INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Exploring The Impact Of Lifestyle Factors On Gestational Diabetes, Risk And Management: Insights From A Preclinical Model Study

Shivaraj Hiremath, Shubham Teli, Mallappa Shalavadi*

Department of Pharmacology, B.V.V Sangha's Hanagal Shri Kumareshwar College of Pharmacy Bagalkote-587101, Karnataka, India

ARTICLE INFO

Received: 11 Sep 2024
Accepted: 15 Sep 2024
Published: 08 Oct 2024
Keywords:
GDM, Type 2 Diabetes Mellitus, Pregnancy, Preclinical.
DOI:
10.5281/zenodo.13904063

ABSTRACT

Gestational diabetes mellitus (GDM) is a serious pregnancy-related illness marked by continuously elevated blood sugar levels. GDM is characterized by insulin resistance, poor glucose tolerance, and pancreatic β cell malfunction, resulting in inadequate insulin production to control glucose levels. Obesity, advanced age, and a genetic predisposition to GDM are all risk factors. GDM consequences may include gestational hypertension, birth difficulties, and preeclampsia. It also raises the risk of long-term problems such obesity, poor glucose metabolism, cardiovascular disease, and macrosomia. Both the mother and the infant are at risk of developing type 2 diabetes mellitus (T2DM) later in life. GDM affects approximately 16.5% of pregnancies worldwide, with around 18 million births occurring each year, and this number is expected to rise due to the increasing prevalence of obesity. The growing incidence of GDM also poses a significant economic burden, emphasizing the importance of early detection as a risk factor for T2DM and cardiovascular disease. It is crucial to identify the long-term complications for both the mother and child, and investigate the underlying causes of GDM. While there are various treatment strategies available, including medication and lifestyle changes, there is currently no standardized approach for diagnosing, treating, or preventing GDM. Therefore, it is essential to develop strategies to optimize GDM management, reduce associated morbidity and complications, and minimize the economic impact. GDM provides a unique opportunity to enhance clinical care by providing an updated summary of its incidence, prevalence, epidemiology, risk factors, complication, diagnosis and management.

INTRODUCTION

Improving maternal health and reducing childhood mortality are two of the eight Millennium Development Goals (MDGs) established by the United Nations. These goals present a significant

***Corresponding Author:** Mallappa Shalavadi
Address: *Department of Pharmacology, B.V.V Sangha's Hanagal Shri Kumareshwar College of Pharmacy Bagalkote-587101, Karnataka, India*
Email ✉: mallu.sha007@gmail.com

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

and challenging task for healthcare providers worldwide [1, 2]. Various organizations, including the International Federation of Gynecology and Obstetrics (FIGO), actively support the MDGs. FIGO specifically focuses on reducing non-communicable maternal diseases (NCDs) and minimizing exposure to risks during pregnancy to enhance the long-term health of women and their children. Their efforts target conditions such as hyperglycemia, obesity, hypertension, and poor nutrition during pregnancy, aiming to prevent the development of diseases like obesity and type 2 diabetes mellitus (T2DM) later in life [2]. Recognizing pregnancy as a crucial period for assessing future health [3], it is often referred to as a "window" into one's well-being. The physiological changes that occur during pregnancy serve as a natural "stress test" for the body. As a result, many women seek medical care during this time, making it an opportune time to provide preventive healthcare guidance. In recent years, there has been a growing understanding of how the intrauterine environment, including maternal nutritional status, influences the health of offspring throughout their entire lives [4, 5]. The field of developmental origins of health and disease (DOHAD) suggests that the conditions experienced in the womb and early infancy have a lasting impact on an individual's metabolism and overall health in the future. The importance of early intervention extends beyond improving maternal health and reducing disease prevalence in subsequent generations [2]. During pregnancy, women commonly experience a physiological change known as glucose intolerance, which leads to high blood sugar levels, a condition referred to as gestational diabetes mellitus (GDM) [6]. GDM is a temporary form of diabetes that occurs due to insulin resistance or dysfunction of the pancreatic β-cells during pregnancy, resulting in insufficient insulin production to regulate glucose levels. In order to maintain glucose balance despite resistance to insulin, the maternal β-cells compensate by increasing in number and by, synthesizing and secreting more insulin. However, if the β-cells are unable to adapt to the metabolic changes that occur during pregnancy, hyperglycemia associated with GDM can develop. GDM was first described as "elevated blood sugar levels similar to those seen in diabetes, occurring during pregnancy" by the World Health Organization (WHO) in 1965 [7]. As a result, in the past, the term "GDM" covered a wide range of maternal hyperglycemia during pregnancy, including hyperglycemia that is initially discovered during pregnancy as well as pre-existing diabetes. GDM was characterized as "impaired glucose tolerance that is first recognized during pregnancy" by the National Diabetes Data Group (NDDG) in 1979 [8]. At the Second International Workshop-Conference on Gestational Diabetes in 1985, this description was later updated to read as follows: GDM is defined as "carbohydrate intolerance resulting in varying degrees of hyperglycemia, with onset or first recognition during pregnancy." Up until recently, this definition was commonly accepted [9]. According to the population under study and the diagnostic procedures used, GDM complicates about 7% of pregnancies overall or more than 200,000 cases per year. The percentage of all pregnancies may range from 1% to 14%. Pregnancy-related GDM is a common medical complication that, if left untreated, can have major negative effects on the mother's and the child's health [10, 11]. There is compelling evidence that mild maternal hyperglycemia raises the risk of fetal morbidity even though it is uncommon [12]. Failing to identify and treat the condition can lead to unnecessary morbidity in some pregnancies. This condition is associated with unfavorable pregnancy outcomes, such as fetal macrosomia, stillbirth, neonatal metabolic disturbances, and related issues [13]. Children of women with GDM

are more likely to grow up with diabetes and obesity, and they also have a higher chance of developing diabetes themselves in the years after giving birth [14–17] The term GDM lacks clarity on whether dietary adjustments alone or treatment with diet, insulin, or oral medications is necessary for the patient. Therefore, it is imperative to implement strategies that enhance GDM management. Accurate diagnosis, suitable treatment, and proactive prevention of GDM are essential to mitigate the morbidity, complications, and economic impact of GDM on society, households, and individuals. Consequently, the growing number of GDM cases poses an additional strain on the healthcare system, necessitating a review of diagnostic methods and treatment approaches. GDM presents a valuable opportunity to examine and summarize current evidence on its impact on maternal and neonatal outcomes and, the potential health risks for future generations. To Address the existing challenges in GDM screening, diagnosis, and management, we delve into incidence, prevalence, epidemiology, risk factors, complication, diagnosis, management and the importance of expanding our scientific knowledge to develop preventive and therapeutic strategies for GDM, thereby enhancing clinical practice.

CLASSIFICATION OF HYPERGLYCEMIA DURING PREGNANCY AND GDM:

The current terminology and diagnostic criteria have made it easier to distinguish between women who had diabetes before pregnancy and those who developed hyperglycemia during pregnancy. Pregestational diabetes encompasses T1DM, T2DM, and other forms of diabetes like cystic fibrosis-related diabetes, steroid/medication-induced diabetes, and monogenic diabetes. The International Association of the Diabetes and Pregnancy Study Groups (IADPSG) has divided hyperglycemia during pregnancy into two distinct categories: "overt diabetes mellitus during pregnancy" (overt diabetes) and gestational diabetes mellitus (GDM) [18] (figure 1).

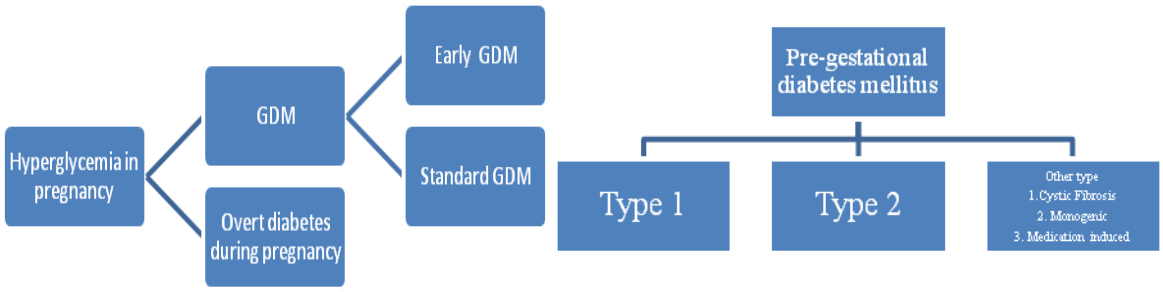

Fig. 1 Flowchart summarizing the contemporary nomenclature for hyperglycemia in pregnancy [18]

INCIDENCE AND PREVALENCE OF GDM:

Gestational diabetes mellitus (GDM) is a commonly encountered medical complication during pregnancy [19]. According to the International Diabetes Federation (IDF), in 2019, approximately 1 in 6 live births worldwide were affected by GDM [20]. The majority of cases of high blood sugar levels during pregnancy occur in low- and middle-income countries [21]. In these countries, the prevalence and severity of maternal and neonatal complications associated with GDM [20, 22] are in stark contrast to the favorable pregnancy outcomes seen in developed countries where GDM is well managed [23]. The prevalence of GDM varies significantly depending on the population and the specific screening and diagnostic criteria employed. A systematic review conducted in 2012 revealed that the worldwide

prevalence of GDM ranged from 2% to 24.5% according to the WHO criteria, 3.6% to 38% according to the Carpenter and Coustan criteria, 1.4% to 50% according to the NDDG criteria, and 2% to 19% according to the IADPSG criteria [24]. Irrespective of the diagnostic criteria or population being considered, the global incidence of GDM continues to rise and is influenced by various epidemiological factors such as the prevalence of type 2 diabetes mellitus, increasing rates of obesity among women of childbearing age, and advancing maternal age [25-32]. The implementation of the revised IADPSG diagnostic criteria has further contributed to more women diagnosed with GDM [33- 35]. In the original HAPO study cohort, the application of the IADPSG diagnostic criteria resulted in GDM incidence rates ranging from 9.3% to 25.5% across different study sites [33]. Recent international prevalence data also highlight significant variations in the rate of GDM, ranging from 6.6% in Japan and Nepal to 45.3% in the United Arab Emirates [36].

EPIDEMIOLOGY:

Previously reported findings indicate that the prevalence of gestational diabetes mellitus (GDM) in pregnant women is often reflective of the prevalence of type 2 diabetes mellitus (T2DM) within the same population [37]. The global trend toward a Western lifestyle characterized by excessive food consumption and sedentary habits has led to a widespread increase in T2DM worldwide [38]. Consequently, this has contributed to a significant rise in the incidence of **GDM.**

However, the exact prevalence of GDM on a global scale remains uncertain because of the lack of systematically synthesized data. Currently available information suggests that the prevalence of GDM varies considerably among countries and even within regions of a single country. This variation can range from as low as 0.6% to as high as 15%, depending on factors such as race/ethnicity and socioeconomic status [37]. Notably, Aboriginal women in Australia, as well as Middle Eastern (Syrian, Lebanese, Iraqi, Iranian, or Afghan) and Pacific Islander women are identified as the major at-risk groups for GDM [37]. The escalating issue of overweight and obesity worldwide significantly contributes to the continuous increase in diabetes incidence, including GDM, among women of reproductive age [39]. According to the International Diabetes Federations 2019 report, approximately 20.4 million women (14.0% of pregnancies) experienced disorders of carbohydrate metabolism, with approximately 80% of these cases being GDM. This means that approximately one in six births was affected by GDM [40]. For a detailed analysis of the geographical distribution of GDM, refer to Table 1 [40, 41].

Table 1. Geographical distribution of the GDM [40, 41]

Middle East and North Africa (MENA)	27.6% (26.9–28.4%)
Southeast Asia (SEA) (Brunei, Burma, Cambodia, Timor-Leste, Indonesia, Laos, Malaysia, the Philippines, Singapore, Thailand, Vietnam)	20.8% (20.2–21.4%)
Western Pacific (WP)	14.7% (14.7–14.8%)
Africa (AFR)	14.2% (14.0–14.4%)
South America and Central America (SACA)	10.4% (10.1–10.7%)
Europe (EUR)	7.8% (7.2–8.4%)
North America and the Caribbean (NAC)	7.1% (7.0–7.2%)

ETIOLOGY:

During pregnancy, the mother's metabolism undergoes significant modifications. While the changes in late pregnancy are primarily catabolic, with increased lipolysis, elevated glycemia, insulinemia, postprandial fatty acid levels, and

decreased maternal fat stores, the changes in the first phase are mostly anabolic, with a progressive increase in maternal adipose tissue. These changes are caused, at least in part, by hormones and other mediators secreted by the placenta. These substances promote the development of peripheral insulin resistance, a physiological condition that can deteriorate with advancing maternal age and pre-pregnancy obesity, and two conditions that have become common in Western nations. After the placenta is delivered, the effects of pregnancy on glucose homeostasis are typically mitigated, allowing glycemia to return to normal levels in 6–12 months. The negative influence of pre-pregnancy overweight or obesity on GDM is underlined by the observation that physical activity both before pregnancy and in early pregnancy by reducing body weight loss and insulin resistance is inversely associated with the risk of GDM [42]. Maternal glucose intolerance develops when insulin secretion is insufficient to counteract the insulin-resistant state in the second half of pregnancy, which may raise the chance of developing GDM (FIG 2). Therefore, β-cell secretory dysfunction is a crucial abnormality in the pathogenesis of GDM. Due to its progressive nature, the β-cell function deficiency is not unique to pregnancy; in fact, it can occur before or after conception and increases the chance of overt diabetes following the index pregnancy. As a result, GDM may be viewed as an early stage of gestational diabetes mellitus (T2DM). To date, there is much evidence pointing to a link between genetics and GDM (FIG 2). Among these are the fallowing: the fact that GDM recurs in at least 30% of women with a previous history of GDM; the growing body of epidemiological research showing some ethnic-group differences in the risk for GDM, independent of the place of residence; and the identification of numerous genetic variants in many genes that are involved in insulin secretion and insulin resistance, as well as in lipid and glucose metabolism, which have been associated with GDM risk. In particular, regarding this latter point, many of the variants identified are associated with increased risk for T2DM, thereby supporting the notion of a continuum between GDM and T2DM. However, research has indicated that, even in the absence of other established risk factors, placental DNA epigenetic alteration is relevant in GDM (FIG 2). Additionally, there is growing evidence that the pathophysiology of GDM may involve dysregulation of immunological and inflammatory activation (FIG 2), since women with GDM have been found to have reduced molecular oxygen and impaired antioxidant defense. Endocrine-disrupting chemical use is also rising, which could be a risk factor for GDM [42].

RISK FACTORS FOR GDM:

MODIFIABLE RISK FACTORS:

BMI, obesity and overweight:

During pregnancy, maternal dyslipidemia is a natural response that provides essential fuel and nutrients for the placenta and developing fetus. The accumulation and enlargement of fat cells in maternal adipose tissue leads to weight gain, which is a common occurrence. However, overweight and obesity pose significant risks for gestational diabetes mellitus (GDM) [43]. Pre-pregnancy body mass index (BMI) plays a crucial role in determining the risk of GDM. The World Health Organization (WHO) defines overweight and obesity on the basis of BMI values greater than 25 and 30 kg/m2, respectively. Given the global obesity epidemic and the increasing prevalence of obesity among women of childbearing age, it is estimated that there are 38.9 million overweight and 14.6 million obese pregnant women worldwide. In overweight and obese individuals, increased lipid production leads to the storage of lipids, particularly triglycerides, in adipose tissue and other organs like the liver. Pregnancy further intensifies obesity-induced hepatic insulin

resistance, increasing the risk of developing GDM. Moreover, being overweight or obese during pregnancy can result in adverse outcomes such as metabolic disorders, hypertension, preterm birth, and stillbirth. Therefore, obstetricians regularly monitor the BMI and weight gain of pregnant women to minimize complications for both the mother and baby. Current strategies for preventing and managing weight gain during pregnancy involve nutritional interventions and improvements in dietary and lifestyle practices [44].

Nutritional diet and metabolic syndrome:

The National Cholesterol Education Program Adult Treatment Panel III coined the term metabolic syndrome to describe the clustering of metabolic disorders, including obesity, dyslipidemia, hypertension, and abnormal glucose metabolism. This condition is often intensified by a Western-style diet that is high in sugars, fats, and processed foods, increasing the risk of gestational diabetes mellitus (GDM) [45]. In additionally, vitamin D deficiency and a high dietary acid load may contribute to the development of GDM. It is crucial to highlight that nutritional therapy is the primary approach for preventing or managing metabolic syndrome because, it plays a vital role in maintaining glucose regulation and overall physiological well-being. Dietary interventions, such as high-fiber and low-glycemic-index diets, have been scientifically proven to improve insulin sensitivity and glucose tolerance, thereby reducing the likelihood of GDM. Recent studies have also emphasized the benefits of probiotic treatment in controlling blood sugar levels by targeting the gut microbiota. In cases where lifestyle modifications alone are insufficient to achieve glycemic control, additional treatment options such as antihyperglycemic medications like insulin therapy and metformin may be considered [46].

Polycystic ovary syndrome (PCOS): GDM and PCOS are the two most prevalent endocrine disorders among women of reproductive age. PCOS is a complex disorder characterized by chronic oligomenorrhea, hyperandrogenism, and insulin resistance. Similar to GDM, PCOS is linked to insulin resistance and obesity [47]. Although the risk of developing GDM is higher for women with PCOS who also have other comorbidities like obesity and advanced maternal age, PCOS itself is not an independent risk factor for GDM. A prevalence study conducted in California revealed that pregnant women with PCOS have more than double the risk of developing GDM compared with women without PCOS or related symptoms. In fact, the prevalence of PCOS is higher in women with GDM than in non-diabetic women [48]. PCOS is often associated with metabolic syndrome, and common prevention strategies include lifestyle modifications and pharmacological treatments.

Pre-eclampsia: Pre-eclampsia, a prevalent hypertensive condition, affects approximately 2%–8% of pregnancies globally. Similar to GDM, pre-eclampsia is associated with glucose intolerance, hyperglycemia, and obesity. The presence of hyperglycemia increases the likelihood of developing pre-eclampsia. Furthermore, in subsequent pregnancies, pre-eclampsia serves as an autonomous risk factor for GDM [49].

Additional modifiable risk factors for GDM:

A few studies have found a link between extended exposure to psychological stress in the environment and maternal hyperglycemia during pregnancy, which may raise the risk of gestational diabetes mellitus (GDM) [50]. Similarly, it has been demonstrated that smoking, using psychotropic and antidepressant drugs, and having poor sleep hygiene are risk factors for GDM [51].

NON-MODIFIABLE RISK FACTORS:

Maternal Age:

Maternal age is a common risk factor for GDM. Studies have shown that maternal age ≥ 25–30

years increases the risk of developing GDM [52]. In a meta-analysis study investigating the relationship between maternal age and the risk of GDM, the authors identified a linear relationship between the risk of GDM and increasing maternal age. It was also indicated that for every successive year after the age of 18, the risk for GDM increases by 7.90%, 12.74%, and 6.52% in the general, Asian, and European populations, respectively.

Gravity and Parity:

Increasing gravidity, defined as the number of times a woman has been pregnant, and parity, i.e., the number of times she has given birth, may represent an additional risk for GDM [52]. This elevated risk of developing GDM has been linked to parity as low as two. The effect of gravidity on the risk of GDM has also been associated with increasing age because more pregnancies are observed in women of advanced maternal age [53]. Ethnicity: Numerous studies have established a connection between GDM development and ethnicity. Various ethnic and racial groups, including Hispanic, African American, and Asian women, have shown an increased risk of GDM [53]. Women of Korean, Chinese, and Filipino descent are more than twice more likely to develop GDM than Caucasian or African American women. The exact mechanisms underlying this association remain unclear, but potential explanations could be related to health predisposition, lifestyle, cultural factors, and socioeconomic stressors [53]. In T2DM studies, South Asians have been found to have reduced fat metabolism, muscle fitness, insulin sensitivity, and insulin secretion, all of which contribute to a higher likelihood of glucose intolerance [54]. Recognizing ethnicity as a risk factor for GDM, healthcare providers must acknowledge that certain ethnic groups may require specialized preventive and culturally sensitive care. Additionally, addressing structural changes, such as combating systemic racism and bias, is essential to address the disparities associated with these preventable NCDs.

Genetics and Family History of Hyperglycemia:

Gestational diabetes mellitus (GDM) is a complex condition influenced by genetic and environmental factors. A family history of diabetes is a significant independent risk factor for the development of GDM. A strong correlation between common gene polymorphisms associated with T2DM and GDM. Among the most commonly identified genes in GDM are transcription factor 7-like 2 (TCFL7L2), melatonin receptor 1B (MTNR1B), CDK5 regulatory subunit-associated protein 1-like 1 (CDKAL1), potassium voltage-gated channel, KQT-like subfamily, member 1 (KCNQ1), and insulin receptor substrate-1 (IRS1). Recent comprehensive studies on the genetic and epigenetic origins of GDM have been reported in various sources [55]. These epigenetic changes can lead to the inheritance of obesity and glucose intolerance across generations. In addition, different types of genetic variations and epigenetic mechanisms may influence the characteristics of various ethnic groups. For instance, research has shown that Asian women have the highest prevalence of GDM. Variation in the relationship between genetic polymorphisms and GDM risk is often linked to ethnicity or population variances, highlighting the importance of conducting population-specific studies on the impact of genetic variations on GDM risk.

SOCIOECONOMIC AND GEOGRAPHIC RISK FACTORS:

Climate and Geographical Location:

The World Health Organization acknowledges the impact of different climates on human health, ranging from extreme winter temperatures to summer temperatures. Research indicates that temperature plays a significant role in various physiological processes, including the regulation of fats and lipids, energy expenditure, hormonal

balance, myocardial infarction, and mortality rates. Additionally, climate seems to have an effect on Gestational Diabetes Mellitus (GDM), with regions experiencing seasonal weather changes showing a higher prevalence of GDM compared with more temperate regions worldwide [56].

Education and Socioeconomic Status:

Many women diagnosed with GDM lack awareness of the risk factors and complications associated with their diagnosis, as indicated by observational studies. Research conducted in Finland revealed a correlation between socioeconomic status and GDM, with lower status individuals being more at risk [57]. It has been noted that uninsured and underinsured patients tend to receive inadequate preventive healthcare or sometimes no healthcare at all. Enhancing the effectiveness of GDM treatment involves integrating health education and government assistance into prenatal care. Effective strategies for raising awareness about GDM and enhancing pregnancy outcomes include web-based education and educational sessions with healthcare providers or dieticians, either individually or in groups.

COMPLICATIONS:

Gestational diabetes mellitus (GDM) is identified by elevated blood sugar levels during pregnancy, which can be influenced by genetic factors, insulin resistance, and inflammation. Although GDM is typically temporary, it can increase the likelihood of developing Type 2 diabetes in the future and pose risks for both the mother and child. This segment outlines the potential metabolic and physical alterations associated with the progression of GDM.

Maternal Complications:

In gestational diabetes mellitus (GDM), elevated blood sugar levels can harm endothelial cells, leading to vascular issues linked with high blood pressure. This connection suggests that GDM can increase the likelihood of hypertension during pregnancy and after giving birth. Diabetes and hypertension are known risk factors for pre-eclampsia, a condition affecting 3% to 5% of pregnancies globally and, characterized by elevated blood pressure and protein in the urine [58]. While hyperglycemia typically resolves post-delivery, some patients with GDM may continue to experience insulin resistance and β-cell dysfunction beyond pregnancy. Consequently, women with a history of GDM face an increased risk of developing T2DM later in life, with a risk as high as 50%. Furthermore, those who had GDM in previous pregnancies may have a recurrence in subsequent pregnancies [59]. Therefore, it is recommended that all women diagnosed with GDM undergo a 2-h glucose tolerance test during their 6-week postpartum check-up.

Fetal Complications:

The developing fetus has a limited capacity to produce glucose; therefore, so it primarily relies on glucose from the mother's blood. While maternal glucose can cross the placenta, maternal insulin cannot. According to the modified Pedersens hypothesis, if maternal glucose levels are high and uncontrolled, excess glucose that passes through the placenta can stimulate increased production of fetal insulin [60]. This phenomenon is supported by the observed increase in the expression of glucose transport proteins (GLUTs) in the placenta of pregnancies affected by insulin-dependent diabetes mellitus. Insulin can also activate mTOR, a powerful regulator of cell growth. When maternal insulin levels rise, placental mTOR activity increases, leading to enhanced cell proliferation and nutrient transport to the fetus through amino acid transporters in the placenta. In a review by Hart et al., the role of mTOR as a nutrient sensor in fetal growth was examined. In cases of gestational diabetes mellitus (GDM), the aforementioned factors, including maternal hyperglycemia and hyperinsulinemia, can result in similar changes in the fetus [60], contributing to increased neonatal adiposity. Excessive nutrient

storage can lead to macrosomia, or a larger size at birth, in neonates. Approximately 15% to 45% of pregnancies affected by GDM result in macrosomic infants [60], with the most of excess adiposity concentrated on the fetal abdomen and shoulders. This increases the risk of shoulder dystocia and birth trauma [61]. Additionally, the presence of GDM, along with other risk factors like hypertension and obesity during pregnancy, may also increase the likelihood of preterm labor and birth, with a global prevalence of approximately 10.6%.

Neonatal Complications:

Neonatal issues may involve potential risks such as asphyxia, hypoglycemia, kernicterus, jaundice, bacterial infections, neonatal respiratory distress syndrome (NRDS), and birth trauma like shoulder dystocia and brachial plexus injury [60]. Neonatal hypoglycemia arises from a sudden halt in the maternal glucose supply during birth, intensified by fetal hyperinsulinemia from GDM, necessitating thorough management and attention in cases of persistent hypoglycemia [62].

Childhood and Adulthood Complications:

The link between gestational diabetes mellitus (GDM) and hyperglycemia in children is well established. A study conducted on Pima Indians in the United States provided initial evidence that maternal hyperglycemia could lead to adult diseases in offspring. Numerous epidemiological studies have shown that the Pima Indian population has the highest prevalence of type 2 diabetes mellitus (T2DM) among both children and adults. In fact, children born to diabetic mothers are more susceptible to developing obesity, hypertension, and dyslipidemia later in life [63]. The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, conducted in 10 countries, revealed that maternal hyperglycemia during pregnancy was significantly associated with an increased risk of hyperglycemia and insulin resistance in the offspring during adulthood. Markers for insulin resistance, such as HOMA-IR, BMI, waist circumference, and triglyceride levels, were also found to be higher in the offspring of mothers with GDM than in those born to mothers with normal glucose levels. It is presumed that the development of insulin resistance increases the risk of the offspring developing diabetes, with approximately 20% of GDM offspring developing T2DM and prediabetes by the age of 22. Furthermore, the increased prevalence of obesity observed in the children of mothers with GDM is also linked to a higher risk of metabolic disorders, including cardiovascular diseases and insulin resistance. Children born to mothers with GDM were found to have significantly higher blood pressure, adiposity, hyperglycemia, and BMI. Due to the heightened cardiovascular risk, GDM offspring are more prone to developing cardiac arrhythmias and being hospitalized for cardiovascular diseases (CVDs). Additionally, GDM offspring have a 29% higher likelihood of developing early-onset CVDs such as heart failure, hypertensive disease, deep vein thrombosis, and pulmonary embolism [64]. Numerous studies have consistently highlighted the significant impact of the prenatal environment on the development of metabolic diseases in offspring. It is crucial to acknowledge this factor as it goes beyond the sole influence of overnutrition, physical inactivity, or genetic factors in explaining the alarming rise in cases of type 2 diabetes mellitus and obesity. In their study, Monterio et al. thoroughly examined the various mechanisms involved in fetal programing specifically in gestational diabetes mellitus.

DIAGNOSIS:

The prompt identification of pregnant women with gestational diabetes mellitus (GDM) is crucial because early and appropriate treatment can effectively reduce both mild and severe complications related to pregnancy. However, there is no universal consensus on various aspects

of GDM screening, such as the timing, diagnostic tests, and appropriate glycemic cut-offs. Until 2010, the World Health Organization (WHO) and the American Diabetes Association (ADA) criteria were widely used for diagnosing GDM. The ADA recommended a 100-g oral glucose tolerance test (OGTT) during early pregnancy (14-18 weeks) for high-risk women and during late pregnancy (28-32 weeks) for medium-risk women, using the Carpenter and Coustan cut-offs [65]. However, these criteria were revised after the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study demonstrated a linear association between maternal glycemia levels and adverse events for both the mother and the fetus. Consequently, the International Association of Diabetes Pregnancy Study Groups (IADPSG) [66] developed more stringent criteria, which recommend fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), or random plasma glucose testing for all pregnant women during their first prenatal visit. According to the revised guidelines, a diagnosis of GDM is made if the results, not indicative of overt diabetes, show an FPG ≥92 mg/dL. Conversely, if FPG is <92 mg/dL, a 2-hour 75-g OGTT should be performed between 24-28 weeks of gestation (Table 4). The gestational glycemic cut-off values during OGTT are lower than those in previous guidelines [65], and a single abnormal glycemia value during OGTT is sufficient to diagnose GDM (Tables 4, 5). As a result, the IADPSG criteria significantly increased the number of GDM cases compared to the previously used criteria [67].

These recommendations were adopted by the ADA, WHO, and the American Association of Clinical Endocrinologists (AACE) (Table 4) [68]. Instead, the Canadian Diabetes Association (CDA) recommends that all women be screened with a 1-h glucose measurement after a 50-g oral glucose load between 24 and 28 weeks of gestation, followed by the 2-h 75-g OGTT only if the threshold has been surpassed (Table 4) [69]. This two-step approach, commonly used in the USA, is supported by the American College of Obstetricians and Gynecologists (ACOG) [70] and recommended by the NIH Consensus Development Conference (Table 4). In contrast, selective screening based on individual risk assessment has been proposed by several international medical societies (Table 4). Because of this, a range of criteria are commonly used to diagnose GDM globally, with variations between and within nations. This is mostly because public funds must be balanced with the need to provide better healthcare for expectant mothers and their babies. In this respect, the adoption of the IADPSG's recommendations has increased in the diagnosis of GDM [67], which has profoundly impacted the healthcare system. It has been calculated that the overall cost of care for a woman with GDM is ~35% greater than that for a woman without GDM. Overall, the one-step approach should be preferred because of its simplicity in execution with greater patient adherence, its accuracy in the diagnosis of GDM, and its closeness to international consensus. Alternatively, to contain the costs, selective screening could be performed only in women at risk for GDM (i.e. women who are overweight or obese, women of advanced maternal age, women with previous GDM or macrosomic infant, women of high-risk ethnic groups or those with a family history of diabetes among first-degree relatives), although studies have shown that selective screening would miss a significant proportion of cases of GDM with minimal cost saving. In order to address this issue, the International Diabetes Federation (IDF) recommends that selective screening be used only in specific clinical and epidemiological settings where it is locally cost-effective [71]. Furthermore, questions have been raised regarding the threshold values provided by the IADPSG in order to establish globally recognized standards for the diagnosis of GDM.

The IADPSG criteria are mostly derived on the HAPO study, which focused primarily on Caucasian women; hence, the results may not be generalizable to other populations. As a result, regardless of the timing of the last meal, the Indian health care system still follows the Diabetes in Pregnancy Study Group India (DIPSI) guidelines, which suggest universal screening twice during pregnancy using the one-step 2-h 75-g OGTT (Table 4) [72]. However, challenging data have been reported on the cost-effectiveness of this approach compared with IADPSG. In addition, although several studies confirmed that the IADPSG criteria allow the identification of more at-risk women; the major efficacy of these criteria in identifying pregnancies at risk for severe adverse outcomes is still controversial compared with other guidelines, while 25% of pregnant women could be reclassified given the poor reproducibility of OGTT. Hence, although the IADPSG criteria are the only outcome-based criteria, some authors suggest a combined strategy that considers the ethnic and regional characteristics of women with GDM and, the different resources available. In this context, by adopting the OGTT thresholds recommended by the IADPSG, we recently proposed the new Capula index that increases the accuracy of selective screening by reducing both the number of potential false negatives and the number of women to be screened [73], thereby reducing the impact of GDM on pregnancy and health care costs. Based on universal predictors of GDM and pregnancy complications, Capula's index allows a better correlation with the risk of maternal and neonatal adverse events [73].

Table 2: Current protocols for the diagnosis of GDM [42]

Current protocols for the diagnosis of GDM							
Step 1							
Society	**Women**	**Time**	**Test**	**Fasting**	**After 1hr**	**After 2hr**	**After 3hr**
ADA	All	24-28 Weeks	75 g OGTT[a]	92 mg/dL (5.1 mmol/L)	153 mg/dL (8.5 mmol/L)	153 mg/dL (8.5 mmol/L)	Not required
AACE	All	24-28 Weeks	75 g OGTT	92 mg/dL (5.1 mmol/L)	153 mg/dL (8.5 mmol/L)	153 mg/dL (8.5 mmol/L)	Not required
WHO	All	24-28 Weeks	75 g OGTT	92 mg/dL (5.1 mmol/L)	153 mg/dL (8.5 mmol/L)	153 mg/dL (8.5 mmol/L)	Not required
ACOG	All	24-28 Weeks	75 g OGTT	Not required	≥130–140	Not required	Not required
DIPSI	All	First Visit	50 g OGTT[c]	Not required	Not required	≥140 mg/dL (7.8 mmol/L)	Not required
CDA	All	24-28 Weeks	50 g OGTT	Not required	≥140 mg/dL (≥7.8 mmol/L)	Not required	Not required
CDA	All	24-28 Weeks	75 g OGTT[a]	92 mg/dL (5.1 mmol/L)	≥180 mg/dL (≥10.0 mmol/L)	153 mg/dL (8.5 mmol/L)	Not required
NICE	At high risk[a]	As soon as possible	75 g OGTT[a]	≥101 mg/dL (≥5.6 mmol/L)	Not required	≥140 mg/dL (7.8 mmol/L)	Not required
ADIPS	At high risk[a]	As soon as possible	75 g OGTT[a]	92 mg/dL (5.1 mmol/L)	≥180 mg/dL (≥10.0 mmol/L)	153 mg/dL (8.5 mmol/L)	Not required
Italian minister	At high risk[a]	14-16 Weeks	75 g OGTT[a]	92 mg/dL (5.1 mmol/L)	≥180 mg/dL (≥10.0 mmol/L)	153 mg/dL (8.5 mmol/L)	Not required
Step 2							
Society	**Women**	**Time**	**Test**	**Fasting**	**After 1hr**	**After 2hr**	**After 3hr**

ADA AACE WHO	----------						
ACOG	Positive women	24-28 Weeks	100 g OGTT[b]	≥95 mg/dL (5.3 mmol/L)	≥180 mg/dL (≥10.0 mmol/L)	155 mg/dL (8.6 mmol/L)	≥140 mg/dL (7.8 mmol/L)
DIPSI	---	24-28 Weeks	75 g OGTT[c]	Not required	Not required	≥140 mg/dL (7.8 mmol/L)	Not required
CDA	Positive women	24-28 Weeks	75 g OGTT[b]	≥95 mg/dL (5.3 mmol/L)	≥191 mg/dL (≥10.6 mmol/L)	≥162 mg/dL (≥9.0 mmol/L)	Not required
CDA	----------						
NICE	Step 1 Negative and at-risk women[b]	24-28 Weeks	75 g OGTT[a]	≥101 mg/dL (≥5.6 mmol/L)	Not required	≥140 mg/dL (7.8 mmol/L)	Not required
ADIPS	Step 1 Negative and at-risk women[b]	24-28 Weeks	75 g OGTT[a]	92 mg/dL (5.1 mmol/L)	≥180 mg/dL (≥10.0 mmol/L)	153 mg/dL (8.5 mmol/L)	92 mg/dL (5.1 mmol/L)
Italian minister	Step 1 Negative and at-risk women[b]	24-28 Weeks	75 g OGTT[a]	92 mg/dL (5.1 mmol/L)	≥180 mg/dL (≥10.0 mmol/L)	153 mg/dL (8.5 mmol/L)	Not required

IADPSG, the International Association of the Diabetes and Pregnancy Study Groups; ADA, the American Diabetes Association; and AACE, the American Association of Clinical Endocrinologists WHO Diabetes in Pregnancy Study Group India (DIPSI), World Health Organization, ACOG (American Congress of Obstetricians and Gynecologists), and CDA ADIPS, NICE (National Institute for Health and Clinical Excellence), and the Canadian Diabetes Association Diabetes in Pregnancy Society of Australasia. aOne value is sufficient for diagnosis; OGTT oral glucose tolerance test, OCGT oral glucose challenge test, bTwo or more values are required for diagnosis, cIrrespective of the last meal

Table 3 Glycemic targets for women with GDM [42]

Glycemic targets for women with GDM			
Society	**Fasting**	**1 h after the food**	**2 h after food**
ADA[221]	90–99 mg/dL (5.0–5.5 mmol/L)	<140 mg/dL (<7.8 mmol/L)	<120–127 mg/dL (<6.7–7.1 mmol/L)
NICE[278]	63 and 106 mg/dL (3.5 and 5.9 mmol/L)	<140 mg/dL (<7.8 mmol/L)	<120 mg/dL (<6.7 mmol/L)
CDA[239]	95 mg/dL (<5.3 mmol/L)	<140 mg/dL (<7.8 mmol/L)	<120 mg/dL (<6.7 mmol/L)
ADIPS [adips.org/]	≤90 mg/dL (≤5.0 mmol/L)	≤133 mg/dL (≤7.4 mmol/L)	≤120 mg/dL (≤6.7 mmol/L)

ADA (American Diabetes Association), NICE (National Institute for Health and Clinical Excellence), CDA (Canadian Diabetes Association), and ADIPS (Australasian Diabetes in Pregnancy Society).

TREATMENT:

Untreated gestational diabetes mellitus increases the risk of numerous negative effects for the mother, fetus, and newborn [74]. In addition, a strong association between maternal glucose concentrations and perinatal complications has been reported in the HAPO study in, women with milder forms of GDM; at glucose levels below those usually considered diagnostic of GDM. Thus, early and effective treatment of these women is decisive in reducing perinatal and obstetrical complications [75]. Most women with GDM can be effectively managed with a lifestyle intervention program comprising dietary counseling and enhanced physical activity, together with self-monitoring of blood glucose [74], which is essential for verifying the effectiveness of treatment and reducing the risk of complications. Although no randomized trial has been conducted to define the optimal treatment targets, substantial uniformity exists in the importance of self-monitoring blood glucose (Table 4). Current general guidelines, in this regard, recommend assessing postprandial glucose levels at 1 and 2 h (Table 4), given that several studies have demonstrated that treatment decisions based on these parameters resulted in fewer complications [76], suggesting that postprandial glucose excursion is of major importance in pregnant women with less elevated HbA1c levels [77]. In order to improve pregnancy outcomes, appropriate nutrition therapy is helpful in meeting the nutritional needs of both the mother and the fetus as well as in achieving and maintaining glycemic control. This helps women with GDM save money on more intensive medical care, such as insulin treatment and other medications. This feature is especially important in light of the recent rise in GDM prevalence. In this regard, general guidelines stress the selection of nutrients that will support appropriate weight gain and euglycemia without causing ketonuria, as well as modest calorie restriction for obese pregnant women [74]. On the basis observation that elevated postprandial glucose concentrations are often associated with adverse pregnancy outcomes in GDM [76], diet therapy for GDM has historically been based on carbohydrate restriction to blunt postprandial hyperglycemia [74]. Nevertheless, as underlined elsewhere, a minimum of 175 g carbohydrate/day should be provided to avoid nutritional deficiencies and ketosis, which can lead to negative consequences for the neonate. However, although larger controlled randomized prospective studies are needed to define the best nutritional intervention for GDM, recent evidence indicates that diets containing greater amounts of complex carbohydrates and fiber and lower amounts of glycemic index carbohydrates and saturated fat can be effective in blunting postprandial glucose excursions and in improving maternal insulin resistance and fetal fat accumulation [78]. Similar to T2DM, with which GDM shares the same pathogenetic mechanisms, a sedentary lifestyle is a risk factor for GDM, whereas regular physical activity can help reduce this risk. The beneficial effect of exercise is mainly explained by the increase in insulin sensitivity that commonly occurs during exercise and its beneficial impact on body weight. Although specific guidelines on exercise prescription (the type, frequency, and intensity of exercise) are lacking, some practical recommendations are made concerning physical activity in women with GDM as an initial step in combination with diet [74]. In particular, a minimum of 30 min of moderate exercise per day is recommended for normal pregnancy, considering that preferable activities are those that avoid excessive and inappropriate abdominal

muscle contraction [74]. If these measures do not ensure optimal glycemic control, subcutaneous insulin injection therapy should be considered. Because insulin does not cross the placental barrier, it is considered harmless to the fetus. Nevertheless, as already reported, insulin therapy has many disadvantages, including initial fear and anxiety, the need for education and skills in injection and dose adjustment, and the risk of hypoglycemia and weight gain. In recent years, many studies have investigated the safety and effectiveness of oral hypoglycemic drugs for treating GDM. Recently, the results of a large randomized controlled trial demonstrated no significant increase in perinatal complications among women with GDM who were randomly treated with metformin compared with women with GDM who were treated with insulin. Accordingly, both the CDA and the National Institute for Health and Clinical Excellence (NICE) recommend metformin as an option for the treatment of GDM [69, 79], although caution should be exercised given the ability of metformin to cross the placenta and the lack of long-term follow-up data from both mother and child. In addition, metformin has not yet been approved for GDM treatment in all countries. Glyburide (glibenclamide) is a sulfonylurea that has been largely investigated in pregnant women with GDM. The safety and effectiveness of glyburide in GDM were recognized and confirmed [80]. However, according to more recent studies, glyburide is inferior to either insulin or metformin and therefore should not be employed for treating women with GDM if insulin or metformin is available [81]. The importance of vitamin D in GDM has been raised in recent studies showing a relationship between hypovitaminosis D and altered glucose homeostasis during pregnancy [82]. However, if there is evidence that the administration of vitamin D can improve insulin resistance and glucose tolerance by acting on pancreatic β-cells and attenuating insulin resistance-associated systemic inflammation [83], further randomized studies are necessary to determine whether vitamin D supplementation effectively improves glycemic control in women with GDM.

PREVENTION:

Given the information provided above regarding the negative effects of GDM on pregnancy and the healthcare system, it is crucial to implement strategies that aim to prevent or minimize GDM. Because being overweight or obese increases the likelihood of developing GDM, studies have primarily focused on the role of diet and exercise in preventing the disease. However, trials involving women with no known risk factors for GDM have not shown significant effects of diet or combined diet and exercise interventions. In overweight and obese pregnant women, one trial demonstrated a reduction in GDM risk, whereas another trial showed a decrease in macrosomia incidence without affecting GDM risk or gestational weight gain. A recent European multicenter trial involving pregnant women with a BMI≥29 kg/m2 found that a healthy eating intervention combined with physical exercise resulted in less gestational weight gain, but had no impact on reducing fasting plasma glucose levels. In contrast, a recent meta-analysis and a randomized controlled trial conducted in a Chinese population have shown the effectiveness of physical activity before and during early pregnancy in preventing GDM [84]. However, due to the heterogeneity of the studies examined, definitive conclusions cannot be drawn, and further trials with larger populations and longer follow-up periods are necessary. Metformin has been shown to reduce the incidence of T2DM in adults with impaired glucose homeostasis and in women with previous GDM [85]. However, its specific effect on GDM incidence remains unclear, except for women with PCOS. A prospective

cohort study on women with PCOS revealed that metformin use before conception was linked to a lower risk of developing GDM and pre-eclampsia [86]. On the other hand, a trial in which metformin was initiated during pregnancy did not confirm these findings. Alternative approaches, such as nutritional supplements and probiotics, have shown promise in reducing the risk of GDM [87]. For instance, trials on myoinositol, an insulin sensitizer from the vitamin B complex group, demonstrated a significant decrease in GDM, macrosomia, and neonatal hypoglycemia [88]. However, these studies were limited to Italy and had small sample sizes, necessitating further research in larger and more diverse populations. Probiotic supplements, which modify maternal gut microbiota, also show potential in improving insulin resistance and reducing GDM risk when combined with dietary interventions [89]. A growing concern in this field pertains to bariatric surgery and its efficacy in addressing obesity and related metabolic issues. Various studies have highlighted the positive impact of weight loss surgery in reducing the risk of GDM and its adverse outcomes in overweight women. Although these findings support the link between bariatric surgery and decreased chances of weight gain during pregnancy, GDM, and gestational hypertension, the potential benefits are offset by the potential for surgical complications as well as nutritional and vitamin deficiencies before and after pregnancy. Moreover, conflicting data regarding the advantages and disadvantages of bariatric surgery in pregnant women exist, underscoring the need for further extensive prospective studies to conclusively determine the effectiveness of bariatric surgery in managing GDM and its associated complications [90].

PRECLINICAL MODELS OF GDM:

To break the cycle of diabetes, it is crucial to gain a deeper understanding of the pathophysiology of GDM and the fetal programing mechanisms triggered by GDM. As mentioned earlier, this is a vital pursuit because GDM poses both short-term and long-term health risks for both the mother and the fetus, potentially leading to long-term health consequences in childhood and adulthood [91]. However, establishing causality in human and epidemiological studies is challenging because of the presence of multiple confounding factors. Therefore, it is imperative to use experimental animal models to investigate the underlying mechanisms and pathophysiology of GDM. Various methods can be employed to generate animal models of GDM, including surgical removal of all or part of the pancreas, the use of pharmacological agents, diet-induced strategies, and genetic models [92].

Surgical Models:

Surgical models encompass various procedures, such as partial or total pancreatectomy, which directly diminish the presence of pancreatic β-cells and significantly disrupt glucose homeostasis. In one particular study, pancreatectomy was performed on a rat model, reducing the pancreatic mass by 95% and leading to impaired uterine function in pregnant rats with mild GDM [93]. However, it is worth noting that this pancreatectomy was performed before pregnancy, which does not accurately replicate the progression of human GDM. Additionally, pancreatectomy has been observed to induce hyperglycemia and diabetes in healthy baboons, although these models are seldom using in the context of pregnancy [94]. While surgically removing the pancreas removes both its endocrine and exocrine components, it is an intrusive and nonspecific procedure that may cause diabetes in a pregnant woman. As such, this could have unintended consequences unrelated to GDM.

Pharmacological Models:

Pharmacological agents such as STZ and Alloxan are commonly used to target pancreatic β-cells and disrupt their function [95]. These chemical agents

provide a convenient method to induce maternal hyperglycemia and diabetes, but their effects can vary based on factors like drug delivery, dosage, species, age, diet, and timing of administration during gestation. While rodents are frequently use in studies on chemical-induced diabetes, nonhuman primates have also been employed, with STZ treatment in female rhesus monkeys resulting in hyperglycemia [96], glucose intolerance, larger placentas and neonates, and a higher rate of stillbirth [97]. However, it is important to note that animal models, whether surgical or chemical, cannot perfectly replicate human GDM. Procedures like pancreatectomy and the use of STZ and alloxan lead to permanent removal of pancreatic endocrine function, resulting in a sustained diabetic state, unlike the transient nature of GDM in humans. Additionally, differences in islet biology between rodents and humans, such as the debate over β-cell compensation during pregnancy, highlight the need for caution when extrapolating findings from animal studies to human conditions [98].

Diet-Induced Models:

Various diet-induced models of gestational diabetes mellitus (GDM) have been studied, including high-fat feeding in animal models to trigger insulin resistance and diabetes. One study using a high-fat diet (HFD) found that non-pregnant female rats, despite being obese, had normal glucose clearance. However, once these rats became pregnant and continued on the HFD, they developed hyperglycemia and glucose intolerance [99]. In a separate study, pregnant female rats were administered continuous glucose infusions in the final week of gestation, resulting in hyperglycemia and hyperinsulinemia [100]. The offspring of these rats exhibited characteristics similar to those of children born to mothers with GDM. Although these obesity-related GDM models may reflect some risk factors for human GDM, they do not account for the genetic and social elements that also play a role in the diseases development.

Genetic Models:

Various genetic models have been used to induce gestational diabetes mellitus (GDM) in animals. Among these models, the db/db mouse model, which is characterized by leptin deficiency, is widely employed to study type 2 diabetes mellitus (T2DM). Typically, female db/+ animals exhibit normal glucose homeostasis; however, during pregnancy, they develop spontaneous GDM, leading to offspring with characteristics similar to those of infants born to mothers with GDM [101]. For instance, offspring of db/+ dams with GDM manifest obesity and insulin resistance in the liver. Another model, the prolactin receptor-deficient (PrlR−/−) mouse, has been identified. PrlR−/− females are unable to sustain a full-term pregnancy, while Prl+/− dams display hyperglycemia and a failure to increase β-cell mass and proliferation during pregnancy, which are crucial for maintaining euglycemia [102]. In the non-pregnant state, these female mice exhibited euglycemia and reduced β-cell mass. Additional genetic models exploring transcription factors and key signaling pathways implicated in GDM have been discussed elsewhere [103]. Although genetic models offer insights into the mechanisms underlying GDM pathogenesis, their conclusions may be constrained by reliance on single gene mutations that do not fully replicate the polygenic and environmental factors contributing to human GDM.

Fetal programing models:

Various novel models of GDM have been established by using the first-generation offspring (F1) of dams (F0) subjected to different intrauterine programing techniques. For instance, in a rat model study, STZ, a toxin that triggers pancreatic β-cell death, was administered F0 female pups to induce diabetes [104]. Following successful mating with non-diabetic males, female

F1 pups were examined to understand GDM during pregnancy. The results showed that non-pregnant F1 pups had normal blood sugar levels but developed high blood sugar and insulin levels during pregnancy. This indicates that exposure to a diabetic intrauterine environment could lead to the development of GDM in female offspring during pregnancy. Another study used a rat model of uteroplacental insufficiency to produce intrauterine growth-restricted (IUGR) offspring [105]. After breeding IUGR female offspring with normal males, pregnant females displayed glucose abnormalities and insulin resistance. The offspring of these female rats exhibited increased body weight, insulin resistance, and impaired glucose metabolism, eventually leading to diabetes. In a separate mouse model, researchers used F1 offspring born to dams fed a low-protein (LP) diet during pregnancy and lactation. F1 females showed glucose intolerance and reduced β-cell growth during pregnancy. These models highlight that exposure to GDM or glucose intolerance during pregnancy increases the risk of offspring (F1) developing GDM [106]. Animal models have also been instrumental in examining the impact of GDM on offspring health, showing that offspring born to mothers with GDM are more prone to obesity, glucose intolerance, and diabetes. In the study conducted by Gauguier et al., female rats were induced with gestational diabetes mellitus (GDM) through continuous glucose infusion during the final week of pregnancy [107]. The female offspring from this study exhibited glucose intolerance and impaired insulin secretion. When these female offspring were bred with control males, the newborn offspring displayed hyperglycemia, hyperinsulinemia, and increased body weight, which persisted into adulthood. These findings suggest that exposure to maternal diabetes during pregnancy can affect the health of multiple generations. Another study by Boloker et al. used an intrauterine programing model of maternal GDM in rats. The offspring in this study also developed glucose intolerance and impaired insulin secretion, which worsened with age. In additionally, the effects of a high-fat diet during pregnancy have been investigated in nonhuman primates. Female Japanese macaques fed a high-fat diet exhibited increased liver triglycerides and an increased risk of nonalcoholic fatty liver disease in their offspring [108]. These studies provide compelling evidence that maternal GDM can have long-lasting effects on the health of the offspring. GDM is a complex disease influenced by genetic, environmental, and epigenetic factors. Therefore, it is unlikely that a single animal model can fully represent human GDM. A more realistic approach would involve animal models with various GDM causes, including both genetic and environmental factors. While larger animals and nonhuman primates may share more physiological similarities with humans, studies used these animal models are more limited due to feasibility and cost constraints compared with studies using mice and rat models. Nonetheless, animal models have significantly contributed to our understanding of maternal GDM, going beyond mere clinical observations. Furthermore, they offer a valuable platform for studying intervention strategies targeting GDM in pregnant women.

CONCLUSION:

Future directions in the study of GDM should focus on further understanding the complex mechanisms involved in its development and progression to diabetes after pregnancy. It is crucial to conduct large-scale screening studies to accurately define the clinical characteristics of evolving autoimmune diabetes and identify genetic factors that may affect insulin resistance and secretion. Additionally, investigating gene-environment interactions and conducting more in-depth studies will provide valuable insights into the pathophysiology of GDM. These efforts will contribute to the development of effective

prevention and treatment strategies, ultimately advancing clinical care for women with GDM.

CONFLICTS OF INTEREST

The authors declare no conflict of interest

FUNDING

Not Applicable

DECLARATION OF COMPETING INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

ABBREVIATIONS

GDM : Gestational diabetes mellitus
T2DM : Type 2 diabetes
MDGs : Millennium Development Goals
NCDs : Non-communicable maternal diseases
FIGO : International Federation of Gynecology and Obstetrics
MTNR1B: Melatonin receptor 1B
TCF7L2 : Transcription factor 7-like 2
IRS1 : Insulin receptor substrate 1
CDKAL1: Cyclin-dependent kinase 5 regulatory subunit-associated protein 1-like 1
GCKR : Glucokinase regulator
G6PC2 : Glucose-6-phosphatase 2
PCSK1 : Proprotein convertase subtilisin/kexin type 1
PPP1R3B: Protein phosphatase 1, regulatory subunit 3B
HKDC1 : Hexokinase domain containing 1
BACE2 : Beta-site amyloid polypeptide cleaving enzyme 2
STZ : Streptozotocin

REFERENCE:

1. Hanson MA, Gluckman PD, Ma RC, Matzen P, Biesma RG. Early life opportunities for prevention of diabetes in low and middle income countries. BMC Public Health. 2012; 12: 1-9.
2. Poon LC, McIntyre HD, Hyett JA, da Fonseca EB, Hod M; FIGO Pregnancy and NCD Committee. The first-trimester of pregnancy - A window of opportunity for prediction and prevention of pregnancy complications and future life. Diabetes Res Clin Pract. 2018; 145: 20-30.
3. Catov JM, Margerison-Zilko C. Pregnancy as a window to future health: short-term costs and consequences. Am J Obstet Gynecol. 2016; 215 (4): 406-7.
4. Godfrey KM, Barker DJ. Fetal programming and adult health. Public Health Nutr. 2001; 4(2B): 611-24.
5. Hoffman DJ, Reynolds RM, Hardy DB. Developmental origins of health and disease: current knowledge and potential mechanisms. Nutr Rev. 2017; 75(12): 951-970.
6. Alejandro EU, Mamerto TP, Chung G, Villavieja A, Gaus NL, Morgan E, Pineda-Cortel MRB. Gestational Diabetes Mellitus: A Harbinger of the Vicious Cycle of Diabetes. Int J Mol Sci. 2020; 21(14): 5003.
7. World Health Organization. Technical Report Series. No 310. Diabetes Mellitus. Report of a WHO Expert Committee. 1965.
8. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes. 1979; 28(12):1039-1057.
9. Freinkel N, Metzger BE, Phelps RL, et al. Gestational diabetes mellitus: heterogeneity of maternal age, weight, insulin secretion, HLA antigens, and islet cell antibodies and the impact of maternal metabolism on pancreatic B-cell and somatic development in the offspring. Diabetes. 1985; 34:1-7.
10. Buchanan TA, Xiang AH, Page KA. Gestational diabetes mellitus: risks and management during and after pregnancy. Nat Rev Endocrinol. 2012; 8(11): 639-49.

11. Crowther CA, Hiller JE, Moss JR, McPhee AJ, Jeffries WS, Robinson JS; Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) Trial Group. Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. N Engl J Med. 2005; 352(24): 2477-86.
12. Sermer M, Naylor CD, Gare DJ, et al. Impact of increasing carbohydrate intolerance on maternal-fetal outcomes in 3637 women without gestational diabetes: the Toronto Tri-Hospital Gestational Diabetes Project. Am J Obstet Gynecol 1995; 173: 146-56.
13. O'Sullivan JB, Gellis SS, Dandrow RV, Tenney BO. The potential diabetic and her treatment in pregnancy. Obstet Gynecol 1966; 27: 683–9.
14. Pettitt DJ, Bennett PH, Saad MF, Charles MA, Nelson RG, Knowler WC. Abnormal glucose tolerance during pregnancy in Pima Indian women: long-term effects on offspring. Diabetes 1991; 40: 126 –30.
15. Damm P. Future risk of diabetes in mother and child after gestational diabetes mellitus. Int J Gynecol Obstet 2009; 104: 525–6.
16. Dabalkea D. The predisposition to obesity and diabetes in offspring of diabetic mothers. Diabetes Care 2007; 30: 169 –74.
17. O'Sullivan JB. Subsequent morbidity among gestational diabetic women. In: Sutherland HW and Stowers JM, eds. Carbohydrate metabolism in pregnancy and the newborn. New York: Churchill Livingstone; 1984; 174 –80.
18. Metzger BE, Gabbe SG, Persson B, et al; International Association of Diabetes and Pregnancy Study Group Consensus Panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010; 33(3): 676-682.
19. Omori Y, Jovanovic L. Proposal for the reconsideration of the definition of gestational diabetes. Diabetes Care. 2005; 28(10): 2592-2593.
20. International Diabetes Federation. IDF Diabetes Atlas. 9th ed. 2019; 114.
21. Guariguata L, Linnenkamp U, Beagley J, et al. Global estimates of the prevalence of hyperglycemia in pregnancy. Diabetes Res Clin Pract. 2014; 103(2):176-185.
22. McIntyre HD, Oats JJ, Kihara AB, et al. Update on diagnosis of hyperglycemia in pregnancy and gestational diabetes mellitus from FIGO's Pregnancy & Non-Communicable Diseases Committee. Int J Gynaecol Obstet. 2021; 154(2): 189-194.
23. Prentice PM, Olga L, Petry CJ, et al. Reduced size at birth and persisting reductions in adiposity in recent, compared with earlier, cohorts of infants born to mothers with gestational diabetes mellitus. Diabetologia. 2019; 62(11): 1977-1987.
24. Hartling L, Dryden DM. Screening and diagnosing gestational diabetes mellitus. Evid Rep Technol Assess (Full Rep). 2012; 210: 1-327.
25. Bottalico JN. Recurrent gestational diabetes: risk factors, diagnosis, management, and implications. Semin Perinatol. 2007; 31(3): 176-184.
26. Anna V, van der Ploeg H, P, Cheung NW, et al. Sociodemographic correlates of the increasing trend in the prevalence of gestational diabetes mellitus in a large population of women between 1995 and 2005. Diabetes Care. 2008; 31(12): 2288-2293.
27. Chu SY, Callaghan WM, Kim SY, et al. Maternal obesity and risk of gestational diabetes mellitus. Diabetes Care. 2007; 30(8): 2070-2076.
28. Torloni MR, Betran AP, Horta BL, et al. Prepregnancy BMI and the risk of gestational

diabetes: a systematic review of the literature with meta-analysis. Obes Rev. 2009; 10(2): 194-203.
29. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. JAMA. 2003; 289(1): 76-79.
30. Mulla WR, Henry TQ, Homko CJ. Gestational diabetes screening after HAPO: has anything changed? Curr Diab Rep. 2010; 10(3): 224-228.
31. Petry CJ. Gestational diabetes: risk factors and recent advances in its genetics and treatment. Br J Nutr. 2010; 104(6): 775-787.
32. Hunt KJ, Schuller KL. The increasing prevalence of diabetes in pregnancy. Obstet Gynecol Clin North Am. 2007; 34(2): 173-199
33. Sacks DA, Hadden DR, Maresh M, et al. Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study. Diabetes Care. 2012; 35(3): 526-528.
34. Agarwal MM, Dhatt GS, Shah SM. Gestational diabetes mellitus: simplifying the international association of diabetes and pregnancy diagnostic algorithm using fasting plasma glucose. Diabetes Care. 2010; 33(9): 2018-2020.
35. Moses RG, Morris GJ, Petocz P, et al. The impact of potential new diagnostic criteria on the prevalence of gestational diabetes mellitus in Australia. Med J Aust. 2011; 194(7): 338-340.
36. Brown FM, Wyckoff J. Application of one-step IADPSG versus two-step diagnostic criteria for gestational diabetes in the real world: impact on health services, clinical care, and outcomes. Curr Diab Rep. 2017; 17(10): 85.
37. Zhu Y, Zhang C. Prevalence of gestational diabetes and risk of progression to type 2 diabetes: a global perspective. Curr Diab Rep 2016
38. American Diabetes Association. Classification and diagnosis of diabetes. Diabetes Care. 2016
39. Chen C, Xu X, Yan Y. Estimated global overweight and obesity burden in pregnant women based on panel data model. PLoS One. 2018; 13(8): e0202183.
40. Wang H, Li N, Chivese T, Werfalli M, Sun H, Yuen L, Hoegfeldt CA, Elise Powe C, Immanuel J, Karuranga S, Divakar H, Levitt N, Li C, Simmons D, Yang X; IDF Diabetes Atlas Committee Hyperglycaemia in Pregnancy Special Interest Group. IDF Diabetes Atlas: Estimation of Global and Regional Gestational Diabetes Mellitus Prevalence for 2021 by International Association of Diabetes in Pregnancy Study Group's Criteria. Diabetes Res Clin Pract. 2022; 183: 109050.
41. Buckley BS, Harreiter J, Damm P, Corcoy R, Chico A, Simmons D, Vellinga A, Dunne F; DALI Core Investigator Group. Gestational diabetes mellitus in Europe: prevalence, current screening practice and barriers to screening. A review. Diabet Med. 2012; 29(7): 844-54.
42. Chiefari E, Arcidiacono B, Foti D, Brunetti A. Gestational diabetes mellitus: an updated overview. Journal of endocrinological investigation. 2017; 40: 899-909.
43. De Souza LR, Berger H, Retnakaran R, Maguire JL, Nathens AB, Connelly PW, Ray JG. First-Trimester Maternal Abdominal Adiposity Predicts Dysglycemia and Gestational Diabetes Mellitus in Midpregnancy. Diabetes Care. 2016; 39(1): 61-4.

44. Qi Y, Sun X, Tan J, Zhang G, Chen M, Xiong Y, Chen P, Liu C, Zou K, Liu X. Excessive gestational weight gain in the first and second trimester is a risk factor for gestational diabetes mellitus among women pregnant with singletons: A repeated measures analysis. J Diabetes Investig. 2020; 11(6): 1651-1660.
45. Moses RG, Brand-Miller JC. Dietary risk factors for gestational diabetes mellitus: are sugar-sweetened soft drinks culpable or guilty by association? Diabetes Care. 2009; 32(12): 2314-5.
46. Kalra B, Gupta Y, Singla R, Kalra S. Use of oral anti-diabetic agents in pregnancy: a pragmatic approach. N Am J Med Sci. 2015; 7(1): 6-12.
47. Bhathena RK. Insulin resistance and the long-term consequences of polycystic ovary syndrome. J Obstet Gynaecol. 2011; 31(2): 105-10.
48. Mustaniemi S, Vääräsmäki M, Eriksson JG, Gissler M, Laivuori H, Ijäs H, Bloigu A, Kajantie E, Morin-Papunen L. Polycystic ovary syndrome and risk factors for gestational diabetes. Endocr Connect. 2018; 7(7): 859-869.
49. Gutaj P, Zawiejska A, Mantaj U, Wender-Ożegowska E. Determinants of preeclampsia in women with type 1 diabetes. Acta Diabetol. 2017; 54(12): 1115-1121.
50. Horsch A, Kang JS, Vial Y, Ehlert U, Borghini A, Marques-Vidal P, Jacobs I, Puder JJ. Stress exposure and psychological stress responses are related to glucose concentrations during pregnancy. Br J Health Psychol. 2016; 21(3): 712-29.
51. Myoga M, Tsuji M, Tanaka R, Shibata E, Askew DJ, Aiko Y, Senju A, Kawamoto T, Hachisuga T, Araki S, Kusuhara K, Morokuma S, Sanefuji M; Japan Environment and Children's Study. Impact of sleep duration during pregnancy on the risk of gestational diabetes in the Japan environmental and Children's study (JECS). BMC Pregnancy Childbirth. 2019; 19(1): 483.
52. Abu-Heija AT, Al-Bash MR, Al-Kalbani MA. Effects of maternal age, parity and pre-pregnancy body mass index on the glucose challenge test and gestational diabetes mellitus. J Taibah Univ Med Sci. 2017; 12(4): 338-342.
53. Dode MA, dos Santos IS. Non classical risk factors for gestational diabetes mellitus: a systematic review of the literature. Cad Saude Publica. 2009; 25(3): 341-59.
54. Hall LM, Moran CN, Milne GR, Wilson J, MacFarlane NG, Forouhi NG, Hariharan N, Salt IP, Sattar N, Gill JM. Fat oxidation, fitness and skeletal muscle expression of oxidative/lipid metabolism genes in South Asians: implications for insulin resistance? PLoS One. 2010; 5(12): 14197.
55. Yahaya TO, Anyebe DA. Genes predisposing to neonatal diabetes mellitus and pathophysiology: Current findings. J Neonatal Perinatal Med. 2020; 13(4): 543-553.
56. Vasileiou V, Kyratzoglou E, Paschou SA, Kyprianou M, Anastasiou E. The impact of environmental temperature on the diagnosis of gestational diabetes mellitus. Eur J Endocrinol. 2018; 178(3): 209-214.
57. Rönö K, Masalin S, Kautiainen H, Gissler M, Raina M, Eriksson JG, Laine MK. Impact of maternal income on the risk of gestational diabetes mellitus in primiparous women. Diabet Med. 2019; 36(2): 214-220.
58. Weissgerber TL, Mudd LM. Preeclampsia and diabetes. Curr Diab Rep. 2015; 15(3): 9.
59. Rayanagoudar G, Hashi AA, Zamora J, Khan KS, Hitman GA, Thangaratinam S. Quantification of the type 2 diabetes risk in women with gestational diabetes: a systematic

review and meta-analysis of 95,750 women. Diabetologia. 2016; 59(7): 1403-1411.

60. Kc K, Shakya S, Zhang H. Gestational diabetes mellitus and macrosomia: a literature review. Ann Nutr Metab. 2015; 66(2): 14-20.
61. ovio U, Murphy HR, Smith GC. Accelerated Fetal Growth Prior to Diagnosis of Gestational Diabetes Mellitus: A Prospective Cohort Study of Nulliparous Women. Diabetes Care. 2016; 39(6): 982-7.
62. Rozance PJ, Hay WW. Hypoglycemia in newborn infants: Features associated with adverse outcomes. Biol Neonate. 2006; 90(2): 74-86.
63. Franks PW, Looker HC, Kobes S, Touger L, Tataranni PA, Hanson RL, Knowler WC. Gestational glucose tolerance and risk of type 2 diabetes in young Pima Indian offspring. Diabetes. 2006; 55(2): 460-5.
64. Yu Y, Arah OA, Liew Z, Cnattingius S, Olsen J, Sørensen HT, Qin G, Li J. Maternal diabetes during pregnancy and early onset of cardiovascular disease in offspring: population based cohort study with 40 years of follow-up. BMJ. 2019; 367: l6398.
65. Coustan DR, Nelson C, Carpenter MW, Carr SR, Rotondo L, Widness JA. Maternal age and screening for gestational diabetes: a population-based study. Obstet Gynecol. 1989; 73(4): 557-61.
66. International Association of Diabetes and Pregnancy Study Groups Consensus Panel; Metzger BE, Gabbe SG, Persson B, Buchanan TA, Catalano PA, Damm P, Dyer AR, Leiva Ad, Hod M, Kitzmiler JL, Lowe LP, McIntyre HD, Oats JJ, Omori Y, Schmidt MI. International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. Diabetes Care. 2010; 33(3): 676-82.
67. Huhn EA et al Fourfold increase in prevalence of gestational diabetes mellitus after adoption of the new International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria. J Perinat Med. 2016; 45 doi:10.1515/jpm-2016-0099
68. Handelsman Y, Mechanick JI, Blonde L, Grunberger G, Bloomgarden ZT, Bray GA, Dagogo-Jack S, Davidson JA, Einhorn D, Ganda O, Garber AJ, Hirsch IB, Horton ES, Ismail-Beigi F, Jellinger PS, Jones KL, Jovanovič L, Lebovitz H, Levy P, Moghissi ES, Orzeck EA, Vinik AI, Wyne KL; AACE Task Force for Developing Diabetes Comprehensive Care Plan. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. Endocr Pract. 2011; 17(2): 1-53.
69. Bhattacharyya OK, Estey EA, Cheng AY; Canadian Diabetes Association 2008. Update on the Canadian Diabetes Association 2008 clinical practice guidelines. Can Fam Physician. 2009; 55(1): 39-43.
70. Committee opinion no. 504: Screening and diagnosis of gestational diabetes mellitus. Obstet Gynecol. 2013; 201; 118(3): 751-753.
71. Gillespie P, Cullinan J, O'Neill C, Dunne F; ATLANTIC DIP Collaborators. Modeling the independent effects of gestational diabetes mellitus on maternity care and costs. Diabetes Care. 2013; 36(5): 1111-6.
72. Scottish Intercollegiate Guidelines Network Maternal and Health Division, National Guidelines for Diagnosis and Management of Gestational Diabetes Mellitus: Ministry of Health and Family Welfare, New Concept Information Systems, New Delhi, India, 2014.
73. Capula C et al (2016) A new predictive tool for the early risk assessment of gestational diabetes mellitus. Prim Care Diabetes. doi:10.1016/j.pcd.2016.05.004.

74. Lapolla A, Dalfrà MG, Fedele D. Management of gestational diabetes mellitus. Diabetes Metab Syndr Obes. 2009; 2: 73-82.
75. Landon MB, Spong CY, Thom E, Carpenter MW, Ramin SM, Casey B, Wapner RJ, Varner MW, Rouse DJ, Thorp JM Jr, Sciscione A, Catalano P, Harper M, Saade G, Lain KY, Sorokin Y, Peaceman AM, Tolosa JE, Anderson GB; Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A multicenter, randomized trial of treatment for mild gestational diabetes. N Engl J Med. 2009; 361(14): 1339-48.
76. de Veciana M, Major CA, Morgan MA, Asrat T, Toohey JS, Lien JM, Evans AT. Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. N Engl J Med. 1995; 333(19): 1237-41.
77. Evers IM, de Valk HW, Mol BW, ter Braak EW, Visser GH. Macrosomia despite good glycaemic control in Type I diabetic pregnancy; results of a nationwide study in The Netherlands. Diabetologia. 2002; 45(11): 1484-9.
78. Hernandez TL, Van Pelt RE, Anderson MA, Reece MS, Reynolds RM, de la Houssaye BA, Heerwagen M, Donahoo WT, Daniels LJ, Chartier-Logan C, Janssen RC, Friedman JE, Barbour LA. Women With Gestational Diabetes Mellitus Randomized to a Higher-Complex Carbohydrate/Low-Fat Diet Manifest Lower Adipose Tissue Insulin Resistance, Inflammation, Glucose, and Free Fatty Acids: A Pilot Study. Diabetes Care. 2016; 39(1): 39-42.
79. Government of India (2008) Diabetes in pregnancy. Revised reprint July 2008. RCOG Press, London. http://www.nice.org.uk
80. Langer O, Conway DL, Berkus MD, Xenakis EM, Gonzales O. A comparison of glyburide and insulin in women with gestational diabetes mellitus. N Engl J Med. 2000; 343(16): 1134-8.
81. Balsells M, García-Patterson A, Solà I, Roqué M, Gich I, Corcoy R. Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. BMJ. 2015; 350: 102.
82. Poel YH, Hummel P, Lips P, Stam F, van der Ploeg T, Simsek S. Vitamin D and gestational diabetes: a systematic review and meta-analysis. Eur J Intern Med. 2012; 23(5): 465-9.
83. Kampmann U, Mosekilde L, Juhl C, Moller N, Christensen B, Rejnmark L, Wamberg L, Orskov L. Effects of 12 weeks high dose vitamin D3 treatment on insulin sensitivity, beta cell function, and metabolic markers in patients with type 2 diabetes and vitamin D insufficiency - a double-blind, randomized, placebo-controlled trial. Metabolism. 2014; 63(9): 1115-24.
84. Wang C, Wei Y, Zhang X, Zhang Y, Xu Q, Su S, Zhang L, Liu C, Feng Y, Shou C, Guelfi KJ, Newnham JP, Yang H. Effect of Regular Exercise Commenced in Early Pregnancy on the Incidence of Gestational Diabetes Mellitus in Overweight and Obese Pregnant Women: A Randomized Controlled Trial. Diabetes Care. 2016; 39(10): 163-4.
85. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002; 346(6): 393-403.
86. Khattab S, Mohsen IA, Aboul Foutouh I, Ashmawi HS, Mohsen MN, van Wely M, van der Veen F, Youssef MA. Can metformin reduce the incidence of gestational diabetes mellitus in pregnant women with polycystic

ovary syndrome? Prospective cohort study. Gynecol Endocrinol. 2011; 27(10): 789-93.

87. Agha-Jaffar R, Oliver N, Johnston D, Robinson S. Gestational diabetes mellitus: does an effective prevention strategy exist? Nat Rev Endocrinol. 2016; 12(9): 533-46.
88. D'Anna R, Scilipoti A, Giordano D, Caruso C, Cannata ML, Interdonato ML, Corrado F, Di Benedetto A. myo-Inositol supplementation and onset of gestational diabetes mellitus in pregnant women with a family history of type 2 diabetes: a prospective, randomized, placebo-controlled study. Diabetes Care. 2013; 36(4): 854-7.
89. Luoto R, Laitinen K, Nermes M, Isolauri E. Impact of maternal probiotic-supplemented dietary counselling on pregnancy outcome and prenatal and postnatal growth: a double-blind, placebo-controlled study. Br J Nutr. 2010; 103(12): 1792-9.
90. Dalfrà MG, Busetto L, Chilelli NC, Lapolla A. Pregnancy and foetal outcome after bariatric surgery: a review of recent studies. J Matern Fetal Neonatal Med. 2012; 25(9): 1537-43.
91. Catalano PM. The impact of gestational diabetes and maternal obesity on the mother and her offspring. J Dev Orig Health Dis. 2010; 1(4): 208-15.
92. Pasek RC, Gannon M. Advancements and challenges in generating accurate animal models of gestational diabetes mellitus. Am J Physiol Endocrinol Metab. 2013; 305(11): E1327-38.
93. 93.Jawerbaum A, Catafau JR, Gonzales ET, Rodriguez RR, Gelpi E, Gomez G, Gimeno AL, Gimeno MA. Eicosanoid production by uterine strips and by embryos obtained from diabetic pregnant rats. Prostaglandins. 1993; 45(5): 487-95.
94. 94.GILLMAN J, GILBERT C, EPSTEIN E, ALLAN JC. Endocrine control of blood sugar, lipaemia, and ketonaemia in diabetic baboons. Br Med J. 1958; 2(5107): 1260-3.
95. Junod A, Lambert AE, Stauffacher W, Renold AE. Diabetogenic action of streptozotocin: relationship of dose to metabolic response. J Clin Invest. 1969; 48(11): 2129-39.
96. Kemnitz JW, Eisele SG, Lindsay KA, Engle MJ, Perelman RH, Farrell PM. Changes in food intake during menstrual cycles and pregnancy of normal and diabetic rhesus monkeys. Diabetologia. 1984; 26(1): 60-4.
97. Mintz DH, Chez RA, Hutchinson DL. Subhuman primate pregnancy complicated by streptozotocin-induced diabetes mellitus. J Clin Invest. 1972; 51(4): 837-47.
98. Genevay M, Pontes H, Meda P. Beta cell adaptation in pregnancy: a major difference between humans and rodents? Diabetologia. 2010; 53(10): 2089-92.
99. Holemans K, Caluwaerts S, Poston L, Van Assche FA. Diet-induced obesity in the rat: a model for gestational diabetes mellitus. Am J Obstet Gynecol. 2004; 190(3): 858-65
100. Gauguier D, Bihoreau MT, Picon L, Ktorza A. Insulin secretion in adult rats after intrauterine exposure to mild hyperglycemia during late gestation. Diabetes. 1991; 40(2): 109-14.
101. Yamashita H, Shao J, Qiao L, Pagliassotti M, Friedman JE. Effect of spontaneous gestational diabetes on fetal and postnatal hepatic insulin resistance in Lepr(db/+) mice. Pediatr Res. 2003; 53(3): 411-8.
102. Huang C, Snider F, Cross JC. Prolactin receptor is required for normal glucose homeostasis and modulation of beta-cell mass during pregnancy. Endocrinology. 2009; 150(4): 1618-26.
103. Jawerbaum A, White V. Animal models in diabetes and pregnancy. Endocr Rev. 2010; 31(5): 680-701.
104. Capobianco E, Fornes D, Linenberg I, Powell TL, Jansson T, Jawerbaum A. A novel rat

model of gestational diabetes induced by intrauterine programming is associated with alterations in placental signaling and fetal overgrowth. Mol Cell Endocrinol. 2016; 422: 221-232.

105. Boloker J, Gertz SJ, Simmons RA. Gestational diabetes leads to the development of diabetes in adulthood in the rat. Diabetes. 2002; 51(5): 1499-506.
106. Szlapinski SK, King RT, Retta G, Yeo E, Strutt BJ, Hill DJ. A mouse model of gestational glucose intolerance through exposure to a low protein diet during fetal and neonatal development. J Physiol. 2019; 597(16): 4237-4250.
107. Gauguier D, Bihoreau MT, Ktorza A, Berthault MF, Picon L. Inheritance of diabetes mellitus as consequence of gestational hyperglycemia in rats. Diabetes. 1990; 39(6): 734-9.
108. Mccurdy CE, Bishop JM, Williams SM, Grayson BE, Smith MS, Friedman JE, Grove KL. Maternal high-fat diet triggers lipotoxicity in the fetal livers of nonhuman primates. J Clin Invest. 2009; 119(2): 323-35.

HOW TO CITE: Shivaraj Hiremath, Shubham Teli, Mallappa Shalavadi , Exploring The Impact Of Lifestyle Factors On Gestational Diabetes, Risk And Management: Insights From A Preclinical Model Study, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 10, 368-392. https://doi.org/10.5281/zenodo.13904063