheless, diabetes prevention in women with a history of GDM is not widely undertaken. In this Review, we discuss current guidelines for postpartum screening and how they might be implemented in individuals with a history of GDM. We also describe possible strategies to prevent the onset of T2DM in high-risk women, with a focus on lifestyle modifications, such as patient education, diet and breast-feeding.

## POSTPARTUM SCREENING FOR TYPE 2 DIABETES MELLITUS

Several professional societies and organizations have provided recommendations for postpartum screening of women with a history of GDM. The ADA recommends screening for diabetes mellitus at 6–12 weeks postpartum by either measurement of fasting plasma glucose levels or with a 75 g oral glucose tolerance test (OGTT).<sup>22</sup> Women should be re-evaluated every 3 years if the results of these tests are found to be normal; however, if impaired glucose tolerance or impaired fasting glucose is detected they should then be screened annually. The American College of Obstetrics and Gynecology (ACOG) acknowledges that postpartum screening for T2DM might be performed at the time of the postpartum visit. By contrast to the ADA, however, ACOG does not clearly propose a recommendation for screening, citing the lack of long-term studies that support the benefits of postpartum testing.<sup>23</sup> The WHO recommends postpartum screening for T2DM at 6 weeks or more after delivery but does not provide recommendations for follow-up screening after this time.<sup>6</sup> The variable recommendations for postpartum screening and continued monitoring of T2DM risk (Table 2)<sup>22,23</sup> might, therefore, promote uncertainty among providers about the appropriate time and methods for screening, and so limit performance of screening protocols.

Given the discrepancies in these guidelines, it is not surprising that women with a history of GDM are not systematically screened for T2DM after delivery. Although ACOG does not clearly endorse a recommendation for postpartum screening, there is some evidence to suggest that providers who are members of ACOG are aware of the significance of such testing. A 1998 survey of Fellow and Junior Fellow members of ACOG found that only 60% of the respondents routinely performed postpartum evaluation of glucose tolerance in women with GDM, with 39% of respondents using the ADA-recommended 75 g, 2 h OGTT.<sup>24</sup> This survey also found that 62% of the respondents believed that women with GDM were at risk of T2DM after delivery.<sup>24</sup> A follow-up survey of ACOG Fellows, published in 2004, found that 75.0% of respondents performed routine postpartum screening, with 50.8% using the ADA-recommended 75 g, 2 h OGTT.<sup>25</sup> These self-reported screening rates are notably higher than those found in other studies that examined the actual postpartum screening rates.

Retrospective studies conducted in academic (i.e. medical school-affiliated) centers found that only 20–45% of women with GDM-complicated pregnancies had either a requisition for blood glucose testing or had undergone the ADA-recommended screening protocol for postpartum T2DM.<sup>26–29</sup> Several of these studies attempted to identify factors associated with low rates of postpartum screening. Attendance at the postpartum visit was the only significant predictor of postpartum screening in a retrospective, cohort study of women with GDM who received prenatal care in a maternal diabetes clinic.<sup>29</sup> The rate of ADA-recommended testing was almost four times higher in women who attended the postpartum visit than in those who did not attend (relative risk 3.74, 95% CI 2.14–6.52;  $P < 0.001$ ).<sup>29</sup> Moreover, even after controlling for demographic, clinical, and health-care characteristics that might influence testing, the screening rate remained three times higher in the women who attended the postpartum visit than in those who did not attend (relative risk 3.04, 95% CI 1.72–5.33;  $P < 0.001$ ).<sup>29</sup>

The low rate of postpartum screening reported in a study by Smirnakis *et al.*<sup>28</sup> was probably not a result of lack of access to postpartum care. Overall, 94% of the women enrolled in this cohort study underwent postpartum Papanicolaou testing, with a median time of 49 days from delivery to the first test. By contrast, only 37% of the women received postpartum glucose testing.<sup>28</sup> Kim *et al.*<sup>27</sup> undertook a study to examine the effect of physician counseling on postpartum screening. In a cohort of predominantly non-Hispanic white, college-educated, affluent women with a history of GDM, women who recalled receiving advice upon receipt of laboratory requisitions for glucose testing were significantly more likely to report receiving the ADA-recommended postpartum screening (adjusted odds ratio 2.07, 95% CI 1.51–2.84) and to have a postpartum OGTT documented by health insurance claims data (adjusted odds ratio 1.64, 95% CI 1.16–2.32) than were those women who did not recall receiving such advice.<sup>27</sup>

Other factors have also been found to be associated with limited postpartum screening, such as type of office setting, degree of provider specialization, and location of postpartum follow-up visit (Box 1). For example, Almario *et al.*<sup>26</sup> found that patients who received care at maternal–fetal medicine offices were more likely to complete postpartum screening than those women who received care at a private generalist office or a resident ambulatory clinic. Furthermore, Russell *et al.*<sup>29</sup> found that women whose postpartum visit was in a hospital-based clinic had a twofold higher likelihood of receiving the recommended postpartum glucose testing than women who attended a hospital-affiliated community clinic.

Confusion about who should assume responsibility for postpartum screening (the obstetrician–gynecologist or the primary care provider) could also contribute to the low rates of postpartum screening.<sup>29</sup> Some women might view their obstetrician–gynecologist as their primary care provider, whereas other women could also be under the care of a general internist. In addition, the specialists who care for women with GDM during pregnancy (maternal–fetal medicine specialists or endocrinologists) might not continue to follow them after delivery, which could result in missing the need for postpartum screening. Moreover, obstetrician–gynecologists might order T2DM screening in association with the 6-week postpartum evaluation. Women rarely attend this appointment after an overnight fast, however, and so are unable to undergo screening coincident with this visit. Potential communication challenges that obstetrician–gynecologists and primary care providers could encounter when implementing a referral for testing include lack of awareness of GDM diagnosis or postpartum T2DM risk, lack of knowledge of the need for postpartum T2DM screening, and lack of patient follow-up with their health-care provider.<sup>26</sup>

## PREVENTION OF TYPE 2 DIABETES MELLITUS

Several opportunities exist for the prevention of T2DM in women with a history of GDM, such as education about risk awareness, implementation of a healthy lifestyle, breast-feeding and pharmacotherapy.

### Risk awareness

Although GDM is a well-established risk factor for T2DM, many women with GDM could be unaware of this increased risk, which might affect compliance with risk-reduction

recommendations.<sup>30</sup> Feig *et al.*<sup>31</sup> conducted a survey of women within 3–5 years of a pregnancy that was either normal or complicated by GDM. When questioned about their risk assessment, 47% of the women with a history of GDM believed that it was “highly possible” or “very possible” that they would develop T2DM, whereas 35% believed it was “somewhat possible” and none reported that it was “not at all possible.”<sup>31</sup> By contrast, a study of women in an academic, managed-care plan revealed that, although 90% of women with a history of GDM were aware of the future risk of T2DM, only 16% believed that they specifically were at risk of developing this condition.<sup>32</sup> In addition, data from populations at high-risk of T2DM, such as Pima Indians<sup>33</sup> and Mexican Americans,<sup>34</sup> revealed that women in these groups did not believe that GDM posed any risks after pregnancy.

Interventions are clearly needed in order to increase awareness and acceptance of the personal risk for the development of T2DM in women with a history of GDM. Public education campaigns, such as that offered by the National Diabetes Education Program in the US,<sup>35</sup> could help to increase patient risk awareness. Moreover, the Centers for Disease Control and Prevention have held regional conferences and provide online information to enhance awareness of the health risks for women with a history of GDM.<sup>36</sup>

### Lifestyle modification

Lifestyle modifications have been shown to be successful in decreasing the progression to T2DM in several populations, including American,<sup>19</sup> Finnish<sup>20</sup> and Asian,<sup>21</sup> so it seems rational to consider similar interventions in women with a history of GDM. The ACOG<sup>23</sup> and the ADA<sup>37</sup> both recommend that women at increased risk for T2DM should be counseled about the benefits of diet, exercise, and weight reduction and/or maintenance in an effort to prevent the development of T2DM.

The DPP<sup>19</sup> clearly demonstrated that intensive lifestyle modification could reduce the incidence of T2DM in individuals with impaired glucose tolerance. Indeed, a 58% decreased incidence of T2DM was observed among those individuals who participated in lifestyle intervention compared with the placebo group, even though the mean weight loss was only 5.6 kg. A subset of the population who enrolled in the DPP—women with a self-reported history of GDM—lost less weight than the general DPP population but still experienced a 55% reduction in the development of T2DM with the lifestyle intervention when compared with those individuals in the placebo group.<sup>16</sup> Of note, however, this study was limited by the self-reporting of GDM and the fact that the diagnosis of GDM was not validated. In contrast to the DPP, which provided an intensive lifestyle intervention, appreciable weight loss was not observed in a study in which women with a history of GDM were simply informed about their risk for T2DM and the importance of lifestyle modification for weight loss.<sup>38</sup> Although 86% of the women enrolled in this study expressed concern about developing T2DM, only a few had changed their lifestyle and/or lost weight after pregnancy. Among the women with a prepregnancy BMI of more than 25 kg/m<sup>2</sup>, only 18% lost at least 5 kg whereas more than 33% had gained weight after delivery.<sup>38</sup>

Several studies have examined the effect of a healthy lifestyle in women after they give birth, but none has specifically assessed a healthy lifestyle intervention in women with a history of GDM.<sup>39</sup> In one such study, O’Toole *et al.*<sup>40</sup> found a 1-year postpartum weight

loss of 7.3 kg in a group of overweight women who received individualized diet and activity recommendations, maintained daily food and activity diaries, and participated in group education sessions. By contrast, a mean weight loss of only 1.4 kg was reported for those participants who did not receive this structured intervention.<sup>40</sup> Leermakers *et al.*<sup>41</sup> examined an intervention that comprised a combination of group sessions, nutrition information mailings, and telephone discussions. Participants who received this intervention were found to have lost more weight by 6 months postpartum than had participants in the control group (7.8 kg versus 4.9 kg, respectively). Postpartum studies of healthy diet and exercise plans should now be performed specifically in women with a history of GDM in order to determine the potential benefit and to evaluate the most effective way to achieve lifestyle modification in this population.

### Breast-feeding

Breast-feeding is associated with reduced blood glucose levels and a reduced incidence of T2DM among both women with a history of GDM<sup>42</sup> and women in the general population.<sup>43</sup> Lactation has also been associated with postpartum weight loss,<sup>44,45</sup> reduced long-term obesity risk,<sup>46</sup> and a lower prevalence of the metabolic syndrome.<sup>47</sup> Stuebe *et al.*<sup>48</sup> reported an inverse association between duration of breast-feeding and T2DM risk among parous women in the Nurses' Health Study and the Nurses' Health Study II. Among women who had given birth in the previous 15 years, there was a 15% decrease in the risk of T2DM for each year of lifetime lactation, even after adjusting for family history of diabetes mellitus, diet, exercise and BMI.

Most diet and exercise intervention studies that examined the effect of lactation on maternal weight loss revealed that women in the intervention groups lost more weight than did the women in the control groups.<sup>39</sup> In order to allay concerns that exercise and diet might compromise breast milk quality, several studies have assessed growth among breast-fed infants whose mothers were trying to lose weight.<sup>49</sup> Of note, no changes in infant weight or length trajectory were observed in the setting of maternal weight loss.<sup>50,51</sup> These data suggest that promotion of a combination of breast-feeding, diet and physical activity could diminish maternal diabetes risk without compromising infant growth, and might be particularly important in women with a history of GDM.

### Pharmacologic interventions

Several randomized clinical trials have specifically studied diabetes prevention with a pharmacologic intervention in women with a history of GDM. The Troglitazone in the Prevention of Diabetes (TRIPOD)<sup>52</sup> study examined the use of troglitazone or placebo in obese Hispanic women with a previous history of GDM (diagnosed by the 100 g OGTT). The authors found a 55% risk reduction in progression to T2DM in women who received troglitazone when compared with those who received placebo. The Pioglitazone in Prevention of Diabetes (PIPOD) study<sup>53</sup> enrolled women who had completed TRIPOD without developing T2DM. These women were randomly allocated to receive either pioglitazone or placebo for a period of 3 years. A 4.6% yearly incidence rate of T2DM was reported in the pioglitazone group. By contrast, the yearly incidence rate in the placebo group was 12.1%. Women with a history of GDM (albeit self-reported) who enrolled in the

DPP had an impressive response to treatment with metformin, which resulted in a 50% reduction in diabetes risk.<sup>16</sup> In the same study, however, treatment with metformin was associated with only a 14% diabetes risk reduction in women without a previous self-reported history of GDM. Although the results of these studies are promising, it should be noted that these medications are not currently approved by the FDA for use in diabetes prevention. Furthermore, additional studies are still needed to evaluate the relative efficacy and cost of these medications alone, or in combination, for the prevention of T2DM in women with a history of GDM.

## CONCLUSIONS

As the prevalence of GDM is increasing in the US, it is crucial to heighten postpartum vigilance for the development of T2DM through early postpartum and long-term screening for T2DM. In addition, women should be encouraged to adopt healthy lifestyle modifications, which focus on diet, exercise, and weight reduction and/or maintenance. Interventions that aim to decrease the risk of the progression of GDM to T2DM, such as a healthy lifestyle, breast-feeding and pharmacologic therapies, still require further evaluation.

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### Learning objectives

Upon completion of this activity, participants should be able to:

1. List negative health outcomes associated with gestational diabetes mellitus.
2. Identify protocols for screening for type 2 diabetes mellitus among women with a history of gestational diabetes mellitus.
3. Specify the effects of breast-feeding among women with a history of gestational diabetes mellitus.
4. Describe means to prevent incident type 2 diabetes mellitus among women with a history of gestational diabetes mellitus.

**Box 1****Barriers to postpartum screening in women with a history of gestational diabetes mellitus**

## Provider factors

- Uncertainty about screening recommendations
- Communication and acceptance of responsibility between obstetrician and primary care provider for ordering screening test
- Continued vigilance beyond immediate postpartum visit
- Office location and/or type (hospital-based or hospital-affiliated community clinic)
- Degree of provider specialization

## Patient factors

- Risk awareness
- Keeping screening visit appointment(s)

**KEY POINTS**

- Gestational diabetes mellitus is increasing in prevalence, paralleling the trends in obesity and type 2 diabetes mellitus
- Gestational diabetes mellitus places women at increased risk for the postpartum development of type 2 diabetes mellitus
- Screening for type 2 diabetes mellitus is recommended to be performed at the 6-week postpartum visit, with additional surveillance testing at regular intervals depending on the risk assessment
- Lifestyle modifications, such as a healthy diet, physical activity and breast-feeding, might serve to reduce, and potentially prevent, progression to type 2 diabetes mellitus
- Further study is needed to determine the efficacy of additional interventions, such as pharmacotherapy, that aim to enhance type 2 diabetes mellitus risk reduction in women with a history of gestational diabetes mellitus

**Table 1**

Diagnostic criteria for gestational diabetes mellitus.

Time point	Criteria (mmol/l)		
	ADA <sup>5,a</sup>	NDDG <sup>3,b</sup>	WHO <sup>6,c</sup>
Fasting	5.3	5.8	7.0
1 h	10.0	10.5	NA
2 h	8.6	9.1	7.8
3 h	7.8	8.0	NA

<sup>a</sup>Glucose tolerance test with 100 g of oral glucose. Two or more abnormal values are indicative of gestational diabetes mellitus. The 75 g, 2 h test can also be used with the same thresholds.

<sup>b</sup>Glucose tolerance test with 100 g of oral glucose. Two or more abnormal values are indicative of gestational diabetes mellitus.

<sup>c</sup>Glucose tolerance test with 75 g of oral glucose. Either an abnormal fasting glucose or 2 h glucose value is indicative of gestational diabetes mellitus.

Abbreviations: ADA, American Diabetes Association; NA; not applicable; NDDG, National Diabetes Data Group.

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Table 2

Recommendations for postpartum screening for type 2 diabetes mellitus in women with a history of gestational diabetes mellitus.

Organization	Immediate postpartum testing	Diagnostic method	Diagnostic criteria (glucose levels measured in mmol/l)	Subsequent testing	Additional comments or recommendations
ADA <sup>22</sup>	At least 6 weeks after delivery	FPG level or 75 g OGTT	Normal: FPG <5.6 and 2 h PG <7.8; IFG: FPG 5.6 but <7.0; IGT: 2 h PG 7.8 and <11.1; T2DM: FPG 7.0 or 2 h PG 11.1 or symptoms of T2DM and a random PG level 11.1	Reassess at a minimum of every 3 years if normal glucose tolerance is detected postpartum. Reassess annually if IFG or IGT is detected postpartum	All patients with a history of GDM should be educated about lifestyle changes, including: <ol style="list-style-type: none"> <li>i. maintenance of normal body weight through a healthy diet and physical activity;</li> <li>ii. avoiding medications that worsen insulin resistance;</li> <li>iii. seeking medical attention if symptoms of hyperglycemia develop.</li> </ol>
ACOG <sup>23</sup>	No specific recommendations, but suggest that testing should be performed at (or around) the time of the first postpartum visit	75 g OGTT might be more advantageous than FPG as the initial test	As per the ADA recommendations	FPG can be used in subsequent testing if both FPG and OGTT are normal postpartum	High-risk individuals should be counseled about diet, exercise and weight reduction or maintenance. Patients with IGT should be identified for future pregnancy counseling.
WHO <sup>6</sup>	6 weeks or more after delivery	75 g OGTT	Normal: FPG <6.1 and 2 h PG <7.8; IFG: FPG 6.1 and <7.0; IGT: 2 h PG 7.8 and <11.1; T2DM: FPG 7.0 or 2 h PG 11.1 or both IFG and IGT	Not detailed	Women are at increased risk of subsequent T2DM

Abbreviations: ACOG, American College of Obstetrics and Gynecology; ADA, American Diabetes Association; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test; PG, plasma glucose; T2DM, type 2 diabetes mellitus.