Gestational Diabetes: A Review

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Gestational diabetes (GD) is a disorder of glucose tolerance resulting in hyperglycemia first diagnosed during pregnancy. Its worldwide prevalence is estimated at 14% but varies regionally. In 2008, new diagnostic criteria were adopted, leading to an increase in diagnosed cases. Biomarkers could potentially serve as an alternative to the current diagnostic criteria in the future, enabling the realization of a universally applicable GD screening program. Risk factors associated with GD encompass a range of factors, including epigenetic factors, inadequate vitamin D levels, family history of diabetes, prediabetes, obesity, fetal death, polycystic ovary syndrome (PCOS), and advanced maternal age. GD can have consequences for maternal health, increasing the risk of hypertensive disorders, premature labor, cesarean delivery, metabolic disorders, and later type 2 diabetes. In children, it may be associated with macrosomia, shoulder dystocia, respiratory insufficiency, and hospitalization in the neonatal intensive care. Offspring born to mothers with GD face heightened susceptibility to childhood and adult obesity, alongside elevated cardiometabolic risk. The consequences and risk factors of GD are not fully understood to this day. Therefore, additional research is warranted to gain a deeper comprehension of the pathophysiology underlying the disease and to ascertain efficacious preventive and therapeutic approaches. Nutritional therapy is often sufficient to achieve normoglycemia objectives. An individualized nutritional program is recommended, providing the necessary nutrients to promote maternal and infant health, attain optimal gestational weight gain and uphold glycemic regulation. However, in some cases, additional antidiabetic therapy is necessary. Insulin remains the most commonly used treatment, but metformin may be a safe and effective alternative. This still needs to be validated by in-depth studies leading to better evaluation of its long-term effects on offspring.

Keywords: Gestational diabetes mellitus, Glucose intolerance, Pregnancy in diabetics, pregnancy outcome.
for mother and child health conditions. Despite
the large number of studies, the pathophysiology
of GD is still unclear. Contemporary evidence
substantiates a multifaceted interplay among
diverse genetic, metabolic, and environmental
factors in the pathogenesis of GD. The majority
of the time, this hyperglycemia is brought on by
poor glucose tolerance resulting from dysfunctional
pancreatic beta-cell function against a background
of ongoing insulin resistance.

For decades, the debate regarding the
diagnosis of GD revolved around two questions:
first, the necessity of screening all parturient
women versus selective screening limited to
individuals with identifiable risk factors; and
second, the utilization of diagnostic procedures
in one or two steps. Screening only women with
risk factors may lead to GD going undiagnosed in
35–47% of pregnant women.

In recent years, GD has gained great
interest among researchers due to the multifactorial
complexity of this disease, which can have long-
term consequences for maternal and child health.
Despite progress made, research on GD is far from
complete, and further studies are still necessary to
uncover the underlying mechanisms of the disease,
its consequences, and effective prevention and
treatment strategies. In this review, we will focus
on the diagnostic criteria, prevalence, risk factors,
consequences, and management of GD while
drawing on recent literature data.

Several electronic databases, including
PubMed, Scopus, Google Scholar, Web of Science,
ScienceDirect, etc., along with other sources of
grey literature, were utilized to conduct this study.
The search strategy encompassed the utilization
of MESH terms and keywords such as gestational
diabetes, diabetes pregnancy-induced, diabetes
mellitus gestational, pregnancy in diabetics,
glucose intolerance, pregnancy, and pregnancy
complications. Based on these keywords, a total
of 91 articles were included in this review.

Diagnostic criteria for gestational diabetes

The diagnostic criteria for GD are not new.
In fact, the 1964 O’ Sullivan and Mahan method
recommended a two-step screening process that
involves administering 50 g of oral glucose and
measuring plasma glucose one hour later. If the
glycemic level surpasses or equals 1.40 g/L (7.8
mmol/L), an GD oral glucose tolerance test (OGTT)
is conducted following the ingestion of 100 grams
of glucose. The diagnosis GD is confirmed when
the glucose level reaches or exceeds 2 g/L (11.1
mmol/L) (5). The criteria mentioned above were
challenged because they were based on data from
the general population and not on indicators of
maternal and fetal morbidity.

Subsequently, in 1999, the World Health
Organization (WHO) embraced alternative
diagnostic criteria for gestational diabetes (GD).
It advocates conducting a 75-gram oral glucose
tolerance test (OGTT) during the gestational
period of 24 to 32 weeks, utilizing the following
thresholds: fasting glucose of 1.26 g/L (7 mmol/L)
and/or a 2-hour glucose level of 1.40 g/L (7.8
mmol/L) following glucose ingestion (7). These
screening criteria for GD do not adequately
differentiate pregnant individuals who are at a
heightened risk of adverse perinatal outcomes,
instead focusing on those with an elevated
susceptibility to postpartum diabetes development.

Following the dissemination of the findings
from the Hyperglycemia Adverse Pregnancy
Outcome (HAPO) study in 2008, involving
25,505 women, novel diagnostic parameters
for GD have been adopted by the International
Association of Diabetes and Pregnancy Study
Groups (IADPSG). Thus, it recommends screening
for pre-existing diabetes in patients early in
pregnancy through fasting blood glucose (FBG)
or glycated hemoglobin (HbA1C) measurements.
Patients with FBG > 1.26 g/L or HbA1C > 6.5% are
considered to have pre-existing diabetes. Patients
with FBG > 2 g/L must undergo a confirmation test
with FBG measurement. If the patient’s FBG levels
fall within the range of 0.92 g/L (5.1 mmol/L)
and 1.26 g/L, the diagnosis of GD is confirmed,
necessitating prompt initiation of treatment. Only
patients with an FBG of 0.92 g/L will undergo a
75-gram OGTT administered within the timeframe
encompassing the 24th week to the 28th week of
gestation. GD is diagnosed when a single test value
exceeds the predetermined thresholds: a glucose
level of 1.80 g/L (10 mmol/L) 1 hour after and/or
a glucose level of 1.53 g/L (8.5 mmol/L) 2 hours
after.

The HAPO study is the first study to
show an association between maternal blood
glucose values and fetal-maternal morbidity.
Therefore, for each additional standard deviation
(SD) of 0.07 g/L of fasting glucose, the risk of macrosomia experienced a 1.38-fold increase. The new IADPSG recommendations suggest a simultaneous modification of the diagnostic strategy and diagnostic thresholds, which are revised downward based on perinatal risks and are widely used worldwide. However, they have led to a threefold increase in the diagnosis of GD, highlighting previous underestimation.

In the same vein, several studies have confirmed the usefulness of using two-step screening tests, which may result in a 3% increase in the prevalence of GDM and a significant reduction in adverse pregnancy outcomes. However, screening may cause anxiety in pregnant women, which may persist beyond the first trimester and have adverse consequences for the health of both maternal and infant. It may also generate stress for physicians and lead to over-medicalization, an increase in the number of consultations, and even iatrogenic effects, such as high rates of cesarean sections, induction of labor, and repeated examinations during pregnancy follow-up. In contrast, other studies have shown the beneficial effect of GDM screening in motivating pregnant women to modify their behavior, particularly with adequate care. An Australian study involving 1000 women, on the other hand, showed that there was no statistically significant difference in maternal anxiety levels between the intervention and control groups, as evaluated using a 6-item self-evaluation scale of maternal anxiety, derived from a modified version of the Spielberger State-Trait Anxiety Inventory.

Currently, investigations are underway to explore the prospective significance of protein biomarkers in the diagnostic and predictive realms of GD. According to recent studies, a compilation of evidence emphasizes 15 protein biomarkers. These can contribute to replacing the IADPSG diagnostic criteria. Certain biomarkers, such as leptin and adiponectin, which are hormones produced by adipose cells, can be used to predict GD. The adiponectin/leptin plasma ratio can be used to predict GD between the 6th and 14th weeks of pregnancy. Other adipokines, such as visfatin, resistin, and omentin, can also be used to diagnose GD, but their effectiveness varies. Placental factors, including Fetuin-A and Sex Hormone-Binding Globulin (SHBG), may also influence the development of GD. Throughout the first trimester of gestation, the decrease in maternal plasma SHBG levels can be utilized for the prediction of GD. Additionally, the use of molecular markers, including single nucleotide polymorphisms (SNPs), microRNAs, and DNA methylation, can enable the detection of GD. There are over 100 miRNAs currently being studied in relation to GD. MiRNAs, SNPs, and certain genetic mutations such as those in adiponectin, glucokinase, and insulin receptor substrate 1 have been correlated with an elevated likelihood of developing GD.

Currently, various organizations recommend universal screening for the entire pregnant population to ensure optimal management of GD. However, the logistical aspect of implementing the HGPO test for all pregnant women constitutes a major obstacle. Precise biomarkers could enable universal screening to become a reality. However, their use in clinical practice is hindered by several challenges, including the need to evaluate their decision threshold, clinical usefulness, sensitivity, and specificity, which still require further investigation.

Prevalence of gestational diabetes

The prevalence of GD demonstrates variability among different countries and regions. Different studies report variable prevalence rates. In a 2019 meta-analysis and systematic review aiming to estimate the prevalence and determinants of gestational diabetes (GD) in Africa, the combined prevalence of GD in the African population was found to be 13.61%. Some studies included in this review reported a high prevalence of GD, such as in Cameroon (32.1%) and Uganda (30.3%). This result can be attributed to the expanded implementation of screening strategies for GD among pregnant women in these countries.

The explanation for the heterogeneity of prevalence is the absence of consensus concerning the diagnostic criteria for GD. According to studies, the prevalence of GD ranges from 1.3% to 19.9% (16). The observed variations may be related to a higher screening rate and easier access to tests in recent years.

In Morocco, reported figures show a prevalence of close to 10%. This prevalence varies in some studies between 7.7% and 24.2%. The potential for an increase in these figures exists due to limited awareness of the condition among a
significant proportion of Moroccan women, leading to restricted access to screening. Furthermore, the ongoing rise in the prevalence of obesity and overweight further contributes to this trend18.

In Europe, the prevalence of GD was estimated at 10.9% in a systematic review including 15,572,847 pregnant women between 2014 and 2019 in 24 European countries. The highest prevalence of GD was in the Eastern region (31.5%), followed by Southern Europe (12.3%), Western Europe (10.7%), and Northern Europe (8.9%)19. The estimated prevalence reported in this study (10.9%) surpasses the findings of a prior meta-analysis conducted in 2015, including 1,778,399 participants, with an estimated prevalence of 5.4%20. Similarly, the 2019 report from the International Diabetes Federation (IDF) underscores substantial variability in the prevalence of GD across seven regions globally, revealing an age-weighted prevalence estimated at 16.3% in Europe25. Differences in population and country estimates could explain the variation between the reported prevalences. The FID included data from women aged only 20 to 45 in 39 countries, while the 2019 systematic review included data from 24 countries for all pregnant women19. The 2015 meta-analysis included data from only 12 countries, which may explain the difference in prevalence20.

The prevalence of GD in Latin American and Caribbean populations obtained from a review of the literature published between 2000 and 2019 reporting maternal and perinatal adverse effects of pregnancies was estimated at 8.5%, which is lower than that in Europe (10.9%) and Africa (13.61%) mentioned above. However, the validity of prevalence comparisons between world regions is limited by the absence of universally accepted diagnostic criteria and screening strategies, as well as by inter-regional variability. Indeed, prevalence in Latin American and Caribbean populations ranged from 2.1% to 15.8%22. In Asia, this variation can range from 1% to 25% depending on the region, showing that this heterogeneity affects different regions of the world23.

Within the 10th edition of the IDF Diabetes Atlas, a meta-analysis is conducted with the aim of standardizing the assessment of GD prevalence across regions and national income levels, utilizing the diagnostic criteria of IADPSG. Based on data from studies conducted between January 1990 and December 2020, standardization of prevalence at 14.2% is obtained, with a slight decrease to 14% after age adjustment24.

To provide an overview of the variability of prevalence between different regions, IDF generated comparable prevalence if IADPSG diagnostic criteria were uniformly used in different regions and pregnant women were aged 25 to 30. Table 1 shows the different prevalences obtained24.

The observed variation in prevalence across regions and countries can be attributed to differences in population characteristics, including but not limited to ethnicity, lifestyle, prevalence of T2D, and obesity. Moreover, the standardized prevalence was assessed based on income level per country, with low-income countries showing a prevalence of 12.7%, high-income countries exhibiting a prevalence of 14.2%, and middle-income countries having a prevalence of 9.2%24.

In conclusion, the prevalence of GD exhibits regional and inter-country variations. Reported GD prevalence estimates may be underestimated due to the lack of awareness of the condition among a large proportion of women. The heterogeneity of prevalence according to the aforementioned studies can be explained by the absence of consensus on GD diagnostic criteria and screening strategies, as well as inter-regional variability. It is important to harmonize diagnostic criteria and screening strategies to improve the prevention and management of GD.

**Risk factors**

Maternal obesity and overweight, belonging to a population characterized by a high prevalence of diabetes (non-white ethnicity: Caribbean black, Asian, or Middle Eastern), a history of prediabetes, familial diabetes, or antecedents of GD, are all recognized as predisposing factors for the development of GD. In addition to these factors, a history of fetal death and the delivery of macrosomic newborns also contribute to the risk of GD. Increasing maternal age and polycystic ovary syndrome (PCOS) are also risk factors for GD25,26.

It is now established that obesity is associated with GD. In fact, the risk of developing GD can be four times higher in obese women and nine times higher in women with severe obesity27. Another systematic review, including 671,945
pregnant women, also confirms the association between obesity and GD. The unadjusted odds ratios for women classified as individuals with obesity (BMI > 29.9 kg/m²), individuals with moderate obesity (BMI 30-35 kg/m²), and individuals with severe obesity (BMI > 35 kg/m²), in comparison to women of average weight, were 3.76, 3.01, and 5.55, respectively (95% CI 3.31-4.28, 2.34-3.87, and 4.27-7.21)\(^2\). In 2021, a review reconfirmed the association between GD and obesity as a risk factor. This review analyzed data from 20 studies conducted between 1985 and 2020, and the risk increased two-fold and exceeded three-fold depending on the type of obesity\(^2\).

The risk of developing GD is positively associated with maternal age. Women between the ages of 35 and 39 exhibit an approximately twofold increase in the risk of developing GD, whereas women aged over 40 have nearly a fourfold increase in risk compared to their younger counterparts\(^3\).

Furthermore, PCOS is a complex disorder characterized by disturbances in ovarian function, primarily marked by elevated androgen levels and the presence of polycystic ovarian morphology\(^3\). It is accompanied by insulin resistance and hyperandrogenemia, which may explain the increased incidence of GD in this category of parturients.\(^3\) GD can affect up to 40% of patients with PCOS.\(^3\) The risk of developing GD can be increased by 2.89 compared to women without this syndrome. However, the majority of studies evaluating the risk of GD in patients with PCOS are mainly retrospective, which limits the availability of conclusive evidence regarding a direct association between PCOS and GD\(^3\).

Furthermore, recent scientific investigations have shed light on the potential role of vitamin D deficiency in the pathogenesis of GD.\(^2\) Inadequate levels of vitamin D can be associated with a 26% increased risk of developing GD, although this risk is lower in patients with a serum vitamin D concentration of 40 to 90 nmol/L.\(^3\) Iron supplementation may also be a potential factor in the development of GD. The risk of adverse outcomes appears to be elevated in pregnant women who receive iron supplementation. However, this hypothesis still requires further in-depth studies.\(^3\) It is also noteworthy that a high concentration of maternal folate combined with a vitamin B12 deficiency may contribute to an increased risk of GD.\(^4\) This highlights the need for an evaluation of the status of different vitamins and micronutrients in women before prescribing any supplementation.

Recent studies suggest that epigenetics, changes in gene expression caused by factors like diet, stress, and environment, can affect the development of GD. These modifications can impact genes that regulate insulin and glucose, contributing to GD pathogenesis. Among the epigenetic mechanisms, DNA methylation has garnered substantial attention as the foremost extensively studied mechanism, characterized by the addition of methyl groups to DNA.\(^3\)

In recent years, numerous studies have explored various likely risk factors associated with GD. Among these factors, obstructive sleep apnea (OSA) is a frequent complication of pregnancy, affecting 3.6% to 22% of pregnant women, and evidence indicates an increased risk of GD in pregnant women with OSA. However, the mechanisms underlying this association remain unclear. Intermittent hypoxemia (IH) and sleep arousals appear to be the most implicated factors.\(^3\) The association between thyroid dysfunction and GD also attracts researchers’ interest. Previous studies have suggested that physiological changes during pregnancy cause dysfunction affecting thyroid function and glucose metabolism. The necessary metabolic adaptations may contribute to the development of GD. Thyroid hormones have been implicated in the process of placental development, which constitutes a pivotal determinant of insulin resistance during the gestational period. Placental dysfunction can contribute to the development of gestational diabetes (GD). Furthermore, in women with detectable anti-thyroperoxidase antibodies, a compromised thyroid response to human chorionic gonadotropin (hCG) can exacerbate insulin resistance and contribute to the pathogenesis of GD. The underlying pathophysiological mechanisms linking GD and thyroid dysfunction remain incompletely understood and warrant further investigation.\(^4\)

Cytokines also receive significant attention from researchers. Tumor necrosis factor (TNF), leptin, and interleukin-6 (IL) have garnered particular interest. A recent systematic review
of 24 studies suggests the possible involvement of these cytokines in the occurrence of GD. All the aforementioned risk factors are far from exhaustive, and this section provides a general overview of the risk factors that have been the subject of numerous studies and others that are currently under investigation. This confirms the complexity of this multifactorial disease and necessitates further research to better understand its pathophysiology and improve its management.

**Consequences of gestational diabetes**

**Consequences for the mother**

Hyperglycemia during pregnancy, even if it is mild, can have consequences for maternal health. It is correlated with an elevated predisposition to hypertensive disorders during the gestational period. There has also been an increase in preterm labor, cesarean delivery, metabolic disorders, and the later development of diabetes.

**Diabetes and subsequent metabolic syndrome**

Studies have shown the involvement of GD in the occurrence of T2D and cardiovascular complications later on. According to studies, the risk was found to be sevenfold higher than that observed in women with normal blood glucose levels during pregnancy. T2D can affect 30% to 50% of women with a history of GD within 10 years. This risk can be partially elucidated by the interplay of shared genetic and environmental predisposing factors underlying both GD and T2D. Furthermore, GD and T2D exhibit comparable pathophysiological mechanisms and display genetic architectural resemblances. However, this result is controversial. On the one hand, this finding is supported by a meta-analysis of 39 studies, encompassing a total of 95,750 women who were followed for a period ranging from 6 months to 20 years. The meta-analysis revealed an estimated relative risk of 2.13 (95% CI 1.52, 3.56) associated with early diagnosis of GD. On the other hand, a Canadian study of 90,000 women showed a very slight increase in the risk of T2D among women with a previous history of GD.

The impact of GD on metabolic health has been extensively investigated, as demonstrated by a systematic review published in 2014. This study, encompassing 5,832 pregnant women, revealed a notable fourfold increase in metabolic risk among individuals with a history of GD (RR = 3.96, 95% CI: 3.99–5.26), with obesity and Caucasian origin being factors that increase the risk. Other studies confirm this result but with smaller samples. For example, a Danish cohort study including 481 women who had previously had GD and 1000 women of the same age without a history of GD revealed, after a follow-up of 9.8 years, a three-fold increase in the prevalence of metabolic syndrome in the previous GD group in comparison to the control group. It is worth noting that the risk of recurrent GD during pregnancy has been estimated at 48% in a meta-analysis combining data from 18 studies.

**Cardiovascular risk**

Several studies confirm the increased cardiovascular risk in parturients with antecedents of GD. This may explain the subsequent development of T2D. However, this link has not been demonstrated in a cohort of 8,191 women diagnosed with GD and 81,262 women without the condition who were included in the study, followed for 11 years. This cohort exhibited an elevated risk of cardiovascular events, regardless of the presence of T2D and metabolic syndrome, as indicated by an adjusted odds ratio of 1.85 (95% CI: 1.21-2.82). The results of a systematic literature review which encompassed data from 5,390,591 pregnant women, revealed that women diagnosed with GD exhibited a two-fold increased susceptibility to subsequent cardiovascular incidents (relative risk [RR] 1.98, 95% confidence interval [CI]: 1.57, 2.50). The T2D incidence rates observed in the studies did not exert any influence on this risk (p = 0.34). This confirms that the risk of cardiovascular events remains independent of concurrent T2D.

**Table 1. Comparable prevalence based on IADPSG criteria among women aged 25 to 30 years**

<table>
<thead>
<tr>
<th>Region</th>
<th>Standardized* Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Middle East And North Africa</td>
<td>27.6%</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>20.8%</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>14.7%</td>
</tr>
<tr>
<td>Afrique</td>
<td>14.2%</td>
</tr>
<tr>
<td>South and Central America</td>
<td>10.4%</td>
</tr>
<tr>
<td>Europe</td>
<td>7.8%</td>
</tr>
<tr>
<td>North America and Caribbean</td>
<td>7.1%</td>
</tr>
</tbody>
</table>

*The standardization was conducted by considering the sample sizes in the studies included in the meta-analysis of the FID and utilizing Poisson regression analysis.*
and instead becomes evident within the initial decade following pregnancy (RR 2.31 [95% CI: 1.57, 3.39])\textsuperscript{51}. Cardiovascular complications, according to a British study published in October 2022, including 13,094 women, are multiple and can include coronary conditions, ischemic strokes, myocardial infarctions, cardiac failures, peripheral artery disease, atrial fibrillations and mitral valve regurgitation\textsuperscript{52}.  

**Other complications**

The risk of pre-eclampsia and cesarean delivery is increased by GD. These risks demonstrate a positive linear association with the severity of initial hyperglycemia\textsuperscript{53}. Several maternal complications related to GD have been described in the literature. These complications may occur in the long term; renal insufficiency is one of them, and the risk can be multiplied by two in women who have a history of GD\textsuperscript{54}. Additionally, studies have demonstrated an elevated risk of long-term ocular morbidity among women with a prior history of GD, in whom the incidence of illnesses such as glaucoma, diabetic retinopathy, and retinal detachment was significantly higher compared to patients without a history of GD\textsuperscript{55}.

**Fetal consequences**

**Short-term consequences**

Maternal hyperglycemia is linked to an augmented risk of fetal macrosomia, perinatal mortality, and delivering infants who are large for gestational age. Macrosomia can affect 12% of newborns from non-diabetic women and 15–45% of newborns from women with GD (56). Indeed, GD alters placental physiology, inducing a modification of the amount of glucose available to the fetus, which could be responsible for abnormal fetal growth and perinatal complications\textsuperscript{57}. An association has also been established between macrosomia, shoulder dystocia, birth trauma, and perinatal asphyxia\textsuperscript{58,59}.

Newborns from women with GD may be admitted to neonatal intensive care units during the immediate postpartum period due to hypoglycemia explained by hyperinsulinemia in the newborn. The risk of respiratory distress is also increased\textsuperscript{60,61}. Evidence now exists that GD can serve as an independent risk factor for respiratory distress in newborns. This risk is further heightened in women with GD who are obese\textsuperscript{62}.

Regarding perinatal mortality, evidence is contradictory regarding the involvement of GD in its increase. Indeed, studies have shown that mortality can reach 30% with GD compared to non-diabetic mothers\textsuperscript{63}. Conversely, other studies suggest that the risk is only present in women with GD controlled by diet alone\textsuperscript{64}. Other studies showed no difference in terms of perinatal mortality. However, paradoxically, other studies showed a reduction in risk in newborns from women with GD. To reduce the risk of maternal and fetal morbidity, scheduled delivery is recommended for women with GD\textsuperscript{65}.

**Long-term consequences**

Offspring from pregnancies affected by GD are at an increased predisposition to childhood and adult obesity and increased cardiometabolic risk\textsuperscript{63}. This is evidenced by the HAPO study, which revealed an increase in neonatal cord C-peptide levels, a marker of insulin resistance. Moreover, neonatal adiposity in newborns of women with GD was positively correlated with maternal hyperglycemia\textsuperscript{60}. A significant increase in the risk of obesity at 10–14 years of age was confirmed by the HAPO follow-up study in children born to mothers with untreated GD compared to those without GD\textsuperscript{66}.

The mechanisms of GD’s effects on childhood and adult diseases are unclear. Metabolic abnormalities caused by GD in pregnant women create an in-utero environment for the fetus. This environment programs the fetus to develop the disease later in life. This “metabolic memory” may explain the obesity that can occur in children and persist into adulthood\textsuperscript{16}. In the same vein, a population-based study in Denmark including over 1.7 million births followed over a period of 30 years found that offspring born to mothers with GD had a high risk of circulatory system disease. A Finnish study also demonstrated that adults born to mothers
with GD had higher levels of insulin resistance and an atherogenic lipid profile compared to those born to mothers without GD63.

Given the multitude of adverse pregnancy outcomes in women with GD, including those demonstrated by various studies and others still under investigation, optimal management of this condition is crucial, and further studies are needed to clarify the various consequences and implement appropriate prevention measures.

**Therapeutic management of gestational diabetes**

In most cases, nutritional therapy alone is sufficient to achieve normoglycemia objectives. However, additional treatment is sometimes necessary67. Women are managed with intensive regimens, based on dietary advice and insulin administration, to limit potential pregnancy complications and improve maternal and infant outcomes, which may include decreased fetal and neonatal mortality, macrosomia, shoulder dystocia, and preeclampsia. However, this same management can be correlated with a high frequency of neonatal hospitalization in intensive care units and induction of labor68. To date, there is no consensus on the anti-diabetic agents to prescribe for patients with GD. In the United States and Canada, insulin is the first-line pharmacological treatment. Conversely, oral therapy is used as first-line therapy in the United Kingdom69. Oral therapy is based on metformin and Glibenclamide. According to American recommendations, insulin can be used in continuous subcutaneous infusion, and insulin analogs can also be safe alternatives to human insulin in the treatment of GD70. However, evidence is still weak to support a specific type of insulin71.

In France, it is recommended to initiate insulin therapy if glycemia is not adequately controlled following a duration of 7 to 10 days of adherence to hygienic-dietary rules. Oral anti-diabetic medications are not authorized for use during pregnancy, even if reassuring data exist regarding their efficacy. They are not recommended for the treatment of GD in the absence of in-depth studies72. For several years, it has been established that the use of insulin is safe as it does not cross the placenta73. However, insulin can cause maternal disorders such as weight gain and hypoglycemia, requiring education of pregnant women in its use. Therefore, oral anti-diabetic medications have received a lot of interest from researchers in recent times63.

Several trials have been conducted to compare the effectiveness of GD treatments. A meta-analysis published in 2018 included 41 clinical trials that compared the efficacy and safety of three treatments, namely metformin, Glibenclamide, and insulin, in the management of GD. The analysis evaluated outcomes such as the quality of glycemic control, premature delivery, neonatal hypoglycemia, gestational weight gain, macrosomia, low birth weight, gestational hypertension, and pre-eclampsia. This meta-analysis shows that metformin could be a safe and effective treatment for GD. It is noteworthy that Glibenclamide is linked to a higher incidence of neonatal hypoglycemia when compared to insulin74. Other recent studies show the effectiveness and safety of metformin utilization in managing GD75. However, these results should be taken with caution due to highly variable transplacental transfer, even though the concentrations found in newborns are generally very low63. Further investigations are warranted to assess the long-term effects on offspring. The most effective treatment remains uncertain, given the evolving population characteristics and diagnostic threshold76.

**Nutritional management of gestational diabetes**

Nutrition is part of the prevention and treatment strategy for GD, and a personalized nutrition program can be developed for women with GD. This program should provide the necessary caloric intake to promote maternal and infant health, achieve appropriate gestational weight gain, and meet glycemic control objectives70. According to recommended dietary allowances for pregnant women, a daily intake of 175 g of carbohydrates, 71 g of protein, 28 g of fiber, and 3 liters of water is advised77. It is recommended to have three main meals and 2-3 snacks per day, with a particular emphasis on a late evening snack around 9:30 p.m., which can help prevent morning ketosis and nocturnal hypoglycemia. Notably, a prospective observational study utilizing the “Myfood24 GDM” online diet and glycemia tool demonstrated improved glycemic control with more frequent meal consumption78. Nonetheless, further research is required to thoroughly assess
the long-term effects of these dietary interventions on both maternal and offspring outcomes.

To evaluate the effect of different nutritional advice in the context of GD, research was conducted in the Cochrane Trials Register and the WOMBAT Perinatal Trials Register in 2012, including 429 women (436 babies), comparing different diets. This comparison did not yield any statistically significant disparities\(^79\). The diets compared in this study were:

- Low GI diet versus moderate GI, high-fiber diet
- Hypocaloric diet versus unrestricted energy diet
- Low-carbohydrate diet
- A diet rich in monounsaturated fats
- Standard fiber diet (20 grams of fiber per day) versus high fiber diet (80 grams of fiber per day)

Overall, these findings suggest that the individualized nutrition program for GD should focus on providing adequate calories, proper nutrients, and appropriate dietary fiber and that more frequent meals may lead to better glycemic control. However, Additional investigations are warranted to ascertain the most favorable dietary strategy for the management of GD.

Due to insufficient evidence regarding the role of nutrition in preventing GD, it appears that the Mediterranean diet can significantly reduce this risk. This diet is primarily composed of fruits and vegetables, which possess numerous antioxidant properties and offer fiber along with micronutrients including magnesium and vitamin C. Additionally, this dietary pattern is distinguished by reduced consumption of red and processed meats and increased intake of high-quality carbohydrates, thereby facilitating the attenuation of free radicals and enhancement of systemic oxidative stress\(^82\).

Low-carbohydrate dietary regimens have sparked much controversy as dietary interventions for patients with GD. Such an intervention may be associated with an increase in fat consumption, which can have a deleterious effect on maternal insulin resistance, ultimately contributing to excessive fetal fat accumulation\(^83\). While low-carbohydrate dietary patterns may attenuate excessive weight gain during gestation, caution must be exercised in their use, as the Institute of Medicine (IOM) suggests an optimal carbohydrate energy percentage (E%) between 46 and 65% and advises a recommended daily intake of at least 175 g of carbohydrates to facilitate brain function development and ensure appropriate fetal growth\(^84\).

The risk of GD onset is augmented with a preconception low-carbohydrate dietary pattern characterized by elevated levels of animal protein and fat. This risk is not observed in a carbohydrate-restricted dietary regimen that is abundant in plant-based proteins and fats. According to the findings of a cohort study comprising 21,457 participants, replacing just 5% of energy derived from animal proteins with vegetable-based proteins was associated with a 51% reduction in the risk of GD. In contrast, replacing 5% of dietary energy derived via carbohydrates with animal proteins led to a 29% increase in GD risk\(^84\).

Supplementation has been associated with a reduction in the incidence of GD. Indeed, probiotics have a protective effect against GD by modifying the intestinal microbiota, which modifies the breakdown of dietary polysaccharides through fermentation and enhances the integrity of the intestinal barrier, resulting in a decrease in the incidence of GD\(^85\). According to studies, the occurrence rate was significantly lower at 13% in the diet/probiotics group compared to 36% in the diet/placebo group and 34% in the control group\(^85\). It has also been demonstrated that administration of myo-inositol supplements during pregnancy significantly reduces the incidence of GD in gravid individuals by sensitizing them to insulin and reducing plasma glucose levels in situations that generate an increase in insulin resistance, including PCOS and the advanced phase of the third trimester of pregnancy\(^86\). Additionally, supplementation with vitamin D has been shown to potentially decrease the risk of premature delivery, hyperalbuminemia, and neonatal hospitalizations. However, further studies are required to elucidate the optimal duration and dosages required for safe supplementation\(^87\). Omega-3 and magnesium supplementation have demonstrated positive effects on patients with GD. These interventions can modulate lipid profile and alleviate insulin resistance in this population\(^88,89\).

It is also important to highlight the role of physical activity in the context of GD. Indeed, physical exercise directly reduces the occurrence of GD and indirectly prevents weight gain during gestation\(^90\). Multiple investigations have confirmed that physical activity can reduce the risk of GD from 23 to 59%\(^91\). The integration of nutritional and
physical exercise interventions has the potential to reduce the incidence and perinatal complications of GD, even though the current level of evidence is moderate.

Nutrition remains a vast field to explore in the context of GD to define adequate dietary interventions. Nutritional therapy for GD is crucial for the mother and fetus health. It should ensure adequate maternal and fetal nutrition while achieving glycemic goals with meals that include energy, vitamins, and macronutrient intake. It is important for women with GD to work closely with a nutrition specialist to create a nutritional plan, as there is no ideal dietary model given the multiple dimensions of nutrition, such as biological, cultural, social, economic, and environmental. Therefore, the nutritional plan must take into account these dimensions while meeting the needs of the woman and the glycemic control imposed by the management of GD.

CONCLUSION

To conclude, GD is a complex disease that requires a multidisciplinary approach combining dietary, behavioral, and pharmacological adjustments to optimize maternal glycemia and avoid pregnancy complications. Nonetheless, early identification of risk factors and screening are crucial for effective management of the disease. It is important to educate pregnant women about the dangers of GD. Scientific advances have improved the management of GD. However, additional research is required to gain a more comprehensive understanding of the disease and improve prevention and treatment.

Recently, great interest has been given to research on GD, and several axes are currently the subject of in-depth investigations. These include, among others, the impact of epigenetics, the identification of new biomarkers for diagnosis and screening, the exploration of underlying risk factors, experimentation with new drugs and nutritional therapy, and the study of the long-term consequences of the disease.

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Conflict of Interest

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