Chapter 32

Gestational diabetes Mellitus: integrative literature review article

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ABSTRACT
Objective: This article aims to discuss gestational diabetes mellitus (GDM), which is increasingly present during the gestational period. Elucidating about pathophysiology, epidemiology, etiology and prevention in order to spread knowledge in the academic and professional environment of the health area, amplifying the number of pregnant women diagnosed and, consequently, treated, to prevent the significant complications of this disease.
Methods: In this work, an integrative literature review was carried out, using articles in the English language between the years 2010 to 2022, electronically searched in the free PubMed and UpToDate database, using the keywords: "Diabetes, Gestational", " Obesity, Maternal", "Hypoglycemic Agents", "Pregnancy Complications", "Metabolic Diseases".
Results: Initially, 61 articles were identified, but 8 of these articles selected in the first instance did not meet the inclusion criteria, being excluded after analysis by the authors of this review article. In all 53 articles selected for the development of the work, they were explored in order to extract all kinds of relevant information and carry out counterpoints according to different dates and authors, resulting in a change and evolution of the methods of treatment and management of pregnant patients since 2010 up to the current scenario.
Conclusion: This article made it possible to identify, through the authors' analysis, that GDM is an underreported pathology, in which pregnant women experience the repercussions of hyperglycemia without the correct treatment. However, when the diagnosis is performed properly, therefore, therapeutic measures are easy to manage.

1 INTRODUCTION

Gestational diabetes mellitus (GDM) is defined by carbohydrate intolerance in varying degrees of intensity, starting after pregnancy, which may or maynot persist after delivery. It is a multifactorial pathology, but it is closely relatedto maternal obesity, physical inactivity and family history of diabetes mellitus. [1]

In addition, GDM is a very common clinical condition during pregnancy, mainly due to the obesity epidemic, which has shown an increase in cases of diabetes mellitus in pregnant and non-pregnant women. [2]

GDM can negatively interfere with intrauterine development, causing macrosomia, neonatal hypoglycemia, jaundice, sudden late fetal death, intrauterine growth restriction (IUGR) and polycythemia, as well as influencing labor, causing complications such as shoulder dystocia and infections . In addition, they also pose a risk to pregnant women, as they are more likely to develop type 2 diabetes mellitus after delivery, as well as diabetic ketoacidosis, maternal hypertensive disorders, diabetic retinopathy, peripheral neuropathy, and miscarriage. [3], [4]

Therefore, in order to avoid such complications during pregnancy and in the puerperium, GDM screening is recommended in all pregnant women, start-ing from the first prenatal consultation, which may differ is the laboratory test re-quested, being either capillary blood glucose fasting, if the pregnant woman isin less than twenty weeks at her first prenatal visit, or the oral glucose tolerance test (OGTT), which is requested between the 24th and 28th week. [5]

It is important to point out that only an altered value in any of these tests already establishes the diagnosis of GDM, excluding the need for a second confirmatory test. that this condition can resolve in the puerperium, or the pregnant woman can progress to type 2 diabetes mellitus . [6]

This study refers to a qualitative exploratory approach to identify productions on the topic of gestational diabetes mellitus, published between 2010 and 2022. An integrative literature review was adopted, since it contributes to the process of systematization and analysis of results, aiming at understanding a given topic, based on other independent studies.

The strategy for identifying and selecting the studies was to search for publications indexed in the *PubMed database*, in the months of February and March 2022. From the articles obtained, a thorough reading was carried out, highlighting those that responded to the objective proposed by this study, in or-der to organize and tabulate the data and results.

The objective of this work is to expose the characteristics of gestational diabetes mellitus, such as pathophysiology, diagnosis and treatment. In additionto presenting the risk factors of this disease, as well as its etiology and complications, emphasizing the diagnosis and treatment, since it is a pathology that offers great risks to the mother and the fetus. For these reasons, the earlier the investigation of the

pathology and the management of the patient, the better theprognosis, thus, it becomes possible to prevent harmful outcomes for both the pregnant woman and the fetus.

2 MATERIALS AND METHODS

This is a qualitative exploratory study to identify productions on the topic of gestational diabetes. An integrative literature review was adopted, since it contributes to the process of systematization and analysis of results, aiming at understanding a given topic, based on other independent studies. The integrative literature review proposes the establishment of well-defined criteria for data collection, analysis and presentation of results, from the beginning of the study.

For that, the six steps indicated for the constitution of the integrative literature review were adopted: 1) selection of the research question; 2) definition of inclusion criteria for studies and sample selection; 3) representation of the selected studies in table format, considering all common characteristics; 4) critical analysis of the findings, identifying differences and conflicts; 5) interpretation of results and 6) clearly reporting the evidence found. The strategy for identifying and selecting the studies was to search for publications indexed in the free database, in the months of February, March and April 2022, being accessed through the PubMed and UpToDate websites.

The following criteria were adopted for the selection of articles: all article categories (original and updated); articles with abstracts and full texts available for analysis; those published in English, between 2010 and 2022, and articles that contained in their titles and/or abstracts the following keywords: “Diabetes, Gestational”, “ Obesity, Maternal”, “Hypoglycemic Agents”, “Pregnancy Complications ”, “Metabolic Diseases”. In this way, a total of 53 articles. 8 were ex- cluded articles that did not meet the aforementioned inclusion criteria. Consequently, they totaled 53 different references.

3 EPIDEMIOLOGY

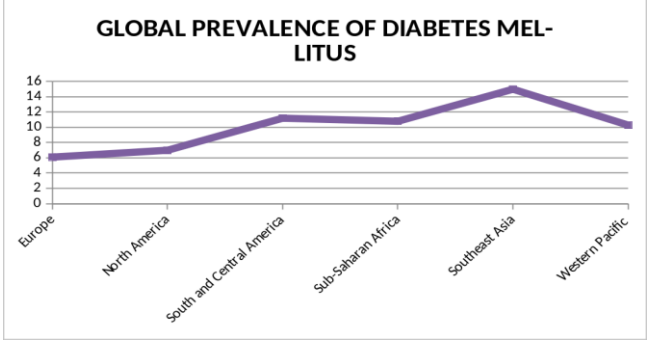
Diabetes Mellitus is an important health problem today, both in terms of the number of people affected, disability, premature mortality, and the costs involved in controlling and treating its complications. The prevalence of GDM, oneof the most common complications of pregnancy, has increased by more than 30% in one to two decades in several countries, including developing countries. [7] GDM has been linked to substantial short- and long-term adverse health out- comes, such as an increased risk of developing cardiometabolic disorders later in life among women and their children global DMG load. Any woman can develop gestational diabetes, however, there is an increased risk in cases of obesity, family history of diabetes, previous history of childbirth with the birth of a baby weighing more than four kilos, stillbirth or with a congenital defect. Thereis also an increased risk when there is excess amniotic fluid (polyhydramnios) and for older women. [8]

The prevalence of GDM varies greatly, depending on the characteristics of the population and the diagnostic criteria used. In 2017, it was estimated that one in seven live births worldwide was affected by GDM. This represented 85% of the total 21.0 million live births affected by diabetes during pregnancy world - wide. [9] This prevalence was higher among overweight and obese pregnant women. An adequate prenatal care should carry out the screening of Gestational Diabetes and promote the treatment of pregnant women diagnosed with these diseases from a correct dietary and nutritional orientation, so that aweight gain is achieved within what is considered desirable and, consequently, good glycemic control. [10]

Another strong risk factor for GDM is race/ethnicity. In countries with multi-ethnic populations, such as the US, Canada, and Australia, notable differences in the specific racial/ethnic prevalence of GDM have been documented. For example, a US study in Northern California reported that the prevalence was highest among Asians (10.2%), intermediate among Hispanics (6.8%), and lowest among non-Hispanic whites (4.5%) Afro -Americans and Americans(4.4%) with the lowest prevalence. [7] In South and Central America, two studies from Brazil reported a 1.3- and 7.5-fold increased risk of T2DM with a cumulative incidence ranging from 8.6 to 30.4% after 6.2 years and 16–24 years.weeks of follow-up, respectively. [11] Brazil is the fourth country in the world among the countries with the highest rates of DM in the adult population, with a total of 14.3 (12.9-15.8) million people aged 20 to 79 years with DM. In the meantime, the graph below shows the GDM sample by World Health Organization (WHO) region - namely: Europe, North America, South and Central America, Sub-Saharan Africa, Southeast Asia and the Pacific West - that the region- specific prevalence of GDM was estimated by calculating the median prevalence of country-specific diseases and estimates within each region **(Fig 1)** . Population estimates of hyperglycemia during pregnancy in Brazil are conflicting, but the prevalence of GDM in the Unified Health System (SUS) is estimatedto be approximately 18%, using current diagnostic criteria. [12]

Finally, emerging risk factors, in addition to diet and lifestyle, indicate a possible contribution of environmental and psychosocial factors to the risk of developing GDM. [13] For example, greater exposure to persistent organic pollutants and endocrine disruptors has been associated with increased risk of GDM. Furthermore, depression in the first and second trimester was prospectively related to this risk. [11]

Fig 1: Reports the global prevalence of GDM from 2005 to 2018. It is possible to illustrate a sample of GDM by WHO region. The region-specific prevalence of GDM was estimated by calculating the median prevalence of country-specific diseases and estimates within each aforementioned region.



4 ETIOLOGY

One of the most common complications in pregnancy, Gestational Diabetes is a metabolic condition exclusive to pregnancy and is due to increased insulin resistance caused by pregnancy hormones. (7)

Women affected by GDM are divided into two distinct groups: women diagnosed with diabetes before pregnancy and those with gestational diabetes mellitus. (15)

The etiology appears to be related to pancreatic beta cell dysfunction or delayed beta cell response to glycemic levels, and marked insulin resistance secondary to placental hormone release. Human placental lactogen is the main hormone related to increased insulin resistance in GDM. (16) Other hormones related to the development of this disease are growth hormone, prolactin, corticotropin-releasing hormone, and progesterone. These hormones contribute to the stimulation of insulin resistance and hyperglycemia in pregnancy. (17)

The factors that most predispose to the development of GDM include overweight, obesity, advanced maternal age and family history or any form of diabetes. In addition, the consequences of disease progression include an in- creased risk of maternal cardiovascular disease and type 2 diabetes. In the fetus, there is a risk of macrosomia and complications in childbirth. (15)

5 PATHOPHYSIOLOGY

In healthy pregnancy, the mother's body undergoes a series of physiological changes to meet the needs of the growing fetus, with insulin sensitivity being an important metabolic adaptation. (18) GDM is the consequence of the in- ability of pancreatic beta cells to respond adequately to the increased needs of pregnancy. (18) In early pregnancy, insulin sensitivity increases, which leads to glucose uptake in adipocyte stores in preparation for the energy demands of pregnancy. (19) This insulin sensitivity decreases markedly in the second and third trimester of pregnancy. (20) Consequently, it promotes insulin resistance, which has been attributed to the effects of hormones released by the placenta, local hormones, such as human placental lactogen (HPL), placental growth hormone (PGH), estrogen, progesterone, leptin, cortisol. (11) This state of insulin resistance makes it less effective in suppressing endogenous glucose production (mainly hepatic) and glucose uptake by peripheral skeletal muscle and adipose tissue, which results in clinical hyperglycemia (20) , that is, , there is an increase in glucose production and a decrease in glucose absorption. This state of maternal hyperglycemia results in the placental transfer of glucose to the fetus, generating fetal hyperglycemia, which can have short-term consequences, suchas fetal overgrowth and preeclampsia, and also long-term consequences, such as metabolic dysfunction in adulthood . (11) Here are some changes during the DMG:

5.1 DYSFUNCTION OF PANCREATIC BETA CELLS

The primary function of pancreatic beta cells is to store and secrete insulin in response to glucose loading. When these cells lose the ability to properly detect the concentration of glucose in the blood, or to release enough insulin in response to the increase in glucose, this is classified as cellular dysfunction. Defects can occur at any stage of the process, such as: proinsulin synthesis, post-translational modifications, granule storage, detection of blood glucose concentrations, or the complex machinery underlying granule exocytosis.It is still possible to observe that most of the susceptibility genes associated withDMG are related to cellular function, including potassium voltage-gated KQT- like 1 channel (Kcnq1) and glucokinase (Gck). Minor deficiencies in machinery are exposed in times of metabolic stress, such as pregnancy. [19] GDM is then shown to be characterized by a transient form of diabetes induced by insulin resistance and pancreatic β-cell dysfunction during pregnancy. [21]

5.2 INSULIN RESISTANCE

Insulin resistance occurs when cells do not respond properly to insulin. Atthe molecular level, insulin resistance is usually a failure of insulin signaling, resulting in the inappropriate translocation of glucose transporter 4 (GLUT4) into the plasma membrane, the primary transporter responsible for bringing glucose into the cell for use as energy. The rate of insulin-stimulated glucose uptake is reduced by 54% in GDM compared to normal pregnancy.

Several of the previously discussed risk factors for GDM are thought to exert their effects by interfering with insulin signaling. For example, saturated fatty acids increase intracellular concentrations of diacylglycerol within myocytes, activating protein kinase C (PKC) and inhibiting tyrosine kinase, IRS-1, and PI3K. Pro-inflammatory cytokines and adiponectin also modify this process,resulting in insulin resistance. [19] Other factors that contribute to insulin resistance are: beverage consumption, fast food consumption, which are significantly associated with a higher risk of GDM, these factors seem to interfere withthe failure of insulin signaling and consequent insulin resistance. [22]

5.3 ADIPOSE TISSUE

Early pregnancy is marked by increased adipose tissue mass, while late pregnancy promotes the mobilization of fats from adipose tissue to fuel fetal growth. Both processes are considered limited in the DMG. DMG is associated with reduced adipocyte differentiation and increased adipocyte size (hypertrophy), accompanied by dysregulated gene expression of insulin signaling regulators, fatty acid transporters and key adipogenic transcription factors. The combination of insulin resistance and reduced adipocyte differentiation hampers the tissue's ability to safely dispose of excess energy, contributing to glucotoxicity and lipotoxicity in other peripheral organs.

It is worth noting that obesity, diabetes mellitus, and GDM are associatedwith an increased number of adipose tissue macrophages that secrete pro-inflammatory cytokines, including TNF, IL-6, and IL-1. Pro-inflammatory cytokineshave been found to impair insulin signaling and inhibit the release of insulin from cells. These factors induce insulin resistance by decreasing insulin receptor (IR) tyrosine kinase activity, increasing serine phosphorylation on insulin receptor substrate 1 of the insulin receptor. Circulating concentrations of pro-inflammatory cytokines are increased in DMG . [19] Many metabolites that are known to be implicated in impaired glucose homeostasis or are specific for inflammation and altered redox balance have been associated with GDM, such as: Catabolic alterations prevail with increased lipolysis and increased blood glucose, insulinemia, postprandial fatty acids and decreased maternal fat stores. [23]

5.4 LIVER

DMG is associated with up-regulated hepatic glucose production (gluconeogenesis). Gluconeogenesis is increased in the fasted state and not adequately suppressed in the fed state. This is not believed to be entirely the result of inaccurate glucose detection due to insulin resistance, as the majority of glucose uptake by the liver about 70% is not insulin dependent.

Common factors between the insulin signaling pathway and the pathways that control gluconeogenesis, such as PI3K, may contribute to these effects. This in-crease in gluconeogenesis contributes to the hyperglycemic state. [19]

5.5 SKELETAL MUSCLE

At the end of pregnancy, one of the signaling molecules present in skeletal muscle, insulin receptor substrate 1 (IRS1), is lower than in non-pregnant women. In addition to decreased IRS1 levels, IRβ autophosphorylation is lower in women with GDM than in pregnant women with normal glucose tolerance, resulting in 25% lower glucose uptake in skeletal muscle. As a result, blood glucose rises. [19]

5.6 INFLAMMATION AND OBESITY

Inflammation, often associated with obesity, has been identified as an- other factor that disrupts the insulin signaling cascade. Tumor necrosis factor (TNF) activates a signaling pathway that increases levels of sphingomyelinase and ceramides, which interfere with insulin receptor tyrosine autophosphorylation, and promotes serine phosphorylation of IRS1, which disrupts the insulin signaling cascade. . In pregnancy, circulating levels of TNF are significantly in- creased and this is correlated with insulin sensitivity, even after adjustment for maternal fat mass . [19] The contribution of obesity is the most salient modifiablerisk factor for the condition and presents an important predictor for GDM, as in

one study estimated the relationship between obesity and overweight and GDM is 46% [confidence interval of 95 % (CI)] 36-56%]. [18]

5.7 PLACENTAL TRANSPORT

The placenta contributes to insulin resistance during pregnancy through the secretion of hormones and cytokines. As a barrier between the maternal and fetal environments, the placenta itself is also exposed to hyperglycemia andits consequences during GDM. This can affect the transport of glucose, amino acids, and lipids across the placenta . [19] These changes are induced, at least in part, by hormones and other mediators secreted by the placenta, which facili- tate the occurrence of a physiological condition of peripheral insulin resistance that can be aggravated by both advanced maternal age and prenatal excess weight gestational. [23]

5.8 PLACENTAL AND LOCAL HORMONES

Historically, insulin resistance during pregnancy has been attributed tothe effects of hormones released by the placenta, such as human placental lactogen (HPL; also known as choriomamotropin) and placental growth hormone (PGH). HL is characterized by being counterinsulin (as are growth hormone, corticotropin-releasing hormone, and progesterone). It begins to be produced in the 2nd trimester, promoting the replacement of the hypoglycemic state of the 1st trimester by an insulin resistance profile, being a physiological process of pregnancy. The pathophysiology of gestational diabetes occurs at this time, whenthe pancreas is unable to bypass this hyperinsulinic state . [19]

6 CLINICAL CONDITION

The clinical picture of gestational diabetes mellitus is predominantly asymptomatic in early stages, and can be established throughout pregnancy. However, among patients who present symptoms, their main clinical manifestations include short-term consequences for the mother and offspring, among them **:** preeclampsia, polyhydramnios, shoulder dystocia, lacerations of the birthcanal, fetal overgrowth (also called macrosomia), neonatal hypoglycemia, jaundice and, in some studies of untreated GDM, mortality of both mother and off- spring. [11] This gradual increase in the risk of maternal, fetal and neonatal complications is directly linked to the increase in maternal glucose. In the long term, it has been proven that there is a seven-fold increased risk of T2DM in women with GDM compared to women with normoglycemic pregnancies . [24] Therefore,for most women, a diagnosis of GDM will cause considerable changes in the perception of pregnancy. A medical diagnosis of GDM will change your pregnancy from 'normal' to 'abnormal' and may be associated with anxiety, compromising maternal health. This anxiety can culminate in several psychological problems, directly affecting the mother's behavior during pregnancy. [11] These psychological symptoms also affect the mother's diet, so polyphagia is another

common symptom in GDM, where this pregnant woman has an increased appetite and, consequently, results in exaggerated weight gain (maternal or fetal), which is an aggravating factor in the clinical picture of the patient. [15]

Complaints of polydipsia can also be found, accompanied by frequency, which are common manifestations in other types of diabetes. [4] Other symp- toms such as tiredness and malaise are frequent, as they are characteristic re- ports of the gestational period itself. As well as edema in the upper and lower limbs, which affect pregnant women during the pregnancy period. [2] In turn, blurred vision is also an indication found in the complaints of patients with GDM,and may be accompanied by recurrent vertigo. This symptomatology may vary from woman to woman, being related to the degree of her GDM, previous problems, lifestyle such as diet, physical activity and body weight, and appropriate multidisciplinary follow-up is recommended for each case. [25]

7 DIAGNOSIS

The forms of diagnosis of DMG underwent several tests since 1960 until the criteria we know today were established. The observational study Hyperglycemia and Adverse Pregnancy Outcome (HAPO) is of great importance in the evolution of the diagnosis of GDM, in order to determine factors that establish the relationship between maternal hyperglycemia and adverse perinatal out-comes. Based on the findings of the HAPO study, the recommendation of the International Association of Pregnancy and Study Groups (IADPSG) for the diagnosis of GDM adopted the following values considered as borderline: fasting glucose up to 92 mg/dL; Oral glucose tolerance test (OGTT) up to 180 mg/dL one hour after 75 g glucose load; and maximum OGTT value equal to 153 mg/dL, two hours after overload, of 75 g of glucose. In 2013, the WHO publishedthe diagnostic criteria for GDM, using the same cutoff points presented by the IADPSG, adding that fasting blood glucose ≥ 126 mg/dL or after overload with a value ≥ 200 mg/dL would be diagnostic criteria for clinical DM and not the DMG. [26]

GDM is one that occurs in women without a previous diagnosis of DM,but who have hyperglycemia detected for the first time during pregnancy. This means that the presence of a fasting blood glucose result ≥126 mg/dL, attested on a second occasion, in the first trimester of pregnancy, indicates pre-pregnancy DM. [27]

The criteria and ways of diagnosing GDM differ globally. For example, in the United States, most guidelines encourage a two-step approach to GDM screening: a 50g non-fasting OGTT test is initially given, followed by a 100 g fasted OGTT test for women who have a positive screening result. However, clinicians can also use the IADPSG/WHO one-step approach using a 75 g OGTT in a 2-hour fast rather than the two-step approach. [27]

According to the Brazilian diagnostic consensus for GDM, universal screening should be performed using fasting glucose and oral glucose tolerancetest (OGTT) 75 g. Thus, the diagnosis of GDM

would be established in the face of fasting glucose ≥ 92 mg/dL and/or at least one of the OGTT values with 75 g

≥ 180 mg/dL in the first hour and ≥ 153 mg/dL in the second hour. Thus, it couldbe concluded that from at least one abnormal exam, this woman would already be classified with GDM. [27] **(Table 1).**

Fasting blood glucose is performed through a blood test, where the blood glucose count is performed. This test is requested in the first prenatal consultation and a result ≥ 92 mg/dL classifies the pregnant woman with GDM. Women with blood glucose levels below 92 mg/dL by fasting blood glucose should undergo OGTT between 24 and 28 gestational weeks. Dosages need to be done on an empty stomach and at 60 and 120 minutes after ingesting 75 g of glucose. [27] In summary, the flowchart below was designed to explain the screening of fasting blood glucose in pregnant women at the 1st prenatal visit **(Fig 2)** .

Fig 2: The flowchart describes how DMG tracking is done. In the 1st prenatal consultation of the pregnant woman, a fasting blood glucose test should be requested, along with other laboratory tests. In view of the results, a blood glucose value ≥ 126 mg/dL does not classify a woman with GDM, but a previous DM, which was only discovered during pregnancy; Values between 92 mg/dL and 126 mg/dL give the woman the diagnosis of GDM; thus, values lower than 92 mg/dL at the first prenatal visit are not considered diagnostic criteria for GDM, but the pregnant woman will still be screened again between 24-28weeks of gestation using the OGTT.

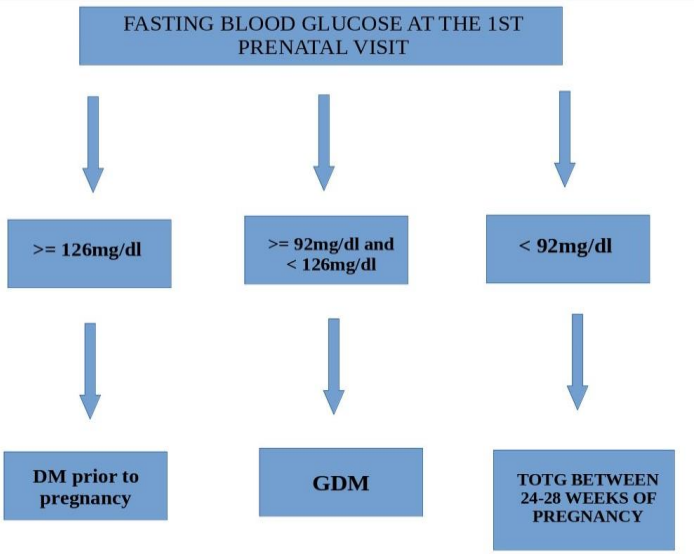


Table 1: This table summarizes the diagnostic criteria used for GDM. Thus, in the face of fasting glucose ≥ 92 mg/dL and/or at least one of the OGTT values with 75 g ≥ 180 mg/dL in the first hour and ≥ 153 mg/dL in the second hour are sufficient to classify the pregnant woman with GDM. .

Criteria for diagnosing GDM	Glucose (mg/dL)
fasting blood glucose	≥ 92 hours
OGTT with 75 mg and collection after 1	≥ 180 hours
OGTT with 75 mg and collection after 2	≥ 153 hours

8 TREATMENT

8.1 NON-PHARMACOLOGICAL TREATMENT

In GDM, the main treatment is non-pharmacological, because only with lifestyle modification (SEM), it is possible to significantly reduce blood glucose.It is estimated that among women diagnosed with GDM, only with SEM it was possible to control blood glucose in 70 to 85% of cases. [28]

The main SEM measures that bring this attenuation of laboratory values consist of a carbohydrate-restricted diet, limited to up to 40% of daily caloric in- take, in addition to moderate physical activity, totaling 150 minutes per week. [29]The guidance may vary according to the patient's preference, and may be 30 minutes of physical exercise five times a week, or 40 to 60 minutes on three different days, recommended for women regardless of their GDM status. [30]

As mentioned, physical activity is extremely important, because it is able to reduce insulin resistance in non-pregnant individuals, in addition to stimulating glucose transporters on the surface of skeletal muscle cells, thus improving glucose uptake. in the organism. [31]

In maternal nutrition, among the macronutrients consumed, carbohydrate is one of the most important, as it ensures adequate fetal growth, as well as the development of brain function, for this reason, the minimum amount to be consumed per day is approximately 175 g of carbohydrates, while these should come from vegetables, legumes, fruits and whole grains, as these foods are richin starch, in addition to having a low glycemic index and a naturally high contentof dietary fiber. [24]

In addition, after the diagnosis of GDM and while pregnant women adopt SEM, it is important to carry out monitoring by measuring capillary blood glucose at least twice a day, the first being fasting and the second one hour after any meal of the day. The ideal values for this control consist of a fasting glucose lower than 95 mg/dL, and lower than 140 mg/dL after 1 h of the meal. [23]

8.2 PHARMACOLOGICAL TREATMENT

When these values are not being reached, despite the implementation of SEM, it becomes essential to start pharmacological therapy. Thus, insulin is the main drug used for the treatment of GDM, as it does not cross the placental barrier, thus, it does not pose risks to the fetus. [32] In addition, this medication facili tates strict glycemic control, however, attention should be paid to the high risk it presents of causing hypoglycemia, for this reason it is important to provide education and knowledge to the patient before starting this therapy. [15]

The most commonly used forms of insulin are those of human origin, including regular insulin, which has rapid action, and NPH, which is of intermediate action. . However, recent studies show that there is also great safety when using insulin analogues, in addition to being safer in terms of the risk of causing hypoglycemia, and may also provide better control of blood glucose. [33]

The most commonly used analogue insulins are aspart and lispro, both ofwhich have an ultra-rapid action, such as detemir, but this is long-lasting. They were created by changes in pharmacokinetics, so changes occur in characteristics such as time to dose application or duration of action, so can be used together to cover immediate meals and subsequent meals. (34)

Both insulin lispro and aspart are approved for use in pregnancy. Similarly, insulin detemir has not demonstrated adverse maternal or neonatal effects and has been approved by the Food and Drug Administration (FDA) for use in pregnancy. (35)

Therefore, the recommendation is insulin as the first therapeutic choice for GDM, however, there are some situations that may require the use of oral antidiabetics, including: non-accessibility to insulin; difficulty in self-administration of insulin; the stress in exacerbated levels for the patient in relation to the administration of this medication; the need for high daily doses of insulin (>100IU) without adequate response in glycemic control. (36)

In these cases, the drug option is metformin, this is a second-generation biguanide that acts by decreasing glycemic levels, in addition, there was also a lower maternal weight gain compared to the use of insulin, as well as a decrease in arterial hypertension. maternal mortality, severe neonatal hypoglycemia and neonatal intensive care admission. (37) However, there was an in- crease in the number of preterm deliveries, as well as an increase in the body mass index in the offspring of the patient who used metformin, which may indicate an increased risk of childhood obesity. (38) The risks of preeclampsia, shoulder dystocia, and cesarean section were not significantly different between the metformin and insulin groups. (39)

9 PREVENTION

A study conducted at Peking University First Hospital reported that the incidence of GDM can be reduced by a certain amount of lifestyle intervention, including education about “proper diet, physical activity, and weight gain during pregnancy.” It is indicated that a diversified diet based on plant foods and cereals should be promoted for the health and prevention of GDM during pregnancy. (40)

Physical exercise is a non-invasive therapeutic option for the prevention and management of GDM. A prospective randomized clinical trial conducted at the First Hospital of Peking University, China, showed that supervised stationary cy-cling three times a week for at least 30 minutes per session started in early pregnancy can decrease the risk of GDM in overweight and obese pregnant women. by 45.8%. Exercise during pregnancy is beneficial for the health of the mother and fetus, including preventing excessive maternal weight gain, keepingfetal weight within the normal range, preventing pregnancy complications, and reducing the risk of macrosomia. an interesting preventive measure. (40)

A meta-analysis published in 2015 provides some evidence that lifestyle modification (diet, physical activity, or both) initiated before the fifteenth gestational week may reduce the risk of GDM.

Prenatal dietary supplementation with myoinositol (a secondary messenger derivative involved in several signaling path- ways, including the insulin pathway) for the prevention of GDM is a comparatively new intervention. In two small clinical trials, myoinositol supplementation reduced the risk of GDM, while in a larger trial, supplementation with a combination of inositol in early pregnancy did not prevent GDM in women with a family history of diabetes. (41) In a global view, there is currently no firm evidence to support the use of probiotics for the prevention of GDM, as demonstrated in some studies. (42)

The focus of preventive efforts will likely need to shift to the preconception period or very early pregnancy to achieve the expected reductions in both GDM prevalence and pregnancy complications. Population efforts to reduce the life- time prevalence of obesity and hyperglycemia, especially in girls and young women, may be needed to reverse the tide of these dual global epidemics and thereby reduce the prevalence of GDM. (42)

10 PROGNOSIS

A detailed assessment of the presence and evolution of clinical complications of diabetes is essential both for preconception counseling and for having adequate conditions for prenatal care. (43)
The most common complications reported in mothers with GDM are described below:

10.1 TYPE 2 DIABETES MELLITUS

Pregnancy produces hormones that cause high insulin resistance, which can trigger diabetes. Furthermore, the endocrine system in this circumstance is unable to produce normal amounts of insulin due to the pregnancy state. (44)

10.2 CARDIOVASCULAR DISEASE

GDM increases the postpartum risk of metabolic syndrome and cardio- vascular disease. Patients with previous GDM are at increased risk for cardio- vascular events such as hypertension, dyslipidemia and obesity. Specifically, the GDM was found to be an independent risk factor for long-term maternal ill - ness risk of non-invasive diagnostic procedures, single-event cardiovascular disease and cardiovascular hospitalizations. (45)

10.3 KIDNEY DISEASE

It appears to be a significant risk factor for long-term, high-morbidity kidney disease. The most common diagnoses in the future will be real hypertensive disease without kidney failure, hypertensive kidney disease with kidney failure, chronic kidney disease and end-stage renal disease. (19)

10.4 EYE DISEASE

GDM has also been reported as a significant risk factor for long-term ophthalmic morbidity: Women with a history of GDM had a significantly higher incidence of ophthalmic morbidity (eg, glaucoma, diabetic retinopathy, retinal detachment), at the joint risk with diabetes type 2 mellitus. (46)

On the other hand, due to GDM, the fetus ends up suffering some consequences, including.

10.5 MATERNAL HYPERGLYCEMIA

Maternal hyperglycemia leads to a hyperglycemic state in the fetus, stimulatingthe fetal pancreas and resulting in hypertrophy and hyperplasia of beta cells, with an increase in the level of insulin in the fetus. In addition, it is responsible for the occurrence of fetal osmotic diuresis leading to an increase in the volume of amniotic fluid and, consequently, to polyhydramnios. (47)

10.6 RESTRICTION OF FETAL GROWTH

The increase in fetal glycated hemoglobin levels, avid for oxygen, favors the decrease of free blood oxygen and tissue hypoxia and can lead to fetal death, which explains the suffering of the fetus. On the other hand, inhibition of lung maturation mechanisms leads to higher rates of respiratory distress syndrome. (48)

10.7 RESPIRATORY DISTRESS SYNDROME

It is characterized by tachypnea, retraction of the intercostal muscles, hypoventilation, hypoxia. Hyperinsulinemia inhibits the action of cortisol in the fetal lung, leading to inhibition of lecithin production by the type 2 pneumocyte. Lecithin isa phospholipid present in surfactant that stabilizes the pulmonary alveolus during expiration, and its decrease leads to respiratory distress syndrome. (49)

10.8 NEONATAL HYPOGLYCEMIA (POSTPARTUM)

The mechanism that causes the newborn to exhibit hypoglycemia is the relative increase in insulin secretion by the pancreas of fetuses exposed to high plasmaglucose levels (Pedersen's theory). It is defined as serum glucose levels below 40 mg/dl in term newborns during the first 12 hours of life. (50)

Fig 3: This figure describes maternal complications related to GDM. The most common manifestations are the emergence of type 2 Diabetes Mellitus, renal, ophthalmologic and cardiovascular disease. All these complications are due to insulin resistance, causing a hyperglycemic state.

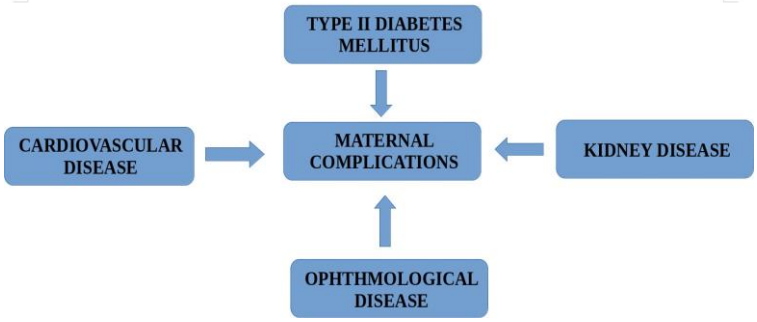
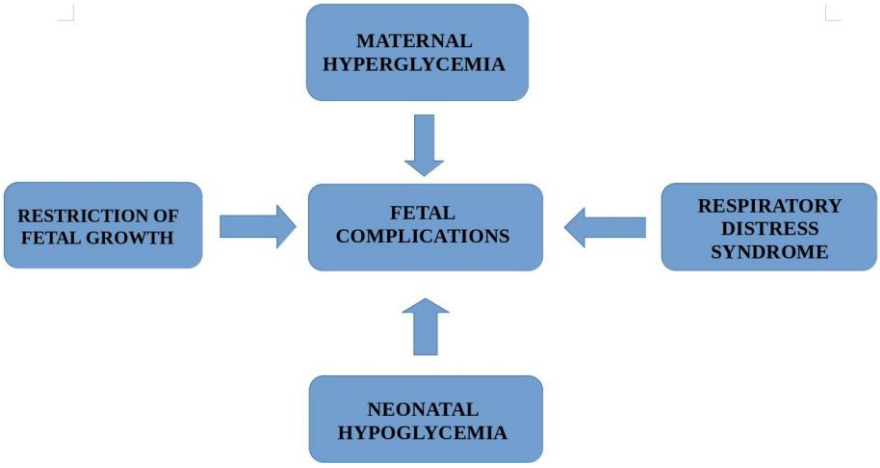


Fig 4: This figure depicts fetal complications related to GDM. The most common fetal complications to be described are due to maternal hyperglycemia andneonatal hypoglycemia. It is worth remembering that fetal growth restriction andrespiratory distress syndrome are closely linked.



11 PSYCHOSOCIAL ASPECTS

GDM has potentially important consequences for the short- and long- term health of both mother and baby. One of the most frequent perinatal consequences of GDM is macrosomia, which can increase the risk of cesarean section and shoulder dystocia. For the mother, there are also consequences, such as an increased risk of type 2 diabetes and an increased risk of cardiovascular disease. GDM is also associated with reduced psychosocial well-being: women with GDM are two to four times more likely to develop prenatal or postpartum depression, which is associated with an increase in caloric intake and a reduction in physical activity, promoting a greater risk of weight gain. [51],[52],[53]

Pregnancy is a vulnerable time for a woman who is adapting and responding to bodily changes such as loss of strength or fitness, which can result in reduced self-esteem. Many women report depression and anxiety during pregnancy due to concern for the baby's well-being. Therefore, a diagnosis of a health condition such as this can have a detrimental effect on the pregnant woman's quality of life. When initially diagnosed with the condition, most womenreported reactions such as guilt, failure, fear, sadness, worry and confusion. In some cases, the diagnosis was positively received and was seen as an opportunity for lifestyle improvements. Thus, the way in which the diagnosis shouldbe made is also an impacting

moment for the woman and her family members. The quality of communication, information and understanding your role as a doctor in this situation should always be valued. [51]

The behavior of the maternal lifestyle is also an important point for the quality of life of the woman and the baby. In view of this, it is very important to work on modifiable risk factors during the gestational and puerperal period, with diet, physical activity and psychosocial well-being. Excessive gestational weightgain is frequent in women with GDM and is strongly associated with lifestyle factors during pregnancy. High fat intake, higher sugar intake, and lower intake of vegetable and fruit fiber are linked to increased fasting blood glucose. An - other important domain that can address risk factors for GDM is physical activity, which decreases insulin resistance, reduces future risk of type 2 diabetes, and decreases gestational weight gain. Thus, physical activity has a protective effect on the development of GDM. [52]

Psychological factors also play an important role in GDM. Greater expo- sure to stress is associated with increased fasting blood glucose levels. Psycho-logical stress may also be associated with higher cortisol levels, which can influence glucose levels. In addition, GDM is a stressful event that can be a risk factor for postpartum depression in women. Management of GDM can induce depressive symptoms attributed to psychological distress. Some studies suggest that diabetes and depression may share several biological origins such as: high pro-inflammatory cytokines, dysregulation of the hypothalamic-pituitary-adrenal axis and insulin resistance. However, future studies are still needed to clarifythe mechanisms that link DMG to postpartum depression. [52],[53]

12 CONCLUSION

The present study exposes GDM, a pathology exclusively related to pregnancy and which has shown an increase in its prevalence in recent years, mainly as a result of the obesity epidemic that occurs in several countries, including the most developed. Among the main risk factors are being overweight, family history of diabetes and physical inactivity, however, the most important thing to remember is that the changes that occur in the mother's body during pregnancy are the biggest reason for developing intolerance to absorption of carbohydrates, due to insulin resistance caused by the increased release of hormones during this period, which triggers a state of maternal hyperglycemia.

This condition can lead to different maternal and fetal complications, for this reason it is extremely important to screen for GDM in all pregnant women, based on the measurement of fasting blood glucose in the 1st trimester, withthe diagnosis being made when the blood glucose value becomes higher is above 92mg/dL. Once the pregnant woman receives this diagnosis, she will carry it with her until the end of pregnancy, as this pathology has no cure, but there are non-pharmacological and drug approaches that alleviate, or even pre- vent the consequences of the disease.

Within the treatment, SEM is the first choice, as about 70% of pregnant women can reduce glucose levels only with a balanced diet and physical exercise. Insulin therapy is reserved for cases in which

glycemic control was not ad- equate, with NPH and regular insulin being used mainly, as there are several studies proving its safety. However, for some reserved cases, metformin is indicated as the second drug of choice.

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REFERENCES

1. Johns EC, Denison FC, Norman JE, Reynolds RM. Gestational Diabetes Mellitus: Mechanisms, Treatment, and Complications. Trends in Endocrinology & Metabolism. 2018 Nov;29(11):743–54.

2. Lende M, Rijhsinghani A. Gestational Diabetes: Overview with Emphasis on Medical Management. International Journal of Environmental Research andPublic Health. 2020 Dec 21;17(24):9573.

3. Mack LR, Tomich PG. Gestational Diabetes: Diagnosis, Classification, and Clinical Care. Obstetrics and Gynecology Clinics of North America [Internet]. 2017 Jun 1;44(2):207–17. Available from: https://www.sciencedirect.com/science/article/abs/pii/S088985451730013X?via%3Dihub

4. Buchanan TA, Xiang AH, Page KA. Gestational diabetes mellitus: risks and management during and after pregnancy. Nature Reviews Endocrinology [Internet]. 2012 Jul 3;8(11):639–49. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4404707/

5. Negrato CA, Montenegro RM, Mattar R, Zajdenverg L, Francisco RPV, Pereira BG, et al. Dysglycemias in pregnancy: from diagnosis to treatment. Brazilian consensus statement. Diabetology & Metabolic Syndrome [Internet]. 2010 Apr 24 [cited 2022 Apr 19];2:27. Available from: https://pubmed.ncbi.nlm.nih.gov/20416099/

6. Tieu J, McPhee AJ, Crowther CA, Middleton P, Shepherd E. Screening forgestational diabetes mellitus based on different risk profiles and settings forimproving maternal and infant health. Cochrane Database of SystematicReviews [Internet]. 2017 Aug 3 [cited 2019 Apr 22]; Available from:https://www.cochrane.org/CD007222/PREG_screening-women-gestational- diabetes-pregnancy-based-whether-they-are-considered-risk-and-different

7. Zhu Y, Zhang C. Prevalence of Gestational Diabetes and Risk of Progressionto Type 2 Diabetes: a Global Perspective. Current Diabetes Reports. 2016 Jan;16(1).

8. Ferrara A. Increasing Prevalence of Gestational Diabetes Mellitus: A public health perspective. Diabetes Care. 2007 Jun 27;30(Supplement 2):S141–6.

9. Johns EC, Denison FC, Norman JE, Reynolds RM. Gestational Diabetes Mellitus: Mechanisms, Treatment, and Complications. Trends in Endocrinology & Metabolism. 2018 Nov;29(11):743–54.

10. Nicolosi BF, Souza RT, Mayrink J, Feitosa FE, Rocha Filho EA, Leite DF, etal. Incidence and risk factors for hyperglycemia in pregnancy among nulliparouswomen: A Brazilian multicenter cohort study. Farias D, editor. PLOS ONE. 2020May 13;15(5):e0232664.

11. McIntyre HD, Catalano P, Zhang C, Desoye G, Mathiesen ER, Damm P. Gestational diabetes mellitus. Nature Reviews Disease Primers [Internet]. 2019 Jul 11;5(1). Available from: https://www.nature.com/articles/s41572-019-0098-8

12. Fundação S, Cruz O, Rio De Janeiro, Rj B, Luísa S, Flor, et al. Luísa Sorio Flor I Monica Rodrigues Campos II Andreia Ferreira de Oliveira III. [cited 2021 May 17]; Available from: https://scielosp.org/pdf/rsp/2015.v49/29/pt#:~:text=No%20Brasil%2C%2049%2C2%25

13. Menke A, Casagrande S, Cowie CC. Contributions of A1c, fasting plasma glucose, and 2-hour plasma glucose to prediabetes prevalence: NHANES 2011–2014. Annals of Epidemiology. 2018 Oct;28(10):681-685.e2.

14. Egan AM, Dow ML, Vella A. A Review of the Pathophysiology and Manage-ment of Diabetes in Pregnancy. Mayo Clinic Proceedings [Internet]. 2020 Jul 28;0(0). Available from: https://www.mayoclinicproceedings.org/article/S0025-6196(20)30202-0/fulltext 10.1016/j.mayocp.2020.02.019.

15. Yahaya TO, Salisu T, Abdulrahman YB, Umar AK. Update on the genetic and epigenetic etiology of gestational diabetes mellitus: a review. EgyptianJournal of Medical Human Genetics. 2020 Mar 23;21(1).

16. McIntyre HD, Catalano P, Zhang C, Desoye G, Mathiesen ER, Damm P. Gestational diabetes mellitus. Nature Reviews Disease Primers [Internet]. 2019 Jul 11;5(1). Available from:https://www.nature.com/articles/s41572-019-0098-8 .

17. Johns EC, Denison FC, Norman JE, Reynolds RM. Gestational Diabetes Mellitus: Mechanisms, Treatment, and Complications. Trends in Endocrinology & Metabolism. 2018 Nov;29(11):743–54.10.1016/j.tem.2018.09.004

18. Plows J, Stanley J, Baker P, Reynolds C, Vickers M. The Pathophysiologyof Gestational Diabetes Mellitus. International Journal of Molecular Sciences [Internet]. 2018 Oct 26;19(11):3342. Available from: https://www.ncbi.nlm.nih.- gov/pmc/articles/PMC6274679/ 10.1038/s41572-019-0098-8.

19. Egan AM, Dow ML, Vella A. A Review of the Pathophysiology and Manage -ment of Diabetes in Pregnancy. Mayo Clinic Proceedings [Internet]. 2020 Jul 28;0(0). Available from: https://www.mayoclinicproceedings.org/article/S0025-6196(20)30202-0/fulltext 10.1016/j.mayocp.2020.02.019.

20. Alejandro EU, Mamerto TP, Chung G, Villavieja A, Gaus NL, Morgan E, etal. Gestational Diabetes Mellitus: A Harbinger of the Vicious Cycle of Diabetes.International Journal of Molecular Sciences. 2020 Jul 15;21(14):5003. 10.3390/ijms21145003

21. Dominguez LJ, Martínez-González MA, Basterra-Gortari FJ, Gea A, Barba- gallo M, Bes-Rastrollo M. Fast Food Consumption and Gestational Diabetes In- cidence in the SUN Project. PLoS ONE [Internet]. 2014 Sep 12;9(9). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4162567/#:~:text=The%20risk%20of%20incident%20gestational 10.1371/journal.pone.0106627

22. Chiefari E, Arcidiacono B, Foti D, Brunetti A. Gestational diabetes mellitus: an updated overview. Journal of Endocrinological Investigation. 2017 Mar 10;40(9):899–909. 10.1007/s40618-016-0607-5.

23. Rasmussen L, Poulsen CW, Kampmann U, Smedegaard SB, Ovesen PG, Fuglsang J. Diet and Healthy Lifestyle in the Management of Gestational Dia- betes Mellitus. Nutrients. 2020 Oct 6;12(10):3050.

24. Mustad, Huynh, López-Pedrosa, Campoy, Rueda. The Role of Dietary Car- bohydrates in Gestational Diabetes. Nutrients. 2020 Jan 31;12(2):385.

25. Silva Junior JR da, Souza ASR, Agra KF, Cabral Filho JE, Alves JGB. Ges- tational Diabetes Mellitus: the importance of the production in knowledge. Brazilian Journal of Maternal and Child Health. 2016 Jun [cited 2021 Jun 17];16(2):85–7.

26. Mack LR, Tomich PG. Gestational Diabetes: Diagnosis, Classification, and Clinical Care. Obstetrics and Gynecology Clinics of North America. 2017 Jun 1;44(2):207-17.

27. Yamamoto JM, Kellett JE, Balsells M, García-Patterson A, Hadar E, Solà I, et al. Gestational

Diabetes Mellitus and Diet: A Systematic Review and Meta- analysis of Randomized Controlled Trials Examining the Impact of Modified Di- etary Interventions on Maternal Glucose Control and Neonatal Birth Weight. Di- abetes Care [Internet]. 2018 Jun 22;41(7):1346–61. Available from: https://care.diabetesjournals.org/content/41/7/1346

28. Szmuilowicz ED, Josefson JL, Metzger BE. Gestational Diabetes Mellitus. Endocrinology and Metabolism Clinics of North America. 2019 Sep;48(3):479– 93.

29. Cremona A, O'Gorman C, Cotter A, Saunders J, Donnelly A. Effect of exer- cise modality on markers of insulin sensitivity and blood glucose control in preg-nancies complicated with gestational diabetes mellitus: a systematic review. Obesity Science & Practice. 2018 Sep 4;4(5):455–67.

30. Kampmann U, Knorr S, Fuglsang J, Ovesen P. Determinants of Maternal In-sulin Resistance during Pregnancy: An Updated Overview. Journal of Diabetes Research [Internet]. 2019 Nov 19 [cited 2020 Sep 22];2019. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6885766/

31. Doyle-Delgado K, Chamberlain JJ, Shubrook JH, Skolnik N, Trujillo J. Phar- macologic Approaches to Glycemic Treatment of Type 2 Diabetes: Synopsis of the 2020 American Diabetes Association's Standards of Medical Care in Dia- betes Clinical Guideline. Annals of Internal Medicine. 2020 Sep 1;

32. Coustan DR. Gestational Diabetes Mellitus. Clinical Chemistry. 2013 Sep 1;59(9):1310–21.

33. Toledano Y, Hadar E, Hod M. Safety of insulin analogues as compared withhuman insulin in pregnancy. Expert Opinion on Drug Safety. 2016 May 17;15(7):963–73.

34. Alfadhli E. Gestational diabetes mellitus. Saudi Medical Journal. 2015 Apr 1;36(4):399–406.

35. Kalra S, Gupta Y, Kalra B, Singla R. Use of oral anti-diabetic agents in preg-nancy: A pragmatic approach. North American Journal of Medical Sciences [In- ternet]. 2015 [cited 2019 Nov 17];7(1):6. Available from: https://www.ncbi.nlm.ni-h.gov/pmc/articles/PMC4325398/

36. Feig DS, Donovan LE, Zinman B, Sanchez JJ, Asztalos E, Ryan EA, et al. Metformin in women with type 2 diabetes in pregnancy (MiTy): a multicentre, in-ternational, randomized, placebo-controlled trial. The Lancet Diabetes & En- docrinology [Internet]. 2020 Oct 1 [cited 2021 Mar 2];8(10):834–44. Available from: https://pubmed.ncbi.nlm.nih.gov/32946820/

37. Hyer S, Balani J, Shehata H. Metformin in Pregnancy: Mechanisms and Clinical Applications. International Journal of Molecular Sciences. 2018 Jul4;19(7):1954.

38.Kitwitee P, Limwattananon S, Limwattananon C, Waleekachonlert O, Ratanachotpanich T, Phimphilai M, et al. Metformin for the treatment of gesta- tional diabetes: An updated meta-analysis. Diabetes Research and ClinicalPractice [Internet]. 2015 Sep 1 [cited 2022 Apr 19];109(3):521–32. Available from: https://pubmed.ncbi.nlm.nih.gov/26117686/

39. Juan J, Yang H. Prevalence, Prevention, and Lifestyle Intervention of Ges- tational Diabetes Mellitus in China. International Journal of Environmental Re- search and Public Health. 2020 Dec 18;17(24):9517. 10.3390/ijerph17249517

40. D'ANNA R, SANTAMARIA A, ALIBRANDI A, CORRADO F, DI BENEDETTO A, FACCHINETTI F. Myo-Inositol for the Prevention of Gesta- tional Diabetes Mellitus. The Brief Review. Journal of Nutritional Science and Vitaminology. 2019 Oct 11;65(Supplement):S59–61.

41. Szmuilowicz ED, Josefson JL, Metzger BE. Gestational Diabetes Mellitus.Endocrinology and

Metabolism Clinics of North America. 2019 Sep;48(3):479– 93. 10.1016/j.ecl.2019.05.001

42. Muche AA, Olayemi OO, Gete YK. Effects of gestational diabetes mellitus on risk of adverse maternal outcomes: a prospective cohort study in Northwest Ethiopia. BMC Pregnancy and Childbirth. 2020 Feb 3;20(1).

43. Cooray SD, Boyle JA, Soldatos G, Wijeyaratne LA, Teede HJ. Prognostic models for pregnancy complications in women with gestational diabetes: a pro- tocol for systematic review, critical appraisal and meta-analysis. Systematic Re- views. 2019 Nov 11;8(1).

44. Sun J, Kim GR, Lee SJ, Kim HC. Gestational diabetes mellitus and the role of intercurrent type 2 diabetes on long-term risk of cardiovascular events. Scien-tific Reports. 2021 Oct 27;11(1).

45. Kan S, Acar U, Kizilgul M, Beyazyildiz E, Cankaya AB, Apaydin M, et al. Tear Film and Ocular Surface Evaluation in Gestational Diabetes Mellitus. Sem-inars in Ophthalmology [Internet]. 2018;33(3):402–6. Available from: https://pubmed.ncbi.nlm.nih.gov/28005448/

46. O'Dwyer V, Russell NM, McDonnell B, Sharkey L, Mulcahy C, Higgins MF. Antenatal prediction of fetal macrosomia in pregnancies affected by maternal pre-gestational diabetes. The Journal of Maternal-Fetal & Neonatal Medicine. 2021 Jul 6;1–5.

47. Joo EH, Kim YR, Kim N, Jung JE, Han SH, Cho HY. Effect of Endogenic and Exogenic Oxidative Stress Triggers on Adverse Pregnancy Outcomes:Preeclampsia, Fetal Growth Restriction, Gestational Diabetes Mellitus and Preterm Birth. International Journal of Molecular Sciences [Internet]. 2021 Sep 19;22(18):10122. Available from: https://pubmed.ncbi.nlm.nih.gov/34576285/

48. Shou C, Wei YM, Wang C, Yang HX. Updates in Long-term Maternal and Fetal Adverse Effects of Gestational Diabetes Mellitus. Maternal-Fetal Medicine.2019 Oct;1(2):91–4.

49. Alrais M, Ward C, Cornthwaite JAA, Chen HY, Chauhan SP, Sibai BM, et al. Type 2 diabetes and neonatal hypoglycemia: role of route of delivery and insulininfusion. The Journal of Maternal-Fetal & Neonatal Medicine. 2021 Aug 4;1–7.

50. Craig L, Sims R, Glasziou P, Thomas R. Women's experiences of the diag- nosis of gestational diabetes mellitus: a systematic review. BMC Pregnancy andChildbirth. 2020 Feb 7;20(1).

51. Gilbert L, Gross J, Lanzi S, Quansah DY, Puder J, Horsch A. How diet, physical activity and psychosocial well-being interact in women with gestational diabetes mellitus: an integrative review. BMC Pregnancy and Childbirth. 2019 Feb 7;19(1).

52. Arafa A, Dong JY. Gestational diabetes and risk of postpartum depressive symptoms: A meta-analysis of cohort studies. Journal of Affective Disorders. 2019 Jun;253:312–6.