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REVIEW

# The Gestational Diabetes Mellitus Approach in Clinical Practice – A Narrative Review

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Gestational diabetes mellitus (GDM) is an increasingly condition in medical practice. In the absence of an effective therapeutic management, it can lead to significant maternal and neonatal complications with adverse health effects. Reducing the risk of morbidity is the goal achived by screening of all pregnant women and active involvement of health care staff and early medical intervention in case of detection of GDM. The aim of this review is to present the nowadays strategy of GDM approach. The management challenge is to maintain blood glucose levels within the targets recommended by current guidelines, which are in relatively narrow ranges. Nutritional intervention and lifestyle changes are of primary importance. If necessary insulin therapy is initiated, insulin analogues are preferable due to lower risk of hypoglycemia. Oral antidiabetics are not recommended in pregnancy, even if they are used in certain circumstances.

**Keywords**: gestational diabetes mellitus, maternal complications, fetal complications

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## Background

Before the discovery of insulin, women with preconceptional diabetes were considered infertile, but with its use the number of pregnancies in this category of patients has increased. Diabetes during pregnancy was first described in 1824 by Bennewitz in Germany. It reported the presence of clinical symptoms of polydipsia associated with persistent glycosuria in a multiparous pregnant woman. Subsequent studies have described the relationship between persistent glycosuria and the presence of obstetric complications, which has now led to risk stratification and the use of active screening in pregnant patients [1-3]. Gestational diabetes mellitus (GDM) is defined as a glucose tolerance disorder that first occurs during pregnancy. Regardless of its severity, the patient requires follow-up and treatment throughout pregnancy [4].

## Epidemiological data of GDM

The prevalence of GDM ranges from 1 to 20%, with an increasing trend worldwide, in parallel with the rising prevalence of obesity and type 2 diabetes mellitus (T2DM). Higher values are found in Africans, Latin Americans, Indians and Asians. With the dramatic increase of GDM cases, the costs associated with perinatal maternal-fetal complications will also increase [5]. Recent studies show that an average of 16% of pregnancies develop GDM, depending on geographical area [6].

Inherited history is a factor found in the risk category for GDM. A higher incidence of GDM has been observed in women with a history of hereditary or collateral diabetes in their father (25% vs 9.7%), mother (12.5% vs 6.8%) and grandmother (15.3% vs 9.2%) in the group of patients with GDM compared to pregnant women without previous inherited history of diabetes [7].

## Pathophysiological aspects of GDM

During a normal pregnancy, insulin resistance appears around the second trimester and continues until the third trimester of pregnancy, reaching its peak. GDM occurs when the pancreas can no longer compensate for insulin resistance in the periphery and beta-cell dysfunction occurs. Hyperinsulinism, consequence of insuline resistance state in a pregnant woman represents one of the main mechanisms in the pathogenesis of GDM. The development of GDM in the second and third trimester of pregnancy correlates with a concomitant decrease in peripheral insulin sensitivity. In the natural course of the disease, GDM may remit postpartum, but the risk of developing long-term diabetes persists. Among the molecules involved in the development of insulin resistance are hormones and adipokines secreted by the placenta (tumour necrosis factor alpha, growth hormones and placental lactogen) [8].

Among the adipokines secreted by adipose and placental tissue, omentin-1 has been studied as a possible mediator of insulin resistance. Two groups of pregnant women with and without GDM were compared and the differences in omentin-1 levels between the two groups were not significant. On the other hand, fetuses born to diabetic mothers had significantly lower omentin-1 values, which could predispose to lifelong insulin resistance [9]. Visfatin, an adipokine also with an important role in GDM pathophysiology, has been shown to be influenced by glycemic values. Its binding to insulin receptor-1 results in an insulin-like hypoglycaemic effect, which can be considered a compensatory response to high glycemic values [10,11]. Adiponec-

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tine, with an important anti-inflammatory effect showed lower values in GDM pregnancies, reflecting the insulin resistance state and furthermore the low values after giving birth may predispose to T2DM and cardiovascular disease [12,13]. Regarding glucose transport proteins (GLUT-1, GLUT-4, GLUT-9) at placental level, an increase of these receptors has been observed especially in placentas from mothers under insulin treatment [14]. In addition to all these pathophysiological processes, increased maternal adipose tissue, lack of exercise and high caloric intake lead to a relative state of glucose intolerance [8].

## Risk factors and risk categories, GDM screening

Risk assessment for GDM and classification of women in the appropriate risk class is done at the first prenatal visit. Risk factors are polycystic ovary syndrome, obesity, history of GDM or birth of macrosomic fetuses, advanced maternal age, family history of T2DM and persistence of glycosuria [15]. Personal factors independent of pregnancy may also be incriminating: maternal birth weight (<2.5 kg or >4 kg), smoking, multiparity, history of impaired fasting glucose (IFG) or impaired glucose tolerance, rapid weight gain in the first 6 months of pregnancy and blood pressure above 135/85 mmHg [16,17].

GDM has a tendency to increase in direct proportion to the increase in the mother's body mass index (BMI). Thus, the risk is doubled in grade one obesity (>30 kg/m2) compared to pregnant women within the normal weight range. GDM is also associated with the presence of hypothyroidism [18,19].

Recent studies show that a glycosylated hemoglobin (HbA1C) value above 5.9% places pregnant women in the high risk category, associating maternal-fetal obstetric complications such as: large fetus for gestational age, macrosomia (over 4000 g), preterm birth with risk of preeclampsia and risk of caesarean section. Also values below the lower limit of HbA1C have been correlated with a high risk for delivery of small-for-gestational-age fetuses and occurrence of neonatal hypoglycemia [20].

The American Diabetes Association (ADA) recommends diagnostic screening for all pregnant women in weeks 24-28 of pregnancy by performing an oral glucose tolerance test (OGTT) with 75 g of glucose, also known as the one step approach endorsed by International Association of Diabetes in Pregnancy Study Group (IADPSG). Pregnant women already diagnosed previously with type 1 diabetes mellitus (T1DM) or T2DM are exempt from this test [15].

The two step approach, recomended to be performed at 24-28 weeks of pregnancy by the American College of Obstetricians and Gynecologist (ACOG), includes a non-fasting OGTT with 50 g glucose and measuring one hour glucose value as step one with theresholds of 130, 135 or 140 mg/dL. Results above the mentioned theresholds in the first test requires a second step, consisting in 3-hour 100 mg glucose test. Carpenter and Coustan criteria are recomended: fasting glucose ≥ 95 mg/dL, 1-hour ≥ 180 mg/dL, 2-hour ≥ 155 mg/dL and 3-hour ≥ 140 mg/dL. Diagnosis of GDM can be made with at least two modified values [21-24].

Diagnostic criteria: a blood glucose value ≥126 mg/dL (7 mmol/L), a HbA1C value above 6.5% or a random blood glucose ≥200 mg/dL associated with classical symptoms are considered pre-pregnancy diabetes. If the fasting blood glucose value is between of 92-126 mg/dL, OGTT is recommended, after which the diagnosis of GDM is confirmed or denied. In weeks 24-28 of gestation the OGTT is performed and if fasting blood glucose ≥92 mg/dL, 1-hour blood glucose ≥180 mg/dL and 2-hour blood glucose ≥153 mg/dL GDM is confirmed. At 4-12 weeks postpartum, measuring HbA1C or performing OGTT is recommended and the patient will be followed up every 3 years [15,25-28].

Choosing between the one-step and two-step approach is a decision made by the physician. A randomized controlled trial highlight that there is no difference in between the incidence values in these two screening methods [29,30]. Other review literature prove the benefits associated with pregnancy outcomes, improving maternal and neonatal sequel of the one-step approach [31,32]. On the other hand, two times more women were diagnosed with GDM according to the IADPSG criteria compared to ACOG criteria, 19,2% vs. 11.8%, with comparable results in maternal and fetal complications [33,34].

## Possible complications in patients with GDM

### Maternal complications

Pre-eclampsia or eclampsia can occur during pregnancy. Clinical manifestations consist of oedema, hypertension and proteinuria. Management is of paramount importance and beta-blockers (labetalol), calcium blockers (nicardipine), centrally acting anti-adrenergic drugs (methyldopa), alpha-1 blockers (prazosin) or magnesium sulphate are recommended and have been shown a rapidly lower the blood pressure and prevent the disease progression [35-37]. Proteinuria is an alarming sign in pregnancy, its occurrence requires initiation of antihypertensive treatment and follow-up of its evolution. Blood pressure monitoring should be routinely performed in all patients, especially those at high risk, with target values ranging from 110-135/85 mmHg [15].

Studies also show that 50% to 70% of pregnant women with GDM may develop T2DM within an average of 24 years postpartum and 5.7% T1DM, therefore individualised follow-up of mothers throughout their lives is recommended [38,39].

### Fetal complications

GDM predisposes the fetus to congenital malformations, affecting the formation of the central nervous system re-

sulting in anencephaly, hydrocephalus, spina bifida. Affections of the heart consist of septal defects and transposition of large vessels. The large amount of amniotic fluid can lead to premature rupture of membranes and the most important complication is macrosomia or large-for-gestational-age fetus [40].

Fetal macrosomia predisposes to birth trauma, fetal hypoxia and metabolic acidosis, respiratory distress syndrome, neonatal hypoglycemia, hyperbilirubinemia, polycythemia and hypocalcemia. In the long term, infants born to mothers with GDM are prone to abdominal obesity and implicit metabolic syndrome, as well as refractive disorders, which are 3 times more common compared to infants born to non-diabetic mothers [41,42].

## Therapeutic strategies in management of GDM

The cornerstone of GDM treatment is maintaining blood glucose levels within target values. The emotional comfort of the pregnant woman during pregnancy is necessary for good adherence to treatment. A comprehensive support system, including family and medical team is essential in maintaining a physiological pregnancy and reducing maternal-fetal risk [43].

### Lifestyle interventions

The first steps in the management of GDM include lifestyle changes, early nutritional intervention, consistent and sufficient exercise within individual tolerance. Maintenance in optimal therapeutic target ranges on glycemic values can be achieved in up to 80-90% of patients with effective nutritional intervention [44].

Glycemic targets during pregnancy are below 95 mg/dL fasting, below 140 mg/dL one hour postprandial and below 120 mg/dL two hours postprandial. Patients are advised to measure their blood glucose during pregnancy approximately 4-7 times a day or use a continuous glucose monitoring system. This allows a better glycemic control close to the physiological state, an avoidance of hypoglycemia and a greater lifestyle flexibility [15].

Weight control during pregnancy is a therapeutic goal to aim for, the total weight gain in pregnancy being individualized according to the mother's initial weight category (Table I) [45]. Lower weight gain is preferable in overweight or obese mothers [46].

The average weight gain is recommended to be 0.5 kg per week for underweight and normal weight pregnant women and 0.3 kg per week for overweight and obese women. Drawing up an eating plan with a registered dietitian nutritionist can increase compliance with the diet, so patients can be informed and actively involved in maintaining good metabolic control. The diet is based on frequent and small meals, including 3 main meals and 2-3 low-calorie snacks.

According to the ADA, macronutrient intake is recommended to be a minimum of 175 g of carbohydrates, 71 g of protein and 28 g fiber, while trans fats are avoided and monounsaturated and polyunsaturated fats are allowed. The glycemic index of food is very important, considering that a consumption of rapidly absorbed carbohydrates leads to high postprandial glycemia [15]. Lower glycemic index foods associated with low fats in a less restrictive diet, individualized for each patient, may improve the adherence and lead to more favorable outcomes in GDM [47,48] (table II).

Physical activity such as moderate aerobic exercises, adapted to the evolution of pregnancy, 30 minutes per day in the absence of contraindications and limitation of dietary intake lead to limiting excessive weight gain during pregnancy [49,50].

### Pharmacological treatment

When glycemic targets are not achieved, insulin therapy is recommended as the first-line pharmacological treatment. Oral antidiabetics are the second-line choice in therapy, with metformin and glibenclamide being two molecules that cross the feto-placental barrier; at present there are controversial views on their use in pregnant women [15].

#### *Oral therapy*

Metformin is recommended to be discontinued until the end of the first trimester in patients with polycystic ovary syndrome who become pregnant [15].

Of the sulfonylureas, glibenclamide has been shown to cross the feto-placental barrier, thus achieving significant plasma concentrations in fetal blood, consequently increasing the risk of macrosomia and neonatal hypoglycemia [51].

Compared to glibenclamide, metformin has a lower risk of neonatal hypoglycemia and decreases insulin resistance, although the fetal plasma concentration of metformin is higher than glibenclamide. Metformin is not indicated for pregnancies with elevated blood pressure, pre-eclampsia or those at risk of having small-for-gestational-age fetuses [52,53].

Metformin would seem to be a good treatment choice, as initial doses of 500 mg per day with dose adjustment

Table I. Weight gain targets during pregnancy

| Initial BMI (kg/m$^2$) | Total weight gain (kg) |
|---|---|
| <18.5 | 14-20 |
| 18.5-24.9 | 12.5-17.5 |
| 25-29.9 | 7.5-12.5 |
| >30 | 5.5-10 |

Table II. Nutritional recommendations

| Carbohydrates | Starchy food with dietary fiber content: vegetables, fruits, whole grains divided throughout the day |
|---|---|
| Proteins | Plants, lean meat, fish<br>Avoid red and processed meat |
| Fats | Low-fat dairy products, mono and polyunsaturated fats |
| Vitamin and minerals (folic acid, 25-hydroxyvitamin D, calcium, iron) | Healthy food choices, supplementation if necessary |

up to 2500 mg per day depending on tolerance and glycemic control; the risk of hypoglycemia is lower than with insulin treatment [54]. Glibenclamide has a higher risk of neonatal hypoglycemia than insulin, therefore it should be avoided in practice [55].

A sistematic review and meta-analysis of 42 trials showed a reduced risk of complications (eg. shoulder dystocia, large-for-gestational-age and macrosomia) in cases where nutritional and pharmacological intervention was made, compared to routine care [56]. Also, metformin is an effective alternative or an associated treatment to insulin because of less maternal weight gain during pregnancy, easy tolerablility and insulin dose reduction [57]. A randomized clinical trial concluded that there were no significant differences between the insulin and metformin treatment groups, including glycemic control, gestational age and weight at delivery, neonatal hypoglycemia [58]. Using metformin in obese pregnant women has not been found effective in declining BMI range and preventing GDM and should not be used in pregnant women without GDM [59].

HbA1C values tend to be lower in pregnant women because there is a tendency for blood glucose averages to fall during pregnancy. Also, increased turn-over and red blood cell count contribute to lower HbA1C values. Studies show that HbA1C can be used during pregnancy in patients with GDM with a high specificity but low sensitivity, as a consequence other diagnostic tests such as fasting blood glucose values and OGTT are also needed [60].

*Insulin therapy*

Regarding insulin therapy versus oral antidiabetics, insulin is the safest, most effective and teratogenic risk-free option in the control and treatment of GDM. Insulin therapy can be initiated according to the patient's glycemic profile. This requires continuous adjustment and adaptation to the mother's weight and gestational age of the fetus [61].

If elevated postprandial glycemia is found, current guidelines recommend to initiate insulin therapy with a rapid-acting insulin analogue (lispro, aspart) 2-4 units before each meal or with one unit of rapid-acting insulin corresponding to 10-15 g of carbohydrates. Subsequently doses require adjustment to premeal and postmeal blood glucose values at one hour mark.

If fasting and premeal blood glucose levels are outside of optimal glycemic targets, basal insulin (preferably NPH or glargine) can be initiated at 0.2 IU/kg/day and adjusted to fasting blood glucose values [62]. Of the current insulin types, insulin analogues are preferred because they are associated with a lower risk of hypoglycemia and better postprandial glycemia [8].

Constant adaptation of therapy to the patient's glycemic profile and continuous self-monitoring represents the key for therapeutic success achievement. Pregnant women with GDM are instructed to monitor their blood glucose levels during the night too. The administration of a basal insulin in combination with a rapid insulin before each main meal is recommended if glycemic values are outside targets. This allows for much greater flexibility in the dietary plan, achieving and maintaining glycemia within target range [63].

Another choice in the management of GDM represent insulin pumps. These provide a more comfortable environment for the patient, less severe hypoglycemia with an improvment of metabolic control. Postpartum, insulin requirements decrease rapidly, the glycemic curve normalises so insulin can be discontinued from the therapeutic regimen, with subsequent follow-up of the pregnant woman according to current protocol [64].

### Follow-up of the patient with GDM

Throughout the pregnancy, the patient is monitored by a multidisciplinary medical team. Monitoring includes glycemic control, HbA1C, weight gain, assessment of kidney function by creatinine clearance and albuminuria, ketonuria, blood pressure measurement and ophthalmological control [65].

Current recommendations advocate carrying to term, 40-41 weeks gestation for pregnant women with GDM with good glycemic control through diet and physical activity, in the absence of risk factors. Caesarean section delivery can be performed at 37-38 weeks gestation in patients with fetuses weighing over 4.5 kg to reduce obstetric risk.

In caesarean operations, rapid morning insulin is stopped and glycemic control is maintained with hourly glycemic monitoring using subbuffered glucose solutions. In case of hypoglycemia (<70 mg/dL) the pregnant woman will receive 10% glucose. The recommended prepartum and intrapartum target values are between 70-126 mg/dL. Natural childbirth is encouraged in the absence of contraindications and in the presence of good glycemic control. Immediately postpartum insulin resistance decreases dramatically, which is why insulin therapy can be discontinued, with diet and lifestyle recommendations maintained. Breastfeeding is also encouraged especially in obese mothers [66].

## Future perspectives

GDM is currently a common condition among pregnant women. Delay in diagnosis and medical intervention leads to complications in pregnancy, with both short- and long-term effects. Given the tight glycemic limits, maintaining blood glucose levels within therapeutic targets is a difficult goal to achieve, requiring very good patient compliance. Awareness of the diagnosis and active involvement of the patient in the therapeutic management of GDM as well as the multidisciplinary medical team are paramount in achieving a pregnancy with minimal risk.

Recent studies have shown the advantages of using a continuous glucose monitoring system in pregnant women with GDM, allowing blood glucose values to be deter-

mined both during the night and during the day [67,68]. The ADA states that the combination of self-monitoring of blood glucose together with a continuous glucose monitoring system allows to reach target HbA1C values [15]. Postpartum follow-up of pregnant women with GDM is important and should be used as a screening method for diabetes.

## Conclusions

Due to the narrow range of target blood glucose values recommended by current guidelines, the management of GDM is a real medical challenge. The aim of this is to ensure that the pregnancy progresses as normal as possible and to prevent maternal and fetal complications. A strict glycemic control represents the key of the therapeutic success with the avoidance of complications. The treatment requires individualization of nutritional intervention combined with lifestyle changes and if necessary with insulin therapy, while oral antidiabetics are not recommended. There is no well-established international consensus specifying the benchmarks for monitoring patients with GDM yet, this field remaining as an open question with future research needed.

## Authors' contribution

O.D., L.M.C. (Conceptualization, Data curation, Investigation, Methodology, Writing – original draft); R.A.S., B.I.B. (Data curation, Investigation, Methodology); A.C.B., M.A.S. (Data curation, Investigation, Writing – original draft); M.C.T. (Conceptualization, Project administration, Supervision, Writing – review & editing).

## Conflict of interest

None to declare.

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