Gestational Diabetes: a Window of Opportunity to Modify Long-Term Health Risks

GDM: Definition and Impact on Short and Long-Term Outcomes in Mothers and Offspring
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Hyperglycemia and Pregnancy
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Gestational Diabetes Mellitus: Definition and Impact on Short- and Long-Term Outcomes in Mothers and Offspring

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Key Messages
Considering the increasing number of women at risk of GDM (e.g. of those who are overweight or obese), it is necessary to identify those at risk and perform screening and diagnostic tests from the first prenatal visit. Diagnosing and treating GDM is very important in order to reduce serious adverse pregnancy outcomes, neonatal complications, the number of cesarean sections, and an increased maternal and offspring predisposition to T2DM later in life.

For many years, gestational diabetes mellitus (GDM) has been defined as any degree of glucose intolerance first diagnosed during pregnancy, regardless whether this condition has already existed before the pregnancy or whether it will persist after it. This definition has resulted in a uniform system for the detection and classification of GDM and for treatment strategies, but this system is limited because of its imprecision [1]. The current, global, and growing prevalence of obesity and type 2 diabetes mellitus (T2DM) means that an increasing number of women of child-bearing age are overweight or obese and that a rising number of pregnant women present with undiagnosed T2DM. It is therefore necessary to perform screening or diagnostic tests in women at risk of T2DM, from the first prenatal visit, using standard diagnostic criteria for the general population. Women diagnosed with abnormal glucose levels during the first trimester of pregnancy should be classified as carriers of pregestational T2DM, while those diagnosed during the second or third trimester should be classified as GDM cases using the current definition [2, 3].

It is important to diagnose and treat GDM because of its association with adverse pregnancy outcomes. Macrosomia, shoulder dystocia, and neonatal hypoglycemia are frequently occurring serious complications. In patients with GDM, a greater number of cesarean sections and an increased risk of pre-eclampsia are common. Jaundice, polyhydramnios, respiratory failure, and hypocalcemia have also been reported as frequent neonatal complications, and increased perinatal mortality. Fetal exposure to hyperglycemia can predispose the child to T2DM later in life [4–6].

Currently, T2DM is the leading cause of death among Mexican women, and obesity is a major risk factor for developing T2DM. In Mexico, it has been estimated that 69% of all women of childbearing age are overweight or obese, and the number of pregnant women with GDM is increasing, with an estimated prevalence between 8 and 12%. These figures should be enough reason for screening of GDM and diagnostic strategies to be performed in all pregnant women in countries with similar percentages, but unfortunately this is not generally the case.

Additionally, a history of GDM puts the mother at an increased risk of recurrence during further pregnancies and of developing T2DM, as well as potentially of cardiovascular disease. Hyperglycemia in GDM is usually mild and of a too short duration to adversely affect a woman’s health. However, an affected woman’s long-term risk of developing overt T2DM is high, ranging between 2.6 and 70% in follow-up studies between 6 weeks and 28 years after delivery [7]. At least one third of all women with GDM show recurrence in a subsequent pregnancy. These risks can be minimized by good glycemic control and adequate obstetric care.

References

Key Messages

The prevention of GDM is key to ensure optimal pregnancy outcomes for mother and infant.

Supplementation with myoinositol and probiotics may prove to be a successful prevention strategy that can be easily adopted by women of childbearing age.

In pregnancy, insulin resistance and secretion increase to ensure an appropriate fetal nutrient supply; however, an excessive rise leads to gestational diabetes (GDM). Worldwide, the prevalence of GDM ranges between 6 and 13%, reaching 25% in some countries [1]. GDM is a multifactorial condition, but maternal overweight/obesity and excessive gestational weight gain (GWG) are important risk factors [2].

GDM is associated with adverse maternal outcomes, such as preeclampsia and future type 2 diabetes mellitus (T2DM), and short- and long-term morbidities in the infant including neonatal hypoglycemia, macrosomia, and future obesity and T2DM [2].

GDM treatment focuses on glycemic control through dietary changes with or without pharmacotherapy (metformin, glyburide, and/or insulin) [2]. However, given the adverse effects of GDM, preventive interventions are crucial. Different types of interventions have reported mixed results due to differences in diagnostic criteria, the use of nonstandardized interventions, and varying levels of adherence, particularly with lifestyle interventions [3].

Dietary modulation fails to reduce the incidence of GDM in lean women and has mixed effects in obese women [3], though a meta-analysis reported a 61% reduction of GDM risk [4]. Physical activity-based interventions in lean women also show conflicting results; and in obese women, they improve fasting glucose and insulin levels without reducing the rate of GDM [3]. Combined diet- and physical activity-based interventions do not reduce the incidence of GDM in lean or obese women, but they reduce GWG in obese women [3].

Specific nutritional interventions to prevent GDM have been tested. Supplement with n–3 long-chain polyunsaturated fatty acids, which may enhance insulin action and improve glucose tolerance, does not consistently reduce the risk of GDM in a few small RCTs [3]. Furthermore, maternal vitamin D deficiency during early pregnancy increases the risk of GDM [5], but its supplementation does not reduce the incidence of GDM. However, most vitamin D studies do not including GDM as an outcome and have methodological flaws [6].

Two promising bioactive ingredients are myoinositol and probiotics (Fig. 1). Four small clinical trials in high-risk Italian women report that supplementation with myoinositol, an insulin-mimicker, reduces the risk of GDM by 60–70% and normalizes birth weight [7, 8]. Larger trials in other populations are warranted to confirm these results. The combination of two probiotic strains, Lactobacillus rhamnosus NCC4007 or BL818, and/or Bifidobacterium lactium NCC2818 or BL818, increased intestinal permeability, and/or controlling low-grade inflammation [12]. Additional insights will come from three on-going trials using the same probiotics mix [9].

References


Fig. 1. Two most promising bioactive ingredients to reduce the risk of GDM.
Hyperglycemia and Pregnancy

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The Vicious Cycle
Obesity, Diabetes, Metabolic Syndrome & Pregnancy

Key Message
Hyperglycemia during pregnancy is related to an increased risk of unfavorable complications for the mother and infant: there is a need to screen pregnant women and apply preventive tools along with changes in lifestyle to ameliorate outcome.

Definition and Pathophysiology of Hyperglycemia during Pregnancy
Gestational hyperglycemia derives from different levels of glucose intolerance, arising or found for the first time during pregnancy. This definition includes also women with undiagnosed preexisting diabetes. So nowadays, the wider concept of “hyperglycemia in pregnancy” is more frequently used, referring to both diabetes developed during pregnancy and diabetes diagnosed for the first time during pregnancy but with earlier onset.

The number of cases with gestational diabetes is rising worldwide due to the increase of specific risk factors, such as obesity, physical inactivity, over- and malnutrition, environmental pollution, and advanced maternal age.

The physiological insulin resistance during pregnancy is mainly due to the action of placental hormones, which is predominantly an insulin antagonist action. The main hormone involved in this mechanism is the placental lactogen hormone (HPL).

Under normal conditions, this new balance induces a compensatory increase in maternal insulin secretion to maintain a euglycemic state. Otherwise, if the additional production of maternal insulin is insufficient, hyperglycemia and consequently gestational diabetes develop.

Obesity and Gestational Hyperglycemia
Among the modifiable risk factors for gestational diabetes, maternal obesity (BMI >30) is a strong associated factor. Obesity, in fact, induces a maternal state of low-grade chronic inflammation due to the secretion of impaired adipokines. This inflammatory state, mainly due to the direct action of TNF-α on insulin receptors, causes a further reduction in insulin sensitivity.

The diagnosis of gestational diabetes (gestational hyperglycemia) is based on the oral glucose tolerance test (OGTT), where 75 g glucose are ingested in a single step. The test is carried out in pregnant women at 24–28 weeks of gestation. In cases with important risk factors, such as a previous pregnancy with gestational diabetes or obesity, the patient is considered at high risk, and the test is recommended to be done precisely at 16–18 weeks of gestation.

Maternal and fetal/neonatal outcomes are directly correlated with the degree of maternal glycemic control. This can in some cases be achieved through a special diet and adequate physical exercise only, in some cases it is necessary to add an insulin therapy. The correct and effective management of these patients requires a multidisciplinary approach which includes the participation of gynecologist, diabetologist, nutritionist, midwife, and general practitioner.

Prevention of Gestational Hyperglycemia
A possible program for the prevention of gestational hyperglycemia can be based not only on physical exercise and diet, but also on the use of probiotics and inositols. A personalized diet combined with regular physical exercise should become part of the lifestyle of women planning to become pregnant, especially in women with important risk factors such as obesity.

In many studies, the use of inositols has been demonstrated to be a possible tool to modulate insulin sensitivity, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients). Myoinositol seems to be an insulin mediator, it has been related to insulin resistance, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients). Myoinositol seems to be an insulin mediator, it has been related to insulin resistance, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients). Myoinositol seems to be an insulin mediator, it has been related to insulin resistance, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients). Myoinositol seems to be an insulin mediator, it has been related to insulin resistance, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients). Myoinositol seems to be an insulin mediator, it has been related to insulin resistance, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients). Myoinositol seems to be an insulin mediator, it has been related to insulin resistance, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients). Myoinositol seems to be an insulin mediator, it has been related to insulin resistance, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients). Myoinositol seems to be an insulin mediator, it has been related to insulin resistance, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients). Myoinositol seems to be an insulin mediator, it has been related to insulin resistance, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients). Myoinositol seems to be an insulin mediator, it has been related to insulin resistance, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients). Myoinositol seems to be an insulin mediator, it has been related to insulin resistance, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients). Myoinositol seems to be an insulin mediator, it has been related to insulin resistance, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients). Myoinositol seems to be an insulin mediator, it has been related to insulin resistance, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients). Myoinositol seems to be an insulin mediator, it has been related to insulin resistance, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients). Myoinositol seems to be an insulin mediator, it has been related to insulin resistance, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients). Myoinositol seems to be an insulin mediator, it has been related to insulin resistance, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients). Myoinositol seems to be an insulin mediator, it has been related to insulin resistance, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients). Myoinositol seems to be an insulin mediator, it has been related to insulin resistance, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients). Myoinositol seems to be an insulin mediator, it has been related to insulin resistance, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients).

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Pre-Pregnancy Management
Given the importance of controlling diabetes and its complications before pregnancy, there is a need to recommend to women planning to get pregnant to achieve euglycemia as soon as possible.

A possible program for the prevention of gestational hyperglycemia can be based not only on physical exercise and diet, but also on the use of probiotics and inositols. A personalized diet combined with regular physical exercise should become part of the lifestyle of women planning to become pregnant, especially in women with important risk factors such as obesity.

In many studies, the use of inositols has been demonstrated to be a possible tool to modulate insulin sensitivity, also in pregnant patients affected by gestational diabetes or at a high risk to develop it (i.e. in obese patients).

In conclusion, effective management requires the participation of general practitioner [2].

References
Gestational Diabetes and Early Life Programming of Obesity and Diabetes

Key Messages
Children born to mothers with gestational diabetes mellitus (GDM) have an increased risk of obesity and metabolic disease in adulthood. There is now evidence suggesting that maternal GDM induces stable modifications of the offspring’s epigenome, resulting in persistent changes in gene expression and programming long-term effects on appetite and metabolism.

Long-Term Effects of Maternal GDM on the Offspring
Alongside the perinatal implications of GDM, infants born to women with GDM are at an increased risk of adiposity and are more likely to develop type 2 diabetes later in life [1–3]. Among siblings, the risk of diabetes is higher in those born after the mother was diagnosed with diabetes, indicating that this risk is related to intra-uterine exposure to hyperglycaemia [3]. Concurrent with the rising prevalence of maternal obesity, the increasing incidence of GDM may now be playing an important role in a worsening intergenerational cycle of metabolic disease [4]. While research suggests that the risks of perinatal complications rise steeply above particular thresholds of maternal glycaemia, both the HAPO study and more recent mother-offspring cohorts show a continuous relation between higher levels of maternal dysglycaemia in pregnancy and greater offspring adiposity [1, 5].

Epigenetic Processes
Epigenetic processes include DNA methylation, post-translational modification of histones, and non-coding RNAs. DNA methylation occurring predominantly at cytosines in cytosine-guanine (CpG) dinucleotides is the most widely studied [4]. These processes induce heritable changes in gene expression without a change in nucleotide sequence and play an essential role in cell differentiation, determining when and where a gene is expressed. Increasing evidence suggests that epigenetic changes induced by the early-life environment make a major contribution to later phenotype [6]. We found that perinatal methylation of a Cpg site in the promoter region of the nuclear receptor RXRA was strongly related to childhood adiposity in two independent cohorts, explaining >25% of the variance in childhood fat mass [7]. Similarly, methylation of specific CpG loci in the promoter of PGClα [8] at age 5 years predicted later adiposity at age 14 years, strongly supporting the hypothesis that developmentally induced epigenetic marks may be valuable predictors of later adiposity, independent of potential confounding influences.

Research to systematically determine the contribution of epigenetic processes in providing the “memory” of how GDM influences obesity and metabolic disease is at an early stage, but evidence from animal models and initial clinical studies point to an important influence (Fig. 1). In humans, methylation changes have been observed in cord blood and placenta in GDM offspring compared to unexposed controls [9, 10]. Current research is now extending these observations to address other epigenetic processes, such as non-coding RNAs, to utilize genome-scale techniques, and to replicate and validate observations in larger cohorts. Epigenetic studies may soon lead to the identification of biomarkers with utility in trials of nutritional and lifestyle interventions to prevent GDM and normalize maternal glucose concentrations during pregnancy, thereby harnessing the development of measures to reduce the risk of overweight and obesity in the offspring.

References