

## Review article

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# Metabolic alterations in pregnant women: gestational diabetes

**Abstract:** Gestational diabetes mellitus (GDM) and controversy are old friends. The impact of GDM on maternal and fetal health has been increasingly recognized. Nevertheless, universal consensus on the diagnostic methods and thresholds has long been lacking. Published guidelines from major societies differ significantly from one another, with recommendations ranging from aggressive screening to no routine screening at all. As a result, real-world practice is equally varied. This article recaps the latest evidence-based recommendations for the diagnosis and classification of GDM. It reviews the current evidence base for intensive multidisciplinary treatment of GDM and provides recommendations for postpartum management to delay and/or prevent progression to type 2 diabetes.

**Keywords:** diagnosis; gestational diabetes; metabolic alterations; treatment.

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## Introduction

Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy or as carbohydrate intolerance of variable severity diagnosed during pregnancy, which may or may not resolve afterward (1). The GDM increases the risk of complications for both mother and child during pregnancy, childbirth, and beyond. Current evidence proposes that early

detection and treatment of disease improve outcomes for both mother and child (2). The GDM is the most common metabolic complication during pregnancy associated with an increased risk of maternal (preeclampsia, hypertension, cesarean section) and neonatal death (macrosomia, birth injury, hypoglycemia, hyperbilirubinemia, hypocalcemia, respiratory distress syndrome) (3). The experience and clinical knowledge of potential risks is essential to provide adequate health care to both mother and baby (4).

The consensus on the classification established as a main groups: type 1 diabetes (T1D), type 2 diabetes (T2D), and GDM (4).

T1D is the classification established for insulin-dependent diabetes associated with the  $\beta$  cell's autoimmune destruction of the islets cells of the pancreas, which leads to insulin deficiency. Markers are often found in the immune destruction of  $\beta$  cells in the islets, including anti-islet cell, anti-insulin, and anti-glutamic acid decarboxylase. This type affects a young population (younger than 25 years) (4, 5).

T2D is the classification set for non-insulin-dependent diabetes associated with insulin resistance. The mechanisms that lead to their appearance are insulin resistance and lack the progressive glucotoxicity insulin. Environmental factors such as obesity, sedentary lifestyle, stress, and diet low in fiber and rich in unsaturated fats have an important role in these mechanisms. This occurs more often in obese adults (older than 35 years) (4, 5).

GDM is defined as glucose intolerance detected during pregnancy. This group of female patients requires further evaluation after pregnancy because this group may include patients not diagnosed with T2D in a previous pregnancy and pregnant women in whom the disease is detected during the third trimester of pregnancy, after a glucose tolerance test (4). This condition has evolved from a diagnosis related with metabolic risk T2D and with a clinical condition associated with increased risks for maternal and perinatal morbidity. T1D and T2D pre-pregnancy are associated with early and late complications in pregnancy, including metabolic complications of the newborn. Meanwhile, GDM is associated with complications in the second half of pregnancy, including also the metabolic complications of the newborn (4).

The ethnic composition of each population group has different rates of T1D and T2D patients. More than 80% of the population with diabetes in the world have T2D. Nordic European and Anglo-Saxon populations have higher rates of T1D. However, Hispanic, Asian, and African populations exhibit higher rates of T2D (4).

The International Association of Diabetes and Pregnancy Study Group (IADPSG) recommends a 75-g oral glucose tolerance test (OGTT) between the 24th and the 28th week of gestation for all women who were not previously diagnosed with diabetes by random testing or a fasting plasma glucose test in the first prenatal visit, with GDM diagnosed according to the IADPSG. The World Health Organization (WHO) protocol is more complete and simple: a glucose tolerance test between the 24th and the 28th week of gestation for all pregnant women exposed to the risk factors for GDM or abnormal fasting plasma glucose (2).

Under the aforementioned guidelines, all studies recommend that all pregnant women with undiagnosed diabetes should undergo an OGTT between the 24th and the 28th week of gestation. However, the interpretation of the results is a significant change. Unlike the criteria of the WHO, the IADPSG guidelines state that an abnormal value after 1 h or after 2 h of fasting can be used for diagnosis of GDM. However, it is suggested that an abnormal OGTT value after 1 h is sufficient. Additionally, unlike the guidelines of the American Diabetes Association (ADA), a single abnormal value is suitable for the diagnosis of GDM (6).

Diabetes treatment in pregnant women is a continuous medical challenge until now, although the prognosis has changed from the earlier times, when the only management was diet modification and maternal survival was unpredictable, to the time when insulin has become available as treatment and maternal survival is the rule, rather than the exception.

The diagnosis of GDM has cost implications. The largest expenditures occur when the number of diagnosed cases increases. The costs include the care provided by nurses, dietitians, and physicians, as well as regular monitoring of glucose and diabetes therapy (7).

## Epidemiology

Despite the growing recognition of the impact of GDM on maternal and fetal health, the universal consensus on the diagnostic methods and parameters for the GDM are far from being achieved (6).

Although the carbohydrate intolerance usually disappears after delivery, one-third of women affected remain with diabetes or altered glucose metabolism postpartum.

It is estimated that 15%–50% of women will develop diabetes in the coming decades after pregnancy (8).

The prevalence of GDM remains a matter of discussion, although it is a common metabolic disorder during pregnancy. The prevalence in the general population is varied and may depend on the country of origin, the nature of the population, and the diagnostic criteria used (3, 9). Spanish and non-Caucasian women have a particularly high risk for diabetes after GDM (8).

A current study from Canada showed that its incidence is 3.3% (9). GDM affects about 5% of pregnant women in England and Wales annually (10). The prevalence of GDM in the USA is 5%, reaching the limit of 14% in high-risk populations, affecting about 135,000 women per year (3, 9, 11).

However, this fee may vary due to the differences in the method of data selection, low response rates, random selection of women, and lack of uniformity of the diagnostic criteria in studies (3).

## Risk factors

There are several factors that increase the risk of developing GDM. These factors are (12) a previous diagnosis of GDM or prediabetes, decreased glucose tolerance, or a change in fasting plasma glucose; family history, i.e., first-degree relatives with T2D; maternal age, with the risk increasing with age (especially for women aged older than 35 years); ethnicity, with African-Americans, Afro-Caribbeans, Native Americans, Hispanics, Pacific Islanders, and South Asians being at a greater risk for developing GDM; overweight, obesity, or severe obesity, which increases the risk of development of GDM in 2.1, 3.6, and 8.6, respectively; excessive fetal growth, polyhydramnios, hypertension, or preeclampsia in the current pregnancy; children with a high birth weight in previous pregnancies (>90th percentile or >4000 g); background obstetric fetal death, neonatal macrosomia, or GDM (13); smoking, with women who smoke having twice the probability to develop GDM; polycystic ovary syndrome; and short stature (14).

However, about 40%–60% of women with GDM are not exposed to any risk factor, and most show no symptoms; for these reasons, it is necessary to carry out screening on all pregnant women (12).

## Metabolic alterations

During pregnancy, there are complex endocrine-metabolic adaptation processes, which include insulin sensitivity,

increased  $\beta$ -cell response, moderate increase in blood glucose levels, and change in free fatty acids (FFA) levels, triglycerides, cholesterol, and phospholipids. However, these changes do not induce a pathological condition; rather they reflect the necessary metabolic adaptation for the normal fetus development. These changes are also important to prepare the maternal organism for delivery and lactation.

In healthy pregnant women, glucose homeostasis is maintained despite insulin resistance through a compensatory increase in insulin secretion. This increase is associated with a hypertrophy and hyperplasia of  $\beta$  cells (15).

These changes are triggered and maintained by placental hormones. The maladjusted  $\beta$  cell is likely to contribute to the development of gestational diabetes. The inability to compensate for insulin resistance may reflect changes in intrinsic  $\beta$  cells, such as glucokinase mutations (16), or extrinsic mechanisms, such as an autoimmune process (<10%) (17). However, most cases fail to recognize an identifiable cell change. In both GDM and T2D, intolerance to carbohydrates is developed when  $\beta$  cell secretion is no longer sufficient to compensate for insulin resistance (18).

Besides the changes in glucose homeostasis, pregnant women with previous GDM are more prone to hypertension, hyperlipidemia, ECG changes, and mortality (19). In 1996, Meyers-Seifer and Vohr (20) reported that total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, blood glucose, and systolic blood pressure were significantly higher in women with GDM, suggesting a condition similar to metabolic syndrome that occurs in these women.

## Glucose metabolism

Until the third month of pregnancy, fasting plasma glucose remains constant. Thereafter, the plasma glucose tends to decrease, 10–15 mg/dL, in the presence of increased concentration plasma insulin. Simultaneously, endogenous glucose production (EGP) is increased by 16%–30% (21) in order to meet the energy requirement. The increase in EGP is almost completely derived from gluconeogenesis. Similar to T2D, increased levels of circulating FFA may contribute to the supporting gluconeogenesis. However, while high plasma FFA levels may reduce glucose oxidation in T2D (22), during physiological pregnancy, the latter is not reduced, rather it is increased (23). This suggests that active gluconeogenesis during pregnancy is likely to be the direct consequence of the hormonal profile rather than the changes in the metabolic environment.

Although the basal plasma glucose levels tend to decrease with the progression of pregnancy, the plasma glucose levels after meal ingestion are higher and with a longer durability due to impaired insulin-mediated glucose utilization, EGP suppression, and inadequate increase in first-phase insulin secretion. It is the exacerbation of these mechanisms that also leads to GDM. In these women, basal EGP increases similarly in patients with GDM and in control women throughout gestation. At the end of the pregnancy, insulin suppression of EGP is less effective in patients with GDM than in control subjects (24), possibly due to a more severe resistance of the liver to the suppressive effect of insulin. Therefore, postprandial hyperglycemia is the most common initial abnormality of glucose homeostasis in GDM, due to the loss of early insulin release, thus contributing to the loss of glucose tolerance. The loss of first-phase insulin release is seen as a marker of the deterioration of the  $\beta$ -cell function and as a defect in insulin secretion, which has been reported by a number of investigators (25, 26). When analyzed as a function of concomitant insulin action, a 67% reduction in pancreatic  $\beta$ -cell compensatory effect was found in women with GDM (27), as compared with normal pregnant women (26).

## Insulin secretion

Insulin secretion increases continuously from the first until the third trimester of the pregnancy, where it reaches a maximum secretion, returning to normal after delivery, in both women with normal pregnancy and with GDM (24, 28). The insulin response to the oral glucose ingestion is associated with a 120% increase in first-phase insulin secretion by the 12th–14th gestational week. The second-phase insulin secretion does not seem to be affected, at least in the first weeks of pregnancy (29). The absence of an increasing rapid phase of insulin secretion characterizes the development of GDM (24). The insulin response after an intravenous glucose tolerance test is increased, compared with the values observed before and after pregnancy, but in women with GDM, there is an unusual loss of first-phase insulin secretion (29–31). These observations are in accordance with the observed delay in the peak concentration of insulin after an oral glucose intake in GDM (31).

## Lipid metabolism in GDM

During pregnancy, metabolic changes occur in the liver and the adipose tissue, which has a great impact on

triglycerides, fatty acids, cholesterol, and phospholipids. After an initial reduction during the first 8 weeks of pregnancy, the plasma levels of lipids tend to increase.

Cholesterol is used in the placenta for the synthesis of steroid hormones, whereas fatty acids are oxidized and used for the synthesis of the cell membrane. Changes in total cholesterol leads to modifications in various lipoprotein fractions. High-density lipoprotein (HDL) cholesterol increases from the 12th week, due to an increase in estrogen, and remains high throughout the gestational period. The total and LDL-cholesterol levels progressively increase in the second trimester. A similar behavior occurs for the plasma levels of very low-density lipoprotein (VLDL) and triglycerides. The triglycerides are increased not only in VLDL but also in LDL and HDL. These changes are most likely explained by an increase in synthesis as well as a reduced clearance of triacylglycerol. It is very probable that the decrease in insulin sensitivity may also contribute to the increase in triglyceride concentration. An increase in VLDL-triacylglycerols is associated with a fast transfer of triglycerides toward HDL by cholesterol ester transfer protein. Accordingly, the decreasing hepatic lipase activity leads to the formation of larger HDL particles, which are rich in triacylglycerols and have a low density (32). At the same time, LDL particles become richer in triacylglycerols (33, 34), become smaller, and have a higher density. These specific changes may induce damage in pregnancy through the activation of atherogenesis. The lipid profile in GDM is similar to that accompanying insulin resistance, such as in metabolic syndrome. Pregnant women with GDM have increased triacylglycerol levels and low LDL-cholesterol levels, compared with healthy pregnant women. The FFAs in the circulation are also increased, a factor that contributes to insulin resistance, which contributes to the development of fetal macrosomia as well, as they can pass through the placenta (35).

## Women and fetus implications

The GDM is a risk to both the mother and the child. This risk is connected to high levels of glucose in the blood and potentiation of their consequences and can happen not only during pregnancy and birth but also during the lifetime of the mother and the child (36).

The Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study confirmed that 23,000 women from 15 different countries who have undiagnosed hyperglycemia during pregnancy are at an increased risk of giving birth to babies with macrosomia (fetal

weight >4000 g), neonatal hyperinsulinemia (reflected in high levels of C-peptide in the umbilical cord), neonatal hypoglycemia, preeclampsia, and lesions at birth, including fractures and nerve paralysis (1, 9). Macrosomia may affect 12% of normal pregnant women, as compared with 20% of pregnant women with GDM (1). The pathological mechanism of GDM leads to complications known as the Pedersen hypothesis. The Pedersen hypothesis states that high maternal glucose leads to increased glucose transport across the placenta. The fetal pancreas responds to the glucose load, thus increasing insulin secretion. Fetal hyperinsulinemia leads to an extreme fetal growth, as the insulin acts as a growth factor. After birth, fetal hyperinsulinemia may continue for some time, increasing the risk of neonatal hypoglycemia, and this may require monitoring of neonatal blood glucose levels and other interventions to reverse the hypoglycemia (1, 6, 9).

The long-term complications for babies whose mothers have experienced GDM include twice the risk of developing childhood obesity and an increased risk of developing T2D in adulthood (9).

The HAPO study established the association between GDM and several adverse outcomes, including excess birth weight, cesarean section, neonatal hypoglycemia, shoulder dystocia, birth injury, preeclampsia, premature delivery, and neonatal hyperbilirubinemia (9).

When GDM is controlled with diet, exercise, and monitoring of glucose levels, the risk of complications at birth is significantly reduced. The traditional setting of GDM involves women without previous knowledge of diabetes, particularly T2D. The results of T2D in pregnancy are as bad, if not worse, as those in T1D. These poor outcomes include high rates of birth defects and perinatal death (1).

Pregnant women with GDM often develop long-term T2D, as GDM masks the  $\beta$  cells' failure to compensate for insulin resistance during pregnancy (1).

A preconception blood glucose analysis is recommended for women with a history of GDM, as the probability of disease recurrence is between 30% and 50% (37). These women should be advised to perform blood glucose tests at the beginning of future pregnancies, preferably around the 16th and 18th week of gestation (9).

## Diagnosis

The diagnosis of GDM involves two distinct temporal phases: fasting glucose at the first prenatal surveillance



visit (screening) and OGTT. This test is recommended by the WHO and the ADA and must be applied in a standardized manner to minimize variability. According to the WHO norms, the test should be performed between the 24th and 28th week of gestation. However, if pregnant women have some risk factors and/or have a positive screening test, tolerance test may be done sooner (37, 38).

### Fasting plasma glucose at the first prenatal surveillance visit

A fasting plasma glucose test must be performed on all pregnant women during their first surveillance visit. The value obtained should be interpreted as follows: (i) a fasting plasma glucose value of <92 mg/dL (5.1 mmol/L) is considered normal but should be followed by an OGTT with an overload of 75 g glucose between the 24th and the 28th week of gestation; (ii) a fasting plasma glucose level between  $\geq 92$  mg/dL (5.1 mmol/L) and <126 mg/dL (7.0 mmol/L) indicates a positive diagnosis of DGM and it is not necessary to perform OGTT with 75 g of glucose between the 24th and the 28th week of gestation; and (iii) a fasting plasma glucose value  $\geq 126$  mg/dL (7 mmol/L) or a casual plasma glucose value >200 mg/dL (11.1 mmol/L) indicates probable diabetes before pregnancy and is first diagnosed in the current pregnancy. This value should be confirmed on a second occasion, on a different day, with another or a casual plasma glucose fasting glucose. These pregnant women should be treated and followed-up as women with prediabetes. According to current WHO recommendations, an HbA1c value  $\geq 6.5\%$  should be interpreted as a diagnostic criterion for probable diabetes. However, this test should not be included among those performed in the surveillance of low-risk pregnancies (37).

### Oral glucose tolerance test

OGTT should be performed on all pregnant women, excluding those who have been previously diagnosed with GDM or probable prediabetes. OGTT is preceded by 3 days of regular exercise and a non-restrictive diet containing 150 g carbohydrates daily. Glucose (75 g, diluted in 300 mL of water) is orally taken in the morning after a fast of at least 8 h but not exceeding 14 h, with blood glucose determinations at 0, 1, and 2 h. During the test, the woman should remain at rest. The diagnosis of GDM is obtained when one or more values are greater than or equal to the reference values reported in Table 1.

	Fasting plasma glucose
Normal	<92 mg/dL (5.1 mmol/L)
GDM	$\geq 92$ mg/dL (5.1 mmol/L)
	<126 mg/dL (7.0 mmol/L)
Treated as prediabetes	$\geq 126$ mg/dL (7 mmol/L)
	>200 mg/dL (11.1 mmol/L) occasional
	HbA1c $\geq 6.5\%$ <sup>a</sup>

**Table 1** Fasting plasma glucose: normal, GDM, and prediabetes reference values.

<sup>a</sup>This examination is not included in the surveillance test of pregnancy.

If the result of the OGTT is below the reference values described in the table, the test is considered negative. According to the recommendations, OGTT should not be routinely performed before the 24th and the 28th week of gestation because of the lack of consistency among the results during in this period. The current GDM diagnosis scheme does not consider a repeated OGTT in third trimester of pregnancy. Pregnant women who only begin surveillance pregnancy after the 28th week should undergo the test using the new diagnostic strategy of GDM: first perform fasting plasma glucose and if it is <92 mg/dL (5.1 mmol/L), perform an OGTT loaded with 75 g of glucose (37).

## Treatment

The main goal of the GDM's treatment is to keep the blood glucose controlled, leading to improvements in pregnancy, such as reductions in macrosomia, clinical neonatal hypoglycemia, and cesarean section rates.

### Non-pharmacological treatment

Most pregnant women with GDM can successfully control blood glucose levels through lifestyle changes and by following a diet and exercise plan.

#### Diet and nutrition

Pregnant women with a diagnosis of GDM should be directed to a nutritionist; their sugar consumption should be decreased, while lean protein and vegetable consumption should be increased. The nutritional recommendations for pregnant women with GDM are different from the recommendations for non-pregnant women with DGM,

as the diet of pregnant women with GDM contains more protein and fat. In pregnant women with GDM, 75%–80% are able to maintain normal levels of glucose through dietary changes.

### Caloric distribution

For caloric distribution, most of the programs suggest three meals and three snacks, distributed throughout the day. However, in pregnant patients with obesity or overweight, snacks are eliminated. The recommended daily caloric distribution is as follows: breakfast, approximately 10% of the total calories assigned (because insulin resistance is higher in the morning); lunch, about 30% of calories; dinner, no more than 30% of calories. Snacks throughout the day should represent 30% of calories. The caloric recommendations by nutrient is that major diet components should be fats (~40%) and carbohydrates (~40%) followed by proteins (20%) (37).

### Physical exercise

The main objective of exercise in the GDM is to decrease glucose intolerance through cardiovascular conditioning, which causes an increase in the affinity of insulin to its receptor by decreasing intra-abdominal fat, an increase in glucose transporter sensitivity to insulin on muscle, an increase in blood flow in insulin-sensitive tissues, and a decrease in FFA levels (37, 39). Moderate physical exercise (1 h per day) is recommended to all pregnant women. However, the intensity and type of exercises should be adapted to avoid security problems for pregnant women.

### Glucose monitoring in pregnant women at home

Pregnant women should be asked to report the results of their glucose measurements after 1 week of monitoring at home and every 2–3 weeks until delivery. Pregnant women should be informed if there are changes to their treatment based on these results (39) (Table 2).

Time, h	Plasma glucose
0	<92 mg/dL (5.1 mmol/L)
1	≥180 mg/dL (10.0 mmol/L)
2	≥153 mg/dL (8.5 mmol/L)

**Table 2** Plasma glucose levels at different times.

## Pharmacologic treatment

Pharmacological treatment is initiated when the changes in lifestyle are not enough to achieve acceptable levels of glucose. However, the glucose level at which the benefits of pharmacotherapy clearly outweigh its disadvantages or harm has not yet been clearly established.

Older recommendations such as those from the American College of Obstetricians and Gynecologists in 2001 suggest that pharmacotherapy should be initiated when fasting plasma glucose is  $\geq 95$  mg/dL, 1-h postprandial plasma glucose is  $\geq 130$ –140 mg/dL, or 2-h postprandial plasma glucose is  $\geq 120$  mg/dL (39, 40).

### Insulin therapy

There are many forms of insulin to treat diabetes. How fast they start to work and how long their effects last classify them in rapid acting (insulin lispro, insulin aspart and insulin glulisine), short acting (regular insulin), intermediate acting (NPH insulin) and long acting (insulin glargine, insulin detemir). Insulin lispro, which is analogous to human insulin (peaking action after an hour of injection), has been shown safe during pregnancy, with no significant increase in birth defects, and significantly improving the postprandial glycemic control and long-term glycosylated hemoglobin. However, there are no differences in relation to the regular insulin and perinatal outcome (39).

## Prevention

Women with GDM have a 70% higher incidence of T2D than the rest of the population. Depending on ethnicity, the rate of progression of GDM to T2D ranges from 50% to 70% over 5–10 years of follow-up. Consequently, the continuous monitoring and annual screening for the detection of diabetes is important because it means the prevention of the disease (10).

Preconception care is crucial when planning to become pregnant, and women must pay close attention to their blood glucose levels (37). Pregnant women diagnosed with GDM should be encouraged to practice a better lifestyle by increasing their physical activity, having better eating habits, and maintaining ideal body weight. These women should be advised to perform tests for diabetes every 1–3 years (9, 41).

Recent data from the Diabetes Prevention Program suggest that lifestyle interventions are equally effective in reducing the risk of progression to T2D, approximately 50% (10).

In the long term, the ADA recommends that women with GDM in a previous pregnancy should screen for

diabetes every 3 years after obtaining normal postpartum results and annually if postpartum results are high.

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