GESTATIONAL DIABETES

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1. DEFINITIONS

- **Gestational Diabetes (GDM):** is defined as any degree of glucose intolerance with onset or first recognition during pregnancy, regardless of the need for insulin treatment, the grade of metabolic alteration, or its persistence after delivery. A patient who has been diagnosed with gestational diabetes should be screened for diabetes in the postpartum period.

- **Overt diabetes during pregnancy** (not previously diagnosed) or **frank diabetes:** pregnant women who present hyperglycaemia at the initial visit for prenatal care. The International Association of Diabetes and Pregnancy Study Groups (IADPSG) establishes the diagnosis when:

    - Fasting plasma glucose ≥ 126 mg/dL (7.0 mmol/L)
    - HbA1C ≥ 6.5% (47.5 mmol/mol)
    - Random plasma glucose ≥ 200 mg/dL (11.1 mmol/L)

2. PATHOGENESIS

Glucose metabolism during second trimester of normal pregnancy is characterized by:

- Increased peripheric insulin resistance, due to high plasma levels of diabetogenic placental hormones, such as prolactin, placental lactogen, progesterone, and cortisol. These adaptations start in mid-pregnancy and reach their maximum at 32 weeks.
- Higher energy needs and therefore increased insulin requirements, essential for weight gain.
- Impaired glucose tolerance due to insulin resistance.

Patients who develop gestational diabetes lack adequate mechanisms to compensate for the considerable physiological changes of pregnancy and, consequently, both postprandial hyperglycaemia and fasting hypoglycaemia appear.

3. CLINICAL IMPLICATIONS

It is estimated that gestational diabetes affects around 7-10% of all pregnancies worldwide, although actual prevalence is hard to estimate. Management of gestational diabetes is usually less complicated than for pregestational diabetes, but this condition is not exempt from risks. Acute maternal complications are rare as the pancreatic insulin reserve is not impaired. Human embryogenesis is not affected in gestational diabetes as hyperglycaemia appears after organogenesis is complete.

Short-term health risks include:

- Preeclampsia.
- Macrosomia (excessive birth weight) or a large for gestational age foetus. These conditions dramatically increase the risk of birth trauma.
- Polyhydramnios.
- Stillbirth (especially between 36 and 42 weeks of pregnancy)
- Neonatal morbidity: hypoglycaemia, hypocalcaemia, hypomagnesaemia, polycythaemia, respiratory distress, and risks associated with maternal hyperglycaemia.
- Organomegaly that affects the liver and spleen.
- Patients who experience hyperglycaemia during organogenesis present a higher risk of miscarriage and congenital anomalies.

Long-term health risks, after delivery:

- Higher risk for developing type II diabetes mellitus.
- Increased risk of obesity, glucose intolerance, and metabolic syndrome in the offspring.

4. RISK FACTORS

Risk factors for developing gestational diabetes include:

- Advanced maternal age (>35 years old)
- Obesity (defined as BMI >30 kg/m^2 or >27 kg/m^2 in the Asian population)
- Previous gestational diabetes or conditions that involve impaired glucose tolerance, such as acanthosis nigricans or polycystic ovary syndrome.
- High suspicion of a previous undiagnosed gestational diabetes (e.g. neonatal birth weight >4000 gr)
- Ethnicity: South-Asian, Latin-American and North-African women are more likely to develop GDM.

Patients who present >1 of the risk factors mentioned above **should be tested in the first trimester** for gestational diabetes, using **fasting plasma glucose (FPG) levels.**

5. DIAGNOSIS

During their first prenatal visit, patients who show glucose levels that meet the criteria for diabetes mellitus (not gestational) should be diagnosed with frank diabetes or overt diabetes during pregnancy and managed according to pregestational diabetes guidelines.
A fasting plasma glucose level ≥ 126 mg/dL (7.0 mmol/L) measured in two occasions, or a random plasma glucose level ≥ 200 mg/dL (11.1 mmol/L) establish the diagnosis with no need for further confirmation tests.

5.1 First trimester screening for gestational diabetes:
Patients who present ≥1 risk factor for GDM in their first prenatal visit should be screened in the first trimester using a fasting plasma glucose test. Cut-off values are as follows:

- FPG <92 mg/dl or 5.1 mmol/l is considered normal and the patient will undergo universal screening in the second trimester.
- FPG 92-125 mg/dl or 5.1-9.6 mmol/l is considered out of range and will require a confirmation test with a 100-gram oral glucose tolerance test (OGTT).

- FPG >125 mg/dl or 7.0 mmol/l is diagnostic for overt diabetes mellitus and a confirmation test is not required. The patient must start follow-up by an endocrinologist.

5.2 Universal gestational diabetes screening

As most pregnant women are not going to present the aforementioned risk factors, a two-step screening approach for gestational diabetes is recommended:

5.2.1 First step: universal screening at 24-28 weeks.

O´Sullivan test: oral administration of 50 g of glucose and measurement of increases in glycemia after 60 minutes. Fasting is not required. If glycaemia after 60 min is > 140 mg/dl (7.8 mmol/l), the result is considered positive and then we should proceed to the second step.

In some cases, this first step of diagnosis (O´Sullivan) should be skipped and an OGTT should be performed directly:

- Pregnant women who were not able to get an O´Sullivan test during the second trimester.
- Patients with a negative result for O'Sullivan in the second trimester who develop complications related to GDM later in pregnancy (large for gestational age foetus, polyhydramnios, etc.).
- Patients who tested positive for O'Sullivan already in the first trimester of pregnancy.

5.2.2 Second step: 100-gram oral glucose tolerance test (OGTT)

Women who test positive for the O´Sullivan should undergo a 100-gram OGTT. This involves measuring FPG and plasma glucose at 60, 120, and 180 minutes after oral intake of a 100-gram glucose solution.
A well-performed OGTT requires:

- Overnight fasting of at least 8 hours.
- The patient must be sitting down and at rest until all glucose measurements are complete.
- No smoking, at least during the test.
- A preparatory three-day diet containing at least 150 g of carbohydrates per day (restricting carbohydrates might cause false positives in OGTT).

National Diabetes Data Group (NDDG) criteria use is recommended. Gestational diabetes is diagnosed when **two or more values exceed** the following thresholds:

- FPG ≥ 105 mg (5.8 mmol/l)
- 1h: ≥ 190 mg/dl (10.6 mmol/l)
- 2h: ≥ 165 mg/dl (9.2 mmol/l)
- 3h: ≥ 145 mg/dl (8.1 mmol/l)

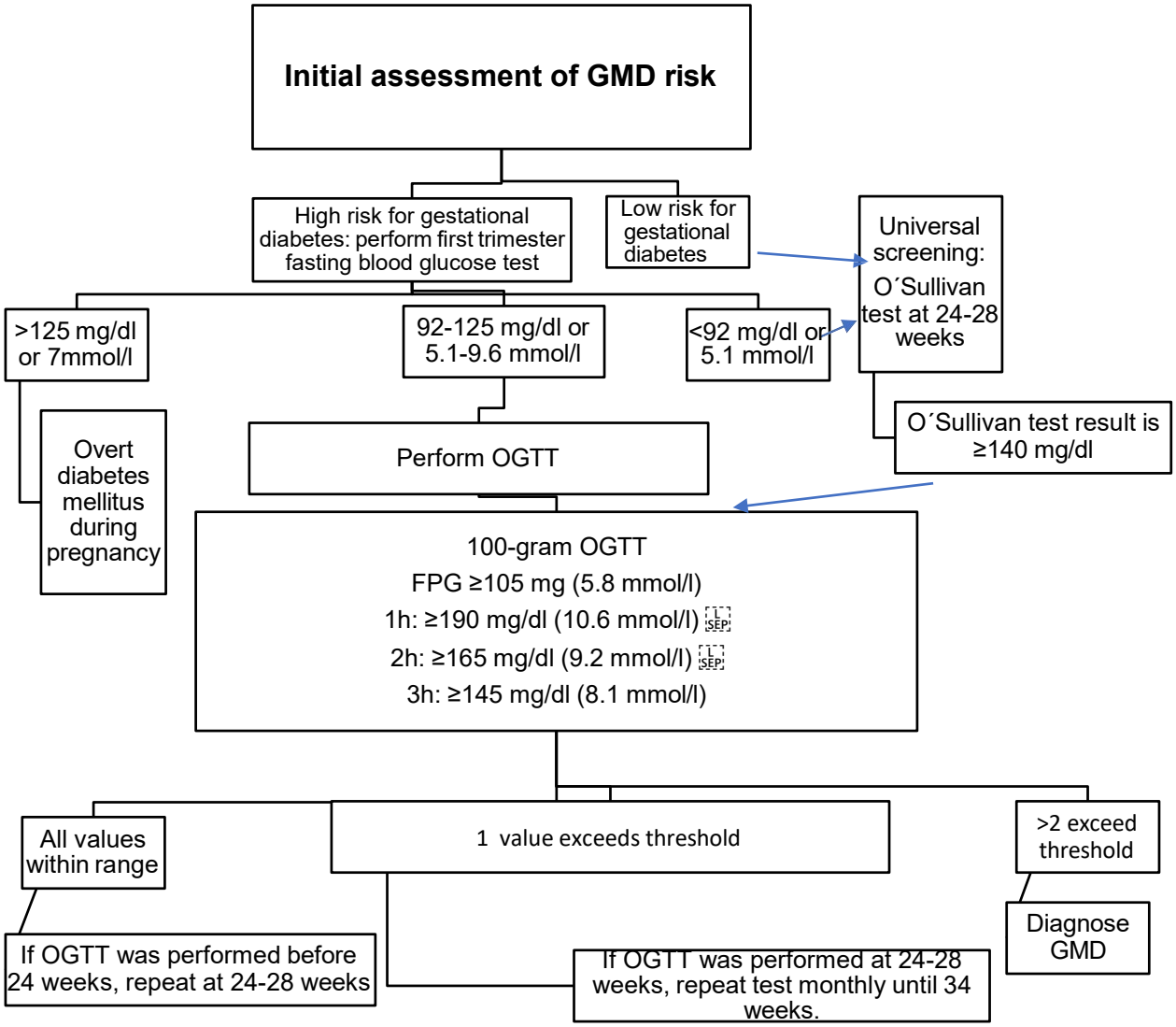
In case only one of these values exceeds the threshold, it indicates that the patient has impaired glucose tolerance, and a new 100-gram OGTT should be performed 3-4 weeks later.
After 34 weeks of pregnancy, repeating the test has shown no benefits and the patient should be categorized as impaired glucose tolerance after the first OGTT.

Some patients may present little tolerance to drinking the 100-gram sugar solution (extreme nausea and/or vomiting), which can make it difficult to complete the test. A hyperosmolar icing solution added to the sugar or the administration of 10 mg of metoclopramide prior to the test might improve tolerance.

We should also be reminded that patients with a history of bariatric surgery should not undergo the OGTT (since it could cause them severe Dumping syndrome).
Even though OTTG is the only validated method available for GDM diagnosis, in these special situations we can offer an alternative that could help identify those suffering from this condition: self-monitoring of blood sugar fasting, and 1-2 hours after meals.

5.3 75-gram OGTT:
It is important to mention that another screening method was proposed by IADPSG based on the results of the HAPO (Hyperglycaemia Adverse Pregnancy Outcomes) study consisting of one-step diagnosis with a 75-gram OGTT. This is a two-hour test with lower thresholds than the 100-gram test (93-180-153 mg/dL or 5.1-10-8.5 mmol/L). In many settings, the implementation of this test would overdiagnose GMD and, therefore, we recommend the 100-gram glucose test method.

Figure 1. Diagnosis algorithm for gestational diabetes.



GMD: Gestational mellitus diabetes. **OGTT:** oral glucose tolerance test. **FPG**: fasting plasma glucose

6. METABOLIC MANAGEMENT IN PREGNANCY

After diagnosis, a tailored treatment plan consisting of medical nutrition therapy, physical activity and weight management should be started.
Caregivers are advised to:

- Give the patient an understandable explanation of the physiopathology of GDM and how it affects the foetus.
- Offer an individualised food plan, adjusted to the patient´s lifestyle and preferences.
- Provide a glucose meter and educate the patient on its use and on how to interpret results. Although the ideal frequency of glucose monitoring has not been established, generally 3-4 daily glucose measurements are advised: fasting and one hour or two hours after the three main meals.

Patients diagnosed with gestational diabetes should aim to achieve normoglycaemia.
Recommended glucose targets are as follows:

- Fasting capillary glucose <95 mg (5.3 mmol/L).
- Absence of fasting hypoglycaemia.
- 1-hour postprandial capillary glucose <140 mg/dL (7.8 mmol/L).
- 2- hour postprandial capillary glucose: <120 mg/L (6.7 mmol/L).

To control the disease, it is of paramount importance to maintain glucose levels regulated according to the cut-off values previously mentioned, which in turn will increase the probability of improved perinatal outcomes. The latter can be achieved through three main interventions:

6.1 Nutrition counselling

A non-restrictive, normocaloric diet plan adapted to the patient´s preferences and lifestyle is paramount in gestational diabetes. Body mass index must be taken into account. An adequate proportion of carbohydrates (40-50%) should be included, as well as protein (20%) and fat (30-40%), preferably coming from monounsaturated sources. It is advisable to have 3 meals and two snacks throughout the day to avoid hypoglycaemic episodes and postprandial hyperglycaemia.

6.2 Physical activity

Daily moderate-intensity aerobic exercise is recommended (e.g. a one-hour walk, fast dancing for 30 minutes, doing water aerobics for 30 minutes). Walking after meals helps reduce postprandial hyperglycaemia. If the patient presents a contraindication for aerobic activity, she should be encouraged to do lower and upper limb strengthening exercises.

6.3 Pharmacological treatment.

When a patient consistently remains out of the glycaemic targets (>2 glucose values exceed the thresholds during a week) despite the nutrition and physical exercise interventions, pharmacological treatment should be introduced.

6.3.1 Insulin represents the first-line treatment in GMD.
Because of its large molecular size, insulin does not cross the placental barrier. The initial dose starts at 0.2 UI/kg/day and should be adjusted depending on the glucose monitoring values.

Fast-acting insulin should be administered for postprandial hyperglycaemia, whereas long-acting insulin is recommended to control fasting or preprandial hyperglycaemia.
Long-acting insulin should be administered before bed and it represents 30-50% of total calculated doses. Fast-acting insulin dosage must be administered before mealtimes and distributed according to postprandial glucose values after each meal.

Table 1 below illustrates the type, onset of action, peak effect and duration of action of insulin available in our setting.

Type of insulin			Onset of action	Peak effect (h)	Duration of action (h)
Insulin analogue	Ultra-fast acting insulin	Lispro	1-15 min	1-2	4-5
		Aspart	1-15 min	1-2	4-5
Human insulin	Fast-acting insulin	Regular	30-60 min	2-4	6-8
	Intermediate-acting insulin	NPH insulin	1-3 h	5-7	13-18
Insulin analogue	Slow-acting insulin	Glargine	1-2 h	No peak	24
		Detemir	1-3 h	Minimum peak at 8-10	18-26

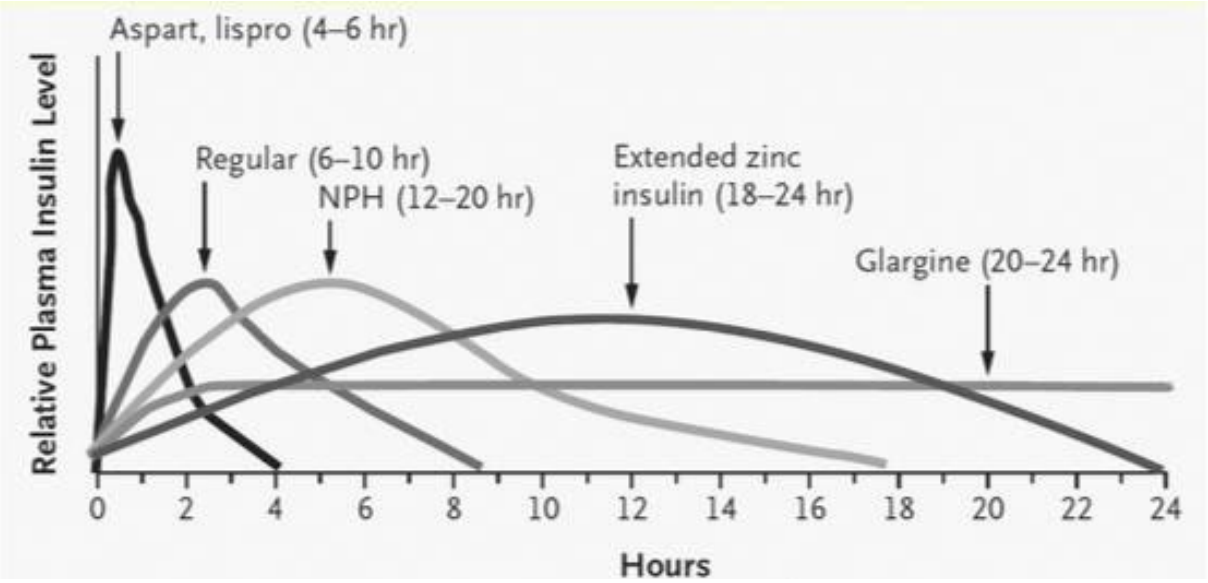


***Table 2**. Pharmacokinetic profile of Human insulin and insulin analogues.*

Considerations on hypoglycaemia when treating with insulin: it must be suspected when the patient presents characteristic symptoms such as sweating, dizziness, and heart palpitations. Perform a capillary glucose measurement immediately and act accordingly:

- If glucose level is <60 mg/dl, give a glass of milk or fruit juice (250 ml) and repeat measurement after 35 minutes.
- If glucose level is <40 mg/dl, add extra 10 grams of sugar to the previous step, and repeat measurement in 15 minutes.
- If a patient is unconscious and is not able to take sugar orally, administer 1 mg of subcutaneous glucagon infusion or 10% glucose intravenous infusion solution.

6.3.2 Metformin

Metformin is a well-known oral hypoglycaemic agent commonly used to treat type II diabetes. There is no strong evidence from randomised trials on the long-term effects when used in pregnancy, and, since this drug crosses the placental barrier, metformin should never be considered as a first-line treatment.
It might be used only in patients who reject insulin treatment or who are not capable of self- administering it safely. Some frequent secondary effects are diarrhoea and mild abdominal pain.
The initial recommended dose is 850 mg at night, which can be increased after a week to 850 mg twice a day. Maximum dose is 2500-3000 mg/day taken 2-3 times/day.

7. OBSTETRIC MANAGEMENT

A multidisciplinary care team consisting of an obstetrician, an endocrinologist and a certified diabetic educator (a nurse or dietician specialised in diabetes) has shown to be beneficial for these patients.
Most women affected by GMD will probably need more frequent prenatal visits, especially if they are resistant to conservative treatment or require insulin. A growth scan is recommended between 28-30 weeks for early detection of macrosomia. If foetal growth is above the 97th percentile, another ultrasound to confirm this finding should be performed after 3-4 weeks.
A routine growth ultrasound is also recommended at 38-39 weeks in these women. After 37 weeks, a confirmation ultrasound is not needed and the foetus will be diagnosed as large for gestational age if growth is >97th percentile.

7.1 Special situations:

7.1.1 Corticosteroids administration for foetal lung maturation.

Foetal lung maturation with corticosteroids leads to a higher glucose level and some additional measurements for lowering it may be needed:

- Preferably administer them between 1-6 pm.
- GMD treated with dietary measures: If fasting plasma glucose is >95 mg/dl or 1-hour postprandial glucose >140 mg/dl, insulin should be started at 0.3 UI/kg/day (distributed in 30-50% long-acting insulin and 50-70% short-acting preprandial insulin)
- Insulin- requiring GMD: dosage should be increased gradually according to the following table.

DAY OF TREATMENT	INSULIN ADMINISTRATION
1	Increase long-acting insulin by 25%
2 and 3	Increase long and fast-acting insulin by 40%
4	Increase long and fast-acting insulin by 20%
5	Increase long and fast-acting insulin by 20%
6	Go back to the initial insulin dose

7.1.2 Threatened preterm labour: if tocolysis is needed**,** atosiban should be used as first choice. Reserve calcium channel blockers like nifedipine as a second-line treatment. B-mimetic drugs should be discouraged due to their hyperglycaemic effect.

8. TIMING AND MODE OF DELIVERY

Most women with gestational diabetes treated with nutritional therapy will achieve the glycaemic targets and will not need insulin. Regarding timing and mode of delivery, adopting expectant management is preferred once term is achieved. If obstetric conditions allow for it, vaginal delivery is recommended as the first option.

In cases in which there is a high suspicion of undiagnosed gestational diabetes or complications such as insulin-requiring diabetes or large for gestational age foetus arise, we should manage the patient as follows:

- Glycaemic goals are achieved: offer induction of labour at 39-40 weeks.
- Glycaemic goals are consistently out of range: we should recommend to the woman an early induction at 37 weeks.
- Consider elective birth before 37 weeks for women with type 2 diabetes who have metabolic or other maternal/foetal complications
- If estimated foetal growth is >4500 g at term: an elective caesarean section is recommended.
- If estimated foetal growth is >4000 g at term: induction of labour at 39 weeks should be advised.

9. INTRAPARTUM CARE

During the intrapartum period, the aim is to maintain maternal normoglycaemia, in an effort to prevent neonatal hypoglycaemia. Glycaemic target values are similar to those during pregnancy (capillary glucose of 70-110 mg/dl).

9.1 Diet-controlled diabetes: patients with diet-controlled diabetes will not require intrapartum insulin. It is advisable to check their glucose level on admission for labour and delivery. If oral intake is restricted, measurements should be performed every 4-6 hours.

9.2 Insulin-requiring diabetes

However, patients with insulin-requiring diabetes will need more frequent blood glucose monitoring. In the latent phase of labour, insulin requirements are low. When the active phase of labour starts, it is important to assure that sufficient glucose is administered so as to avoid fasting ketosis, and blood glucose levels should be measured every 1-2 hours. We should act according to the following glucose values:

- Intrapartum normoglycaemia (<95 mg/dl): administer 5% glucose intravenous infusion solution every 6 hours.
- Intrapartum hyperglycaemia (>110 mg/dl): administer 10% glucose intravenous infusion solution + 10 mEq ClK every 6 hours+ short-acting intravenous insulin at the following doses, depending on capillary blood glucose measurement:

  - < 70 mg/dl (3.9 mmol/l) -> 0 units IV push.
  - 70-100 mg/dl (3.9-5.5 mmol/l) ->1 unit IV push.
  - 101-130 mg/dl (5.5-7.2 mmol/l) ->2 units IV push.
  - 131-160 mg/dl (7.2-8.9 mmol/l) ->3 units IV push.
  - 161-190 mg/dl (8.9-10.5 mmol/l) ->4 units IV push.
  - > 190 mg/dl (10.5 mmol/l) ->5 units IV push.

9.3 Other clinical scenarios

- Caesarean section: since this procedure requires fasting, blood glucose, IV fluid administration, as well as a 5% glucose solution to avoid ketosis are recommended. Fast-acting insulin can be used if glycaemic targets are not met.
- Induction of labour: If fasting is required or food intake is reduced, basal insulin should be reduced by 50%. Fast-acting insulin can be used if glycaemic targets are not met.

After delivery, insulin treatment is discontinued and fasting glucose levels should be measured daily in hospital postpartum.

Neonatal care must focus on early detection of hypoglycaemia. Early initiation of breastfeeding helps avoid neonatal hypoglycaemia and improves glucose metabolism.

10. POSTPARTUM CARE

We must inform women with gestational diabetes that they are at high risk for developing type 2 diabetes in the future. For these reasons, they must be tested for diabetes in the early postpartum period (6-8 weeks following delivery). The recommended method is a two-hour 75-gram oral glucose tolerance test, as it is used in the non-pregnant populations.

Results are evaluated according to American Diabetes Association (ADA) criteria:

Prediabetes:

- Fasting blood glucose level of 100-125 mg/dl.
- An OGTT two-hour blood glucose level of 140-199 mg/dl.
- HbA1C of 5.7-6.4%.

Diabetes Mellitus

- Fasting blood glucose greater than or equal to 126 mg/dl. Must be confirmed a second time.

- 75-gram glucose test with blood sugar level greater than or equal to 200 mg/dl after two hours. Must be confirmed a second time.
- Random blood glucose greater than 200 mg/dl and classic symptoms of high glucose.
- HbA1C greater than or equal to 6.5%

The risk of recurrent gestational diabetes in future pregnancies should not be overlooked and the patient must be informed about it. Diabetes screening is recommended every 3 years for these patients in a primary care setting.