

Diagnosis, prevention and management of gestational diabetes mellitus



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Introduction

Gestational diabetes mellitus (GDM) is diabetes diagnosed during pregnancy that is not clearly type 1 or 2 diabetes.¹ Approximately 84% of hyperglycemia cases during pregnancy are due to GDM, while the remaining 26% are due to preexisting type 1 or 2 diabetes, which is defined as diabetes in pregnancy (DIP). The International Diabetes Federation indicates that 1 in 6 infants are born to mothers with some form of hyperglycemia during pregnancy.²

Accumulated evidence has shown that hyperglycemia during pregnancy not only increases perinatal morbidity and mortality in mothers and children but also increases the manifestation of disease later in life.² For example, women with GDM have a higher incidence of preeclampsia (PE), cesarean deliveries, and birth trauma. Their offspring are more likely to be large for gestational age and premature, and to have neonatal respiratory distress syndrome and congenital malformation. Moreover, both the mother and the offspring are

at a higher risk of obesity, type 2 diabetes mellitus (T2DM), and metabolic syndrome later in life. The main pathophysiological features are insulin resistance and hyperinsulinemia caused by excess maternal circulating glucose, lipids, and amino acids.³ It is important to know that the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) Study also indicated that mild hyperglycemia in pregnancy can cause poor outcomes and that the risks of poor outcomes directly correlated with maternal blood glucose levels but without clear inflection points.⁴

The risk factors for GDM include older age, family history of diabetes, overweight and obesity, excessive weight gain during pregnancy, poor history of pregnancy outcomes, and high-risk ethnicity group.⁵ China is a country with a high prevalence of diabetes. A national survey conducted by the China Noncommunicable Disease Surveillance Group reported that in 2010, the prevalence of diabetes in China reached 11.6%, which is much higher than the rates in 1994, 2000–2001, and 2007 (2.5%, 5.5%, and 9.7%, respectively).⁶ Furthermore, with the development of the social economy, the urbanization, the adoption of a Western lifestyle, and the gradual implementation of the two-child policy, an increasing number of Chinese women of reproductive age become pregnant at an advanced age, with overweight or obesity, a history of GDM, and a high risk of hyperglycemia during pregnancy.

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Screening for and treatment of GDM have a significant impact on cost-effectiveness estimates. Numerous studies have shown that the implementation of screening and intervention for GDM can reduce the risks of perinatal and, most likely, long-term diseases. Thus, the costs of diagnosis and intensive treatment of GDM permit significant monetary savings in terms of costs linked to maternal and neonatal morbidities.^{7,8} Thus, a focus on prevention, screening, early diagnosis, and management of GDM is of great importance.

Diagnosis of GDM

The International Federation of Gynecology and Obstetrics (FIGO) Initiative on Gestational Diabetes Mellitus in 2015 adopts and supports the recommendations of the International Association of Diabetes in Pregnancy Study Groups (2010) and the World Health Organization (WHO; 2013) on the diagnosis of GDM and the WHO (2013) criteria for the diagnosis of DIP.²

Specifically, GDM needs to be defined using a single-step 75-g oral glucose tolerance test (OGTT) between 24 and 28 gestational weeks or at any other period during pregnancy. When the fasting plasma glucose (FPG) level is 5.1–6.9 mmol/L (92–125 mg/dl) and/or ≥ 10.0 mmol/L (180 mg/dl) 1 h post 75-g OGTT and/or 8.5–11.0 mmol/L (153–199 mg/dl) 2 h post 75-g OGTT, GDM needs to be diagnosed.^{9,10} A diagnosis of DIP should be made at any time during pregnancy when the FPG level is ≥ 7.0 mmol/L (126 mg/dl) and/or the 2-h plasma glucose level is ≥ 11.1 mmol/L (200 mg/dl) after a 75-g OGTT or the random plasma glucose level is ≥ 11.1 mmol/L (200 mg/dl) with symptoms of diabetes.¹⁰ However, FIGO emphasizes that all countries need to consider resource settings, and adopt and promote pragmatic options to ensure highly cost-effective GDM screening and testing methods.²

The recommendation for testing and diagnosis of GDM published by the National Health and Family Planning Commission in China in 2014 was similar to the FIGO guidelines.⁵ However, China is a country with a vast territory and unbalanced distribution of health resources. Thus, to reduce the clinical economic burden, the two-step approach of screening with FPG level followed by a 75-g OGTT is recommended for low-resource rural areas. First, screening for FPG level should be performed between the 24th and 28th gestational weeks. If the FPG level is < 4.4 mmol/L (80 mg/dl), no further testing is needed. If FPG level is ≥ 5.1 mmol/L (92 mg/dl), GDM can be diagnosed without a 75-g OGTT. Only women with 4.4 mmol/

$L \leq \text{FPG} < 5.1$ mmol/L need to return for the 75-g OGTT. Based on this strategy, approximately one-half of the standard 75-g OGTTs in China can be potentially avoided.¹¹

Another study in China also showed that FPG levels of ≥ 5.1 mmol/L (92 mg/dl) in the first trimester could not be used to diagnose GDM. Only 37.0%, 52.7%, and 66.2% of women with FPG levels of 5.10–5.59, 5.60–6.09, and 6.10–6.99 mmol/L, respectively, in the first trimester developed GDM. Thus, the 75-g OGTT needs to be performed between the 24th and 28th gestational weeks to rule out GDM and women with 6.10 mmol/L \leq FPG levels < 7.00 mmol/L in the first prenatal visit considered as having GDM to be treated with diet and exercise. Meanwhile, women with 5.10 mmol/L \leq FPG levels ≤ 6.09 mmol/L should be considered a high-risk group for developing GDM and provided proper nutrition and exercise recommendation.¹²

Prevention and management of GDM

Planning and preparation before pregnancy

China is a country with a high burden of diabetes, and the age at onset of T2DM among women is decreasing. Furthermore, women of reproductive age usually do not receive regular physical examination or know their blood glucose levels. Thus, sometimes, hyperglycemia is already present at conception. Studies have shown that hyperglycemia during organogenesis can markedly increase the risk of spontaneous abortions and congenital anomalies, while satisfactory glycemic control could reduce these risks.¹ Thus, all women, especially women with diabetes, impaired glucose tolerance, impaired fasting glucose, and a history of GDM need to plan for pregnancy and seek pre-pregnancy counseling early. They should also have their blood glucose levels evaluated as early as possible to determine their glucose metabolism conditions; before pregnancy is the ideal time, but if this is difficult, evaluation should be done at least in the first prenatal visit. Women with diabetes who are planning pregnancy and those using insulin should control their hemoglobin A1c (HbA1c) levels at $< 6.5\%$ and $< 7.0\%$, respectively, to prevent hyperglycemia.¹³

All women are encouraged to adopt good dietary and lifestyle habits before pregnancy, especially those who are underweight or overweight/obese. As a woman's body mass index (BMI) prior to pregnancy is of high importance, both low and high BMIs are closely related to poor pregnancy outcomes.¹⁴ However, these are

modifiable risk factors. Zhang et al¹⁵ found that adherence to a low-risk lifestyle (healthy body weight, healthy diet, regular exercise, and non-smoking) before pregnancy is associated with a low risk of GDM [47.5%; 95% confidence interval (CI): 35.6–56.6%].

Lifestyle modification

Lifestyle modification is the first-line preventive strategy and management of GDM, which includes nutrition therapy and physical activity. It should be implemented throughout pregnancy, that is, prior to pregnancy, during pregnancy, and postpartum.

Nutritional therapy is an individualized food plan that limits carbohydrate consumption but offers adequate nutrition to maintain appropriate weight gain. For all pregnant women, especially women with GDM risk factors, GDM, and DIP, individual diet counseling needs to be provided repeatedly and advice should be given on the deficient and excess nutrients. Through nutritional education, women can understand the quantity and quality of food needed. Carbohydrate, protein, and fat intakes should account for 50–60%, 15–20%, and 25–30% of the daily dietary total energy, respectively.¹⁶ Potential beneficial factors for dietary structure include fruit, green leafy vegetables, poultry and fish, nuts, fiber, or a Mediterranean diet.^{14,17} The ideal calorie intake per day is 1800–2000 kcal and should not be <1500 kcal; otherwise, the risk of ketonemia will increase, thus affecting the development of the offspring's nervous system.² Fiber intake per day needs to be ≥ 28 g.² Moreover, the glycemic index (GI) of food is worthy of attention. Food with a high GI may show higher postprandial values, while food with a low GI may reduce postmeal glycemic excursion, birth weight, and the frequency of insulin use.¹⁸

Exercise has been recognized as an effective way of controlling weight gain and improving glucose homeostasis by enhancing insulin sensitivity.¹⁹ A recent meta-analysis, including 10 randomised controlled trials (RCTs), of physical activity and GDM from 1966 to 2014 showed that exercise intervention reduced the incidence of GDM by 28% [95% CI: 9–42%; relative risk (RR) = 0.72, $P = 0.005$] compared with the control. Moreover, Halse et al²⁰ showed that exercise during pregnancy may help to maintain daily postprandial normoglycemia in women with diet-controlled GDM. However, there is no unified and clear guideline for physical activity during pregnancy. Many organizations such as the American College of Obstetricians and Gynecologists, the Canadian Diabetes Association, and the Sports Medicine Australia recommend that for

women without contraindications to exercise, an accumulated time for moderate exercise of ≥ 30 min on most, if not all, days of the week (at least 150 min/week) is needed during pregnancy and the postpartum period. Before exercise therapy begins, pregnant women need to undergo a comprehensive physical assessment, and obtain professional and individualized exercise guidance.²¹ Aerobic activities and strengthening exercises involving large muscle groups are recommended. Sports involving risks of falling, trauma, or collisions should be avoided.²² Women need to monitor fetal activity and their blood glucose levels before and after exercise to ensure the safety of exercise and prevent the occurrence of hypoglycemia. Healthy eating and exercise habits should continue after delivery.

Medical therapy

When lifestyle modification is insufficient to maintain normoglycemia in women with GDM, drug treatment is needed. Current medication treatments of hyperglycemia during pregnancy include insulin therapy and oral antidiabetic agents (OADs).

Insulin is a traditional, safe, and effective medication treatment of GDM. Many kinds of insulin preparations are available, such as rapid-acting insulin (e.g., regular human insulin), intermediate insulin (e.g., neutral protamine hagedorn), and long-acting insulin (e.g., insulin detemir). Rapid-acting insulin usually works from 30-min or 1-h post subcutaneous injection, reaching its peak effectiveness between 2 and 4 h, and the effect can last for about 6–8 h. Intermediate insulin works for 1–2 h post subcutaneous injection, reaching its peak effectiveness between 4 and 8 h, and its effect can last for about 12–18 h. Long-acting insulin works for 3–4 h post subcutaneous injection, reaching its peak effectiveness between 8 and 10 h, and its effect can last as long as 20 h. Thus, it is beneficial to combine these insulin preparations to simulate the daily physiological insulin secretion. Insulin administration should start with a small dose, which should be gradually increased, and the insulin type and regimens should be individualized.

In the past, OADs were not recommended during pregnancy because of concerns about its teratogenic effects. However, many organizations now suggest that they be used as an adjunct therapy for GDM.^{23,24} In the United States, OADs have become the first option for drug treatment of hyperglycemia during pregnancy.²⁵ Glyburide and metformin are two more commonly used drugs. However, inconsistencies were found among studies in terms of the effects of insulin and OAD therapies. For example, some studies showed that

glyburide, metformin, and insulin had the same ability to control the fasting and postprandial blood glucose levels of women with GDM, and no significant differences in the incidence rates of adverse maternal and neonatal outcomes were found among them.^{26,27} However, a recent RCT showed that the failure rates of metformin and glyburide therapies for GDM were 25% and 23.8%, respectively, although the sample size was small.²⁸ Another study indicated that glyburide therapy could possibly increase the incidence of neonatal hypoglycemia and macrosomia, while metformin therapy was associated with a higher rate of preterm birth.²⁹ In addition, the FIGO emphasizes the lack of evidence on the long-term security of OADs.²

The FIGO recommends OADs because of their low cost, and easy and convenient administration. Thus, for pregnant women who refuse to use insulin or in areas with low insulin resources, OADs could be used as an alternative treatment.² However, no evidence-based medical research has been conducted to evaluate the effect of OADs on the management of GDM in Chinese pregnant women, and glyburide and metformin were not included in the registered medicines for treating GDM in China. Thus, we suggest that for Chinese women who reject insulin use during pregnancy, OADs could be used with caution and patient consent.

Postpartum follow-up

The postpartum period is also a crucial time span for the management of GDM. It is an important time to address intrapartum problems and initiate intervention for both the mother and the offspring, who are at increased risk of future obesity, T2DM, hypertension, and metabolic syndrome. The recommendation is to conduct the first postpartum follow-up at 6–12 weeks after childbirth. All women with hyperglycemia during pregnancy need to undergo the 75-g OGTT to evaluate their blood glucose levels. If their blood glucose levels meet the diagnostic criteria for diabetes or pre-diabetes at this point, they should be advised to see an endocrinologist and make follow-up visits every 1–3 years. Moreover, women with a history of GDM should ideally have an intrapartum interval of >1 year and plan to get pregnant. In addition, they need to undergo the 75-g OGTT prior to or at least in the early stage of next pregnancy.

Lifestyle intervention is also the most fundamental and effective method for postpartum management. Furthermore, metformin has been shown to be effective in preventing diabetes in women with hyperglycemia

during pregnancy. Ratner et al³⁰ randomized 350 women with recently diagnosed GDM to standard lifestyle and placebo or metformin therapy, or to lifestyle intervention group, and found that in the fourth year after childbirth, lifestyle intervention and metformin therapy can both reduce the incidence of diabetes by approximately 50% from that with the standard lifestyle and placebo.

Moreover, breastfeeding can also reduce the risk of type 2 diabetes in women with GDM. Gunderson et al³¹ conducted a prospective, observational cohort study of women with a history of GDM to evaluate lactation and the 2-year incidence of diabetes after GDM pregnancy. In their study, the incidence of diabetes after GDM pregnancy was inversely associated with lactation intensity, and the adjusted hazard ratios were 0.64, 0.54, and 0.46 for mostly formula or mixed/inconsistent, mostly lactation, and exclusive lactation in comparison with exclusive formula feeding, respectively (P for trend = 0.016). The longer the breastfeeding duration, the lower the 2-year incidence of diabetes after GDM pregnancy. In addition, a large clinical cohort study conducted by Bider-Canfield et al³² indicated that breastfeeding for ≥ 6 months was associated with a decreased risk of childhood overweight at age 2 years.

Currently, the postpartum follow-up rate is low worldwide, mainly owing to the lack of self-efficacy and social support, and the lack of professional knowledge among health providers.³³ Thus, obstetricians, internists, pediatricians, and other healthcare providers must cooperate to provide support for postpartum follow-up.

Conclusion

In conclusion, GDM is associated with a higher risk of adverse health outcomes for both mothers and offspring, not only during the perinatal phase but also in the long term. Thus, the prevention and management of GDM must be given enough importance throughout pregnancy, that is, prior to pregnancy, during pregnancy, and postpartum. Nutrition counseling and physical activity should be the primary and major strategies. If lifestyle modification alone fails to maintain normoglycemia, OADs and insulin should be considered. Postpartum care should not be overlooked, as it plays a critical role in the prevention of future chronic non-communicable diseases.

Conflicts of interest

There are no conflicts of interest to report.

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