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REVIEW ARTICLE

Gestational Diabetes Mellitus: Prevalence, Risk Factors, Pathophysiology, Diagnostic Criteria and Intervention Strategies – A Narrative Review

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Abstract

Background: Introduction: Gestational Diabetes Mellitus (GDM) is a prevalent complication of pregnancy affecting about 25% of pregnancies worldwide, having a higher burden in low and middle income countries. GDM is a condition characterised by glucose metabolic disorder which poses a public health concern during pregnancy and is associated with long-term adverse effects on both maternal and fetal health. This review is aimed at summarizing the current understanding of GDM, prevalence, pathophysiology, risk factors, current approaches in the diagnosis, management and care of individuals with gestational diabetes mellitus with a view to understanding the progress made so far, challenges and future prospects in curbing of this menace. **Methods:** Data were obtained from PubMed and other databases and include published randomized studies, narratives and systematic reviews. **Results:** The absence of universally accepted diagnostic criteria for Gestational Diabetes Mellitus (GDM) complicates its definition and understanding of its prognosis. However, early diagnosis, along with blood glucose control through exercise and dietary interventions, has been shown to be beneficial. **Conclusion:** The incidence and prevalence of gestational diabetes is on the rise, hence the need to promote its prevention and early diagnosis via having a unified method of diagnosis is very important.

Keywords: gestational diabetes mellitus; diabetes care; medical nutrition therapy; hyperglycemia; pregnancy; glucose imbalance

Introduction

Gestational diabetes is a condition characterised by varying degrees of glusose intolerance that first appears during pregnancy (Gyasi-Antwi *et al*., 2020). It is the most common metabolic disorder of public health concern occurring during pregnancy (Santangelo *et al*., 2016) that is associated with both maternal and fetal outcomes. It presents an intermediate glucose level ranging between normal levels for pregnancy and glucose levels diagnostic of diabetes in the non-pregnant state which has been linked with perinatal mortality and morbidity (Embaby *et al*., 2016) of the fetus and an increased risk of diabetes type 2 and cardiovascular disease in the future (Wang *et al*., 2020). Gestational diabetes mellitus affects 25% of pregnancies worldwide (Sparks *et al*., 2022) with a vast

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majority of cases occurring in low and middle income countries where access to maternal healthcare may be limited, and as a result, it is responsible for a higher incidence of maternal and fetal morbidity and mortality (IDF, 2020).

Though it has been established that gestational diabetes mellitus can occur following autioimmune diabetes, diabetes occurring as a result of insulin resistance or diabetes occurring as a result of other factors (genetic mutation, diseases of the endocrine glands or chemically-induced), most cases of gestational diabetes mellitus occur as a result of B-cell dysfunction which is the basis of chronic insulin resistance to which insulin resistance in normal pregnancy may play a role (Chiu *et al*., 1994; Damm *et al*., 1994; Bucanan and Xiang, 2005).

Despite the prevalence of GDM, it remains poorly understood with its management often below standard. This review, therefore, aims to provide a comprehensive overview of the current understanding of GDM with respect to its prevalence, pathophysiology, diagnosis, intervention strategies and complications. By synthesizing the existing literature, we hope to provide a clearer understanding of GDM and its implication for maternal and fetal health.

Materials and Methods

This review was done using studies published from online databases that include PubMed, google scholar, WHO-based guidelines and National Institute for Health and Care Excellence (NICE) guidelines. The search was performed using keywords such as gestational diabetes mellitus, diabetes care, GDM management, pregnancy, interventions and medical nutrition therapy. Recent publications, narrativse and systematic reviews as well as controlled trials, observational studies and current guidelines for practice were also included. The literatures reviewed were restricted to those written in English.

Results

Prevalence of GDM

A wide variation has been observed on the prevalence of GDM globally and this has been attributed to the use of different diagnostic criteria. Results from a recent meta-analysis report a global prevalence of 14.7% based on the criteria of the International Association of Diabetes and Pregnancy Study Groups (Saeedi *et al*., 2021). In Africa, the prevalence of GDM was found to range between 7-12% (Lendoye *et al*., 2022; Ahmad *et al*., 2023). while in Nigeria, the prevalence of GDM was reported to be 11.0% (Azeez *et al*., 2021).

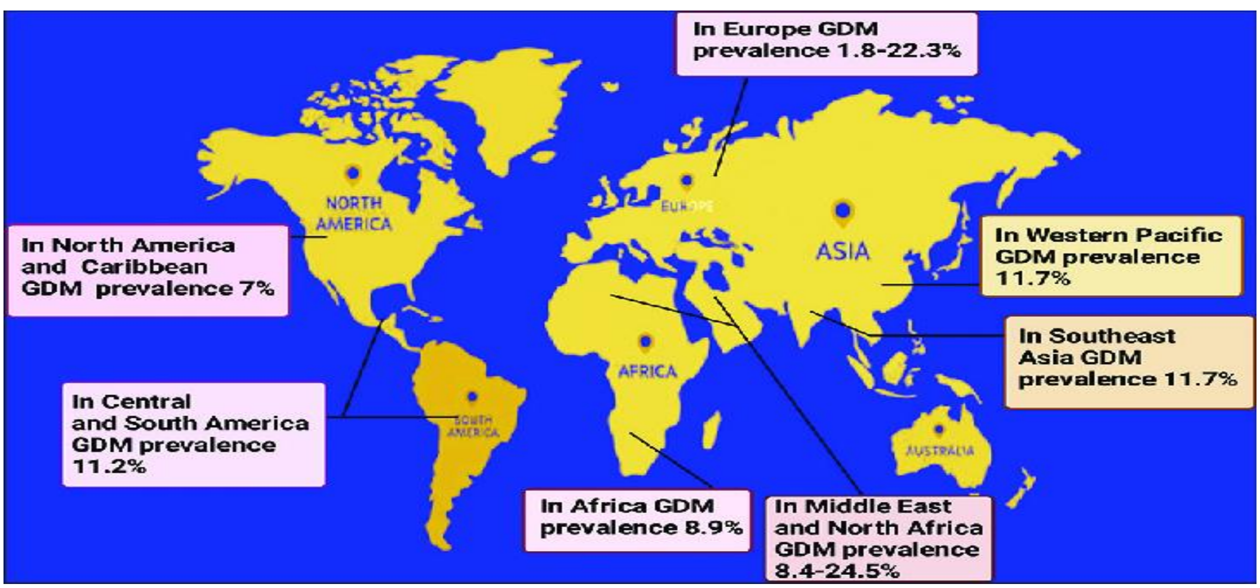

Fig. 1: Global Prevalence of GDM Based on Regions (Ahmad *et al*. 2023)

Predisposing factors

The etiology of GDM is believed to be multifactorial although the exact cause is yet to be established (Giannakou *et al*., 2019). A lot of factors have been associated with the occurence and prevalence of GDM ranging from genetics to epigenetic factors. These include being black, obesity prior to pregnancy, history of GDM (Lendoye *et al*., 2022), overweight, advanced maternal age, family history of GDM or any form of diabetes (Plows *et al*., 2018), micronutrients deficiency, westernized diets high in saturated fats and refined sugars, red and processed meats (Zhang *et al*., 2006; Bowers *et al*., 2012). Other risk factors include high protein diets (Bao *et al*., 2013; Maslova *et al*., 2017; Pang *et al*., 2017), recurrent abortions, previous history of large babies, history of still birth, chronic hypertension, maternal smoking (Kampmann *et al*., 2015), non-white ethnicity (Dugan *et al*., 2019) and early age at menarche (Li *et al*., 2017). Environmental pollution has also been linked with the occurence of GDM in some areas (Rammah *et al*., 2020).

Pathophysiology of Gestational Diabetes

The pathophysiology of GDM is based on pregnancy-related changes (Mdoe *et al*., 2021). A healthy pregnancy is characterized by transient insulin resistance and hyperlipidaemia that causes an increase in insulin secretion aimed at maintaining normal glucose tolerance (Sorensen *et al*., 2022). Maternal genetic predisposition, obesity, over-nutrition and excessive gestational weight gain are some factors that can lead to dysfunctional pancreatic B-cells with resultant hyperglycaemia, deteriorated glucose tolerance and ultimately gestational diabetes (Plows *et al*., 2018; Sorensen *et al*., 2022).

Changes in maternal metabolism is one of the significant changes associated with normal pregnancy (Lain and Catalano, 2007). Oestrogen and progesterone stimulate maternal B-cell hyperplasia and insulin secretion in early pregnancy. These help in the maternal storage of nutrients in the adipose tissues and liver in order to support fetal growth as pregnancy advances (Brown *et al*., 2017). At this stage, insulin sensitivity is maintained and sometimes even increased. But as pregnancy progresses toward the third trimester, there is a decline in insulin sensitivity by about 50% (Barbour *et al*., 2007) which has been linked to placental hormones, cytokines released from adipose tissues, increased free fatty acids and lower adiponectin concentrations (Clapp, 2006; Devilieger *et al*., 2008); as well as a 40% to 60% decrease in postprandial peripheral glucose disposal (Barbour *et al*., 2007).

In normal pregnancy, maternal glycaemia is maintained by about 200%-250% rise in insulin secretion (Suman Rao *et al*., 2013) while for women who develop GDM, they have significant reductions in insulin sensitivity in pregnancy and are unable to increase insulin secretion enough to maintain postprandial euglycaemia. Other factors linked to the pathophysiology of GDM are impaired insulin signalling due to sub-clinical inflammation, decreased secretion of adiponectin from adipocytes (Brown *et al*., 2017) and history of periodontitis (Bendek *et al*., 2021).

Diagnosis of GDM

Although there is a worldwide variation in the definition, method of screening and management of GDM, the International Association of Diabetes in Pregnancy Study Groups have recommended a one-step approach for the screening of pregnant women for GDM (Lende and Rijhsinghani, 2020) which entails a 75g oral glucose tolerance test (OGTT) between 24-28 weeks gestation (IADPSG, 2010). Though this recommendation was adopted by WHO, it was observed that the one-step approach led to an increased workload and, in some cases, unnecessary medicalization of care. To eliminate this, most European countries still make use of the two-step screening approach which, in addition to the OGTT, also has a glucose challenge test (Benhalima *et al*., 2018). In the same vein, there is currently no universal guideline for the diagnosis of GDM (Dempsey *et al*., 2022) though based on the National Institute for Health and Care Excellence (NICE), women should be diagnosed with GDM if they either have a fasting plasma glucose level of 5.6 mmol/litre or above (NICE, 2015).

Table 1: IADPSG, International Association of Diabetes and Pregnancy Study Groups; ADA, American Diabetes Association; WHO, World Health Organisation. (Nayak *et al.*, 2013)

Criteria	Diagnosis
IADPSG (75 gram OGTT) (Metzger *et al*., 2010)	At least one value meeting the threshold: Fasting plasma glucose > 5.11 mmol/1 1-h plasma glucose > 10 mmol/1 2-h plasma glucose > 8.5 mmol/1
Old ADA (lOOg OGTT) (WHO**, 1999**)	At least two values meeting the thresholds: Fasting plasma glucose > 5.28 mmol/1 1-h plasma glucose > 10 mmol/1 2-h plasma glucose >8.61 mmol/1 3-h plasma glucose > 7.78 mmol/1
WHO (75 g OGTT) (P S A D A , 2 0 1 0)	**At least one value meeting the threshold:** Fasting plasma glucose > 7 mmol/1 2-h plasma glucose > 7.78 mmol/1

Interventions for Women with GDM

Exercise

Sedentary lifestyle predisposes an individual to a wide range of adverse effects, and pregnancy has been described as a period of reduced physical activity, sports and exercise (Fell *et al*., 2009). Exercise improves blood supply to skeletal muscles, counteracts lipid-induced insulin resistance as well as modify the hormonal regulation of hepatic glucose output (Jensen *et al*., 2004; Schenk *et al*., 2005). It also enhances glucose uptake in skeletal muscles, improves glucose homeostasis and most of the insulin mediated post-receptor events that leads to increased expression of GLUT4 from intracellular stores to the muscle cell membrane (Asano *et al*., 2014; Brown *et al*., 2017). Glucose enters the skeletal muscle cells via facilitated diffusion with the help of glucose transporter (GLUT4) while its clearance largely depends on blood flow to the muscles, expression of glucose transporters and utilization of glucose through glycolysis and glycogenesis (Richter *et al*., 2001). Insulin sensitivity in skeletal muscles is related to the degree of physical activity (Asano *et al*., 2014).

The ameliorative effects of physical exercise in the control of hyperglycaemia among women with GDM was observed with increased levels of moderate intensity in physical exercise which reduces/reverses pregnancy-induced insulin resistance (Clapp and Capeless, 1991; Clapp *et al*., 1992). Fasting blood glucose and fasting insulin levels were effectively reduced by moderate intensity exercises in women that were at risk of developing GDM (Embaby *et al*. 2016) though the amount of exercise required to achieve that effects was slightly higher than the recommended moderate intensity exercise of 30 mins per day particularly after a meal (NICE, 2015; Erlich *et al*., 2021). In a systematic review and meta-analysis, it was found that exercise only interventions reduces the odds of gestational diabetes, gestational hypertension and pre-eclampsia by 38% though most of the exercise only interventions used in the study does not reduce the risk of GDM on their own (Davenport *et al*., 2018). In a randomized controlled trial carried out in China in order to assess the effectiveness of regular exercise in the prevention of GDM, exercise demonstrates high potential in reducing the risk of GDM and improving glucose metabolism (Wang *et al*., 2016), while resistance exercise may help to avoid insulin therapy (Brankston *et al*., 2004), sustain insulin sensitivity and improve glucose clearance (Bung *et al*., 1991).

Although the effects of exercise activities alone do not have significant effects on the overall incidence of GDM, the incidence of GDM was 24% lower in the intervention group than in the control group (Nasiri *et al*., 2019), and the effect was significant (Zheng *et al*., 2017). Furthermore, physical activity interventions may have different impacts depending on pre-pregnancy body weight status (Nasiri-Amiri *et al*., 2019).

Medical Nutrition Therapy

Nutrition is a cost effective early stage intervention in the management of GDM. Besides being fiscally reasonable and culturally sensitive, it was found to be effective in reducing the need for medication and intensified healthcare resource use (Hernandez and Brand-Miller, 2018).

Medical nutrition therapy is being utilized in the treatment of GDM because carbohydrate has been implicated as the main causative agent due to the role it plays in glycaemia (Aloke *et al*., 2022). Medical nutrition therapy aims to achieve and maintain euglycaemia through consumption of foods with lower glycaemic index (GI) Moreno-Castilla *et al*., 2016; Brown *et al*., 2017). Despite heterogeneity in dietary interventions administered in different studies, a moderately favourable effect of diet was observed on maternal glycaemic outcomes (Yamamoto *et al*., 2018) and the risk of GDM (Bennett *et al*., 2018). Furthermore, low GI diets reduces the amount of insulin required to maintain optimal glycaemic control in pregnancies complicated by GDM (Louie *et al*., 2010), while low GI diet in combination with dietary fibre improves pregnancy outcomes in GDN (Mousa *et al*., 2019). On the contrary, in a randomized trial among Australian women at risk of GDM, no differences were found between low GI diet versus high fibre diet / moderate GI diets with respect to pregnancy outcomes (Markovic *et al*., 2016). Similarly, a 2015 meta-analysis reveals that diet interventions, such as partial meal replacement, in order to aid in appropriate energy balance, promotes nutritious eating, and/or energy intake counselling and does not result in a statistically significant reduction in the risk of GDM (Rogozinska *et al*, 2015).

In addition, findings from the meta-analyses also suggest that previous trials do not result in a physiologically relevant attenuation of gestational weight gain to lessen GDM risk because diet interventions targeting weight reduction through decreased energy intake was implemented too late for individuals who became pregnant while still being overweight or obese (Rogozinska *et al.*, 2015; Markovic *et al*., 2016). Elevated post-prandial glucose levels is associated with adverse pregnancy outcomes in women with GDM (De Veciana *et al*., 1995).

Medication

Although the use of oral agents in the management of GDM remains controversial (Barbour *et al*., 2018), oral medication therapy is an effective and safe treatment regimen for GDM and, in some circumstances, may serve as the first-line therapy when exercise and nutritional modification fails (Bergel *et al*., 2016). According to the American College of Obstetrics and Gynaecologists, insulin is still the preferred pharmacologic treatment for GDM (Bishop *et al*., 2019) as other alternatives such as metformin and glyburide have been associated with long term metabolic risk in the child (Barbour *et al*., 2018). In the same vein, the Society for Maternal-Fetal Medicine endorses metformin as a safe alternative to insulin in the management of GDM and was preferred to glyburide (SMFM, 2018), though researches following this declaration suggest that metformin has the potential to inhibit mitochondrial activity and may exhibit adverse effect on function, growth or differentiation of fetal and placental tissues (Heckman-Stoddard *et al*., 2017).

Precision Medicine

Precision medicine refers to the tailoring of prevention, diagnosis and treatment of a particular health issue so that each patient receives optimal personalized therapy (Krook and Mulder, 2022). It usually relies on precision diagnostics and is embedded with the potentials to offer direct clinical benefits to patients. It is more cost effective for society as time and resources are not wasted on less effective treatments (Krook and Mulder, 2022). The aetiology of GDM is multifactorial and complex though genetics and environmental factors have been implicated (Johns *et al*., 2018). These factors have been classified as modifiable and non-modifiable risk factors (Sparks *et al*., 2022). Risk factors based on genetics and demography are known as non-modifiable risk factors, while those associated with lifestyle, habits or environment are defined as modifiable risk factors.

Seeing that individuals who develop GDM are exposed to different risk factors, an understanding of their individualized risk factor will help determine the nature and type of intervention to be administered. Recent findings have revealed that among genetic variants related to nutrition, single nucleotide polymorphisms plays a key role in the FTO affecting body weight and composition. The carriers of the FTO rs9939609 AA genotype are likely to be more obese than the non-carriers (Frayling *et al*., 2007). This variant is considered to be one of the strongest risk factors for polygenic obesity. Nevertheless, the increased susceptibility to obesity by the AA risk allele can be modified either by physical activity or reduced energy intake (Hetherington and Cecil, 2009). As observed in this review, cost effective behavioural interventions such as exercise and diet have been shown to be effective in the prevention and management of GDM and other diseases irrespective of their genetic predisposition.

Self-monitoring and Capillary Blood Glucose

Self-monitoring of blood glucose is the collection of detailed information about blood glucose levels by patients at many points during the day on a day-to-day basis so as to guide adjustments in therapy and lifestyle activities, thereby ultimately improving glycaemic control and also preventing diabetes-related complications (Benjamin, 2002). And this is achieved with the use of conventional personal glucose meters used to measure finger prick blood samples several times a day (Czupryniak *et al*., 2014). Glucose monitoring in pregnancy is very important in GDM management so as to ensure appropriate glycaemic control and to reduce the associated risks (Byford *et al*., 2023). In pregnancy, the universally-accepted method of glucose monitoring is self-monitoring of blood glucose (SMBG) with intermittent capillary glucose finger-stick tests (Hewapathirana *et al*., 2013). These SMBG tests are recommended before and after meals and also before going to bed. In individuals with GDM, the current methods of glucose monitoring include measuring glycosylated haemoglobin (HbA1c), self-monitoring of capillary glucose and continuous glucose monitoring (Byford *et al*., 2023). The continuous glucose monitoring systems comprises a disposable subcutaneous glucose-sensing device that measures glucose levels in subcutaneous tissues every 10 seconds electrochemically, thereby providing an average interstitial glucose value every 5 minutes (Hewapathirana *et al*., 2013).

Discussion

We reviewed the prevalence, predisposing factors, pathophysiology, diagnosis and interventions associated with GDM risk and management based on published literatures. With the rising prevalence of obesity worldwide, there is also an increase in the incidence of metabolic diseases. Gestational diabetes mellitus is the leading metabolic disorder associated with pregnancy whose prevalence is on the rise particularly in low and middle income countries and is linked to short and long term adverse effects in both mother and offspring. Its diagnosis allows for the identification of a population that is highly susceptible to type II diabetes mellitus and other metabolic syndromes, thus providing an easy and ideal tool that matches routine anthropometric and biochemical factors, dietary assessments and genetic make-up in clinical practice (Franzago *et al*., 2018). There is currently no consensus with respect to the definition, screening, diagnosis and management of GDM (Agarwal, 2018) and this has created major problems in addressing the prevalence, complications, efficacy of treatment and follow-up for women with GDM (Ozgu-Erdinc, 2020).

In the management of women with GDM, dietary intervention plays a major role. This is because nutrition is a major modifiable factor that has the ability to interact with both the genome and epigenome by modulating gene expression in response to different dietary components and nutrient requirements in order to influence health (metabolic and transgenerational) diseases and fertility (Franzago *et al*., 2020). Though the norm in diabetes care has been to limit all types of carbohydrates in order to control blood glucose levels, most women are unable to adhere strictly to such diets due to anxiety. Hence, they end up substituting high fat foods for carbohydrates, thereby unintentionally enhancing lipolysis, elevated free fatty acids and worsening maternal insulin resistance (Hernandez *et al*., 2018). The increase in maternal insulin resistance may facilitate nutrient shunting across the placenta promoting excess fetal fat accumulation. Research-based evidence suggests that liberalizing higher quality, nutrient dense carbohydrates results in controlled fasting as well as postprandial blood glucose, lowers free fatty acids, improves insulin action, vascular benefits and may decrease excess fetal adiposity (Hernandez *et al*., 2018).

The approach to the management of GDM requires a multidisciplinary approach which includes dietary modification, exercise, nutrition monitoring, lifestyle changes, maternal weight gain management and self-monitoring of blood glucose levels. With dietary modification, adequate exercise and lifestyle changes, about 70-85% of GD cases can be managed (Johns *et al*., 2018).

Conclusions

The findings from this review highlighted the need for enhanced screening and management strategies to mitigate the adverse effects of GDM outcomes in Nigeria. The findings from this review have important implications for public health policy and clinical practice in Africa, particularly in Nigeria. We found that the incidence and prevalence of gestational diabetes is on the rise, hence there is the need to promote its prevention and early diagnosis via a unified method of diagnosis. Thus, further studies using anthropometric studies is required.

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References

Agarwal M. M. (2018). Consensus in Gestational Diabetes MELLITUS: Looking for the Holy Grail. *Journal of Clinical Medicine*, *7*(6), 123. https://doi.org/10.3390/jcm7060123

Ahmad, Rahnuma & Narwaria, Mahendra & Haque, Mainul. (2023). Gestational Diabetes Mellitus Prevalence and Progression to Type 2 Diabetes Mellitus: A Matter of Global Concern. *Advances in Human Biology*. 10.4103/aihb.aihb_65_23.

Aloke, C., Egwu, C. O., Aja, P. M., Obasi, N. A., Chukwu, J. Akumadu, B. O., Ogbu, P. N. and Achilonu, I. (2022). Current Advances in the Management of Diabetes Mellitus. *Biomedicines, 10,* 2436. https://doi.org/10.3390/biomedicines10102436

Asano, R. Y., Sales, M. M., Browne, R. A., Moraes, J. F., Coelho Júnior, H. J., Moraes, M. R., and Simoes, H. G. (2014). Acute effects of physical exercise in type 2 diabetes: A review. *World Journal of Diabetes*, *5*(5), 659–665. https://doi.org/10.4239/wjd.v5.i5.659

Azeez, T. A., Abo-Briggs, T., & Adeyanju, A. S. (2021). A systematic review and meta-analysis of the prevalence and determinants of gestational diabetes mellitus in Nigeria. *Indian Journal of Endocrinology and Metabolism*, *25*(3), 182–190. https://doi.org/10.4103/ijem.ijem_301_21

Bao, W., Bowers, K., Tobias, D. K., Hu, F. B., and Zhang, C. (2013). Prepregnancy dietary protein intake, major dietary protein sources, and the risk of gestational diabetes mellitus: a prospective cohort study. *Diabetes Care*, *36*(7), 2001–2008. https://doi.org/10.2337/dc12-2018

Barbour, L. A., McCurdy, C. E., Hernandez, T. L., Kirwan, J. P., Catalano, P. M., and Friedman, J. E. (2007). Cellular mechanisms for insulin resistance in normal pregnancy and gestational diabetes. *Diabetes Care, 30 Suppl 2*, S112–S119. https://doi.org/10.2337/dc07-s202

Barbour, L.A.; Scifres, C.; Valent, A.M.; Friedman, J.E.; Buchanan, T.A.; Coustan, D.A. (2018). cautionary response to SMFM statement: pharmacological treatment of gestational diabetes. *American Journal of Obstetrics and Gynecology*, 219(4), 367. e1-367.e7. https://doi.org/10.1016/j.ajog.2018.06.013

Bendek, M.J.; Canedo-Marroquín, G.; Realini, O.; Retamal, I.N.; Hernández, M.; Hoare, A.; Busso, D.; Monteiro, L.J.; Illanes, S.E.; Chaparro, A. (2021). Periodontitis and Gestational Diabetes Mellitus: A Potential Inflammatory Vicious Cycle. *International Journal of Molecular Sciences*, 22(21), 11831. https://doi.org/10.3390/ijms222111831.

Benhalima K, Van Crombrugge P, Moyson C, et al. (2018). The sensitivity and specificity of the glucose challenge test in a universal two-step screening strategy for gestational diabetes mellitus using the 2013 World Health Organization criteria. *Diabetes Care*, 41(7):e111–e112. doi: 10.2337/dc18-0556

Benjamin, E.M. (2002). *Self-monitoring blood glucose: The basis of clinical diabetes*, 20, 45-47.

Bennett, C.J.; Walker, R.E.; Blumfield, M.L.; Gwini, S.M.; Ma, J.; Wang, F.; Wan, Y.; Dickinson, H.; Truby, H. (2018). Interventions designed to reduce excessive gestational weight gain can reduce the incidence of gestational diabetes mellitus: A systematic review and meta-analysis of randomised controlled trials. *Diabetes Research and Clinical Practice*, 141, 69-79. https://doi.org/10.1016/j.diabres.2018.04.010.

Bergel, R.; Hadar, E.; Toledano, Y.; Hod, M. (2016). Pharmacological Management of Gestational Diabetes Mellitus. *Current Diabetes Reports*, 16(11), 118. https://doi.org/10.1007/s11892-016-0802-y.

Bishop, K.C., Harris, B.S., Boyd, B.K., Reiff, E.S., Brown, L.; Kuller, J.A. (2019). Pharmacologic Treatment of Diabetes in Pregnancy. *Obstetrics and Gynecology Survey*, 74(5), 289-297. https://doi.org/10.1097/OGX.0000000000000671.

Bowers, K., Tobias, D. K., Yeung, E., Hu, F. B., and Zhang, C. (2012). A prospective study of prepregnancy dietary fat intake and risk of gestational diabetes. *The American*

Journal of Clinical Nutrition, 95(2), 446–453. https://doi.org/10.3945/ajcn.111.026294

Brankston, G. N., Mitchell, B. F., Ryan, E. A., and Okun, N. B. (2004). Resistance exercise decreases the need for insulin in overweight women with gestational diabetes mellitus. *American Journal of Obstetrics and Gynecology, 190*(1), 188–193. https://doi.org/10.1016/s0002-9378(03)00951-7

Brown, J., Alwan, N. A., West, J., Brown, S., McKinlay, C. J., Farrar, D., and Crowther, C. A. (2017). Lifestyle interventions for the treatment of women with gestational diabetes. *The Cochrane Database of Systematic Reviews, 5*(5), CD011970. https://doi.org/10.1002/14651858.CD011970.pub2

Buchanan, T. A., and Xiang, A. H. (2005). Gestational diabetes mellitus. *The Journal of Clinical Investigation, 115*(3), 485–491. https://doi.org/10.1172/JCI24531

Bung, P., Artal, R., Khodiguian, N., and Kjos, S. (1991). Exercise in gestational diabetes. An optional therapeutic approach?. *Diabetes, 40* (Suppl 2), 182–185. https://doi.org/10.2337/diab.40.2.s182

Byford, A.R.; Forbes, K.; Scott, E.M. (2023). Glucose treatment target a review of evidence by and guidelines. *Current Diabetes Reviews,* 19. e220422203917.

Chiu, K. C., Go, R. C., Aoki, M., Riggs, A. C., Tanizawa, Y., Acton, R. T., Bell, D. S., Goldenberg, R. L., Roseman, J. M., and Permutt, M. A. (1994). Glucokinase gene in gestational diabetes mellitus: population association study and molecular scanning. *Diabetologia, 37*(1), 104–110. https://doi.org/10.1007/BF00428785

Clapp J. F. (2006). Effects of Diet and Exercise on Insulin Resistance during Pregnancy. *Metabolic Syndrome and Related Disorders, 4*(2), 84–90. https://doi.org/10.1089/met.2006.4.84

Clapp, J. F., and Capeless, E. L. (1991). The changing glycemic response to exercise during pregnancy. *American Journal of Obstetrics and Gynecology, 165*, 1678–1683. https://doi.org/10.1016/0002-9378(91)90014-i

Clapp, J. F., Rockey, R., Treadway, J., Carpenter, M., Artal, R. and Warnes, C. (1992). Exercise in Pregnancy. *Medical Science Sports and Exercise, 24*: S294-S300

Czupryniak, L.; Barkai, L.; Bolgarska, S.; Bronisz, A.; Broz, J.; Cypryk, K. (2014). Self-monitoring of blood glucose in diabetes: from evidence to clinical reality in Central and Eastern Europe--recommendations from the international Central-Eastern European expert group. *Diabetes Technology and Therapeutics* 16(7), 460-475. https://doi.org/10.1089/dia.2013.0302.

Damm, P., Kühl, C., Buschard, K., Jakobsen, B. K., Svejgaard, A., Sodoyez-Goffaux, F., Shattock, M., Bottazzo, G. F., & Mølsted-Pedersen, L. (1994). Prevalence and predictive value of islet cell antibodies and insulin autoantibodies in women with gestational diabetes. *Diabetic Medicine: A Journal of the British Diabetic Association, 11*(6), 558–563. https://doi.org/10.1111/j.1464-5491.1994.tb02035.x

Davenport, M. H., Ruchat, S. M., Poitras, V. J., Jaramillo Garcia, A., Gray, C. E., Barrowman, N., *et al.* (2018). Prenatal exercise for the prevention of gestational diabetes mellitus and hypertensive disorders of pregnancy: a systematic review and meta-analysis. *British Journal of Sports Medicine, 52*(21), 1367–1375. https://doi.org/10.1136/bjsports-2018-099355

de Veciana, M., Major, C. A., Morgan, M. A., Asrat, T., Toohey, J. S., Lien, J. M., and Evans, A. T. (1995). Postprandial versus preprandial blood glucose monitoring in women with gestational diabetes mellitus requiring insulin therapy. *The New England Journal of Medicine, 333*(19), 1237–1241. https://doi.org/10.1056/NEJM199511093331901

Dempsey, A.; Mumby, C.; Bernatavicius, G.; Roberts, S.A.; Myers, J.E. (2022). Metformin treatment vs a diabetes model of prenatal care in women with mild fasting hyperglycemia diagnosed in pregnancy: a feasibility study. *Journal of Maternal, Fetal and Neonatal Medicine,* 35(23), 4469-4477. https://doi.org/10.1080/14767058.2020.1852209.

Devlieger, R., Casteels, K. and Van Assche, F. A. (2008). Reduced adaptation of the pancreatic B cells during pregnancy is the major causal factor for gestational diabetes: Current knowledge and metabolic effects on the offspring. *Acta Obstetricia et Gynaecologra Scandinavica, 87*(12): 1266-1270. https://doi.org/10.1080/00016340802443863

Dugan, J. A., and Ma Crawford, J. (2019). Managing gestational diabetes. *JAAPA: Official journal of the American Academy of Physician Assistants, 32*(9), 21–25. https://doi.org/10.1097/01.JAA.0000578760.60265.e0

Ehrlich, S. F., Ferrara, A., Hedderson, M. M., Feng, J., and Neugebauer, R. (2021). Exercise During the First Trimester of Pregnancy and the Risks of Abnormal Screening and Gestational Diabetes Mellitus. *Diabetes Care, 44*(2), 425–432. https://doi.org/10.2337/dc20-1475

Embaby, H., Elsayed, E., and Fawzy, M. (2016). Insulin Sensitivity and Plasma Glucose Response to Aerobic Exercise in Pregnant Women at Risk for Gestational Diabetes Mellitus. *Ethiopian Journal of Health Sciences, 26*(5), 409–414. https://doi.org/10.4314/ejhs.v26i5.2

Fell, D. B., Joseph, K. S., Armson, B. A., and Dodds, L. (2009). The impact of pregnancy on physical activity level. *Maternal and Child Health Journal, 13*(5), 597–603. https://doi.org/10.1007/s10995-008-0404-7

Franzago, M.; Fraticelli, F.; Di Nicola, M.; Bianco, F.; Marchetti, D.; Celentano, C.; Liberati, M.; De Caterina, R.; Stuppia, L.; Vitacolonna, E. (2018). Early Subclinical Atherosclerosis in Gestational Diabetes: The Predictive Role of Routine Biomarkers and Nutrigenetic Variants. *Journal of Diabetes Research,* 9242579. https://doi.org/10.1155/2018/9242579.

Franzago, M.; Santurbano, D.; Vitacolonna, E.; Stuppia, L. (2020). Genes and Diet in the Prevention of Chronic Diseases in Future Generations. *International Journal of Molecular Sciences,* 21(7), 2633. https://doi.org/10.3390/ijms21072633.

Frayling, T.M.; Timpson, N.J.; Weedon, M.N.; Zeggini, E., Freathy, R.M.; Lindgren, C.M.; Perry, J.R.; Elliott, K.S.; Lango, H.; Rayner, N.W. (2007). A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science*, 316(5826), 889-894. https://doi.org/10.1126/science.1141634.

Giannakou K., Evangelou E., Yiallouros P., Christophi C.A., Middleton N., Papatheodorou E., Papatheodorou S.I. (2019). Risk factors for gestational diabetes: An umbrella review of meta-analyses of observational studies. *PLoS ONE,* 14:e0215372.

Gyasi-Antari, P., Walter, L., Moody, C., Okyere, S., Salt, K., Ottie-Baokye, D., Asah-Opuke, K., Asibey, S., Sarfo-Kantanta, O., Baffour-Agyei, E., Shaw, I. and Adams, G. (2020).

Global Prevalence of Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis. *The American Journal of Medicine 6*(3): 1-10.

Heckman-Stoddard, B.M.; DeCensi, A.; Sahasrabuddhe, V.V.; Ford, L.G. (2017). Repurposing metformin for the prevention of cancer and cancer recurrence. *Diabetologia*, 60(9), 1639-1647. https://doi.org/10.1007/s00125-017-4372-6.

Hernandez, T. L., and Brand-Miller, J. C. (2018). Nutrition Therapy in Gestational Diabetes Mellitus: Time to Move Forward. *Diabetes Care, 41*(7), 1343–1345. https://doi.org/10.2337/dci18-0014

Hernandez, T. L., Mande, A., and Barbour, L. A. (2018). Nutrition therapy within and beyond gestational diabetes. *Diabetes Research and Clinical Practice, 145,* 39–50. https://doi.org/10.1016/j.diabres.2018.04.004

Hetherington, M.M.; Cecil, J.E. (2010). Gene-environment interactions in obesity. *Forum Nutrition*, 63, 195-203. https://doi.org/10.1159/000264407.

Hewapathirana, N.M.; O'Sullivan, E.; Murphy, H.R. (2013). Role of continuous glucose monitoring in the management of diabetic pregnancy. *Current Diabetes Reports*, 13(1), 34-42. https://doi.org/10.1007/s11892-012-0337-9

IADPSG Consensus Panel (2010). International association of diabetes and pregnancy study groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care,* 33(3):676-82. [DOI: 10.2337/dc09-1848]

International Diabetes Federation. (2020). Gestational Diabetes Mellitus.

Jensen, L., Bangsbo, J., and Hellsten, Y. (2004). Effect of high intensity training on capillarization and presence of angiogenic factors in human skeletal muscle. *The Journal of Physiology, 557*(Pt 2), 571–582. https://doi.org/10.1113/jphysiol.2003.057711

Johns, E. C., Denison, F. C., Norman, J. E., and Reynolds, R. M. (2018). Gestational Diabetes Mellitus: Mechanisms, Treatment, and Complications. *Trends in Endocrinology and Metabolism: TEM, 29*(11), 743–754. https://doi.org/10.1016/j.tem.2018.09.004

Kampmann, U., Madsen, L. R., Skajaa, G. O., Iversen, D. S., Moeller, N., and Ovesen, P. (2015). Gestational diabetes: A clinical update. *World Journal of Diabetes, 6*(8), 1065–1072. https://doi.org/10.4239/wjd.v6.i8.1065

Krook, A., and Mulder, H. (2022). Pinpointing precision medicine for diabetes mellitus. *Diabetologia, 65*(11), 1755–1757. https://doi.org/10.1007/s00125-022-05777-4

Lain, K. Y., and Catalano, P. M. (2007). Metabolic changes in pregnancy. *Clinical Obstetrics and Gynecology, 50*(4), 938–948. https://doi.org/10.1097/GRF.0b013e31815a5494

Lendoye, E., Ngoungou, E.B., Komba, O.M., Benjamin Ollomo[6], Mezui-Mbeng, M.N., Bekale, S., Yacka-Mouele, L., Obounou, B.W.O., Ntyonga-Pono, M., Edouard Ngou-Milama, E. (2022). Prevalence and factors associated to gestational diabetes mellitus among pregnant women in Libreville: a cross-sectional study. *Pan African Medical Journal. 41:129. [doi: 10.11604/pamj.2022.41.129.28710]*

Lende, M. and Rijhsinghani, A. (2020) Gestational Diabetes: Overview with Emphasis on Medical Management. *International Journal of Environmental Research and Public Health*, 17, 9573. https://doi.org/10.3390/ijerph17249573

Lendoye, E., Ngoungou, E. B., Komba, O. M., Ollomo, B., N'negue-Mezui, M. A., Bekale, S., Yacka-Mouele, L., Obounou, B. W. O., Ntyonga-Pono, M. P., and Ngou-Milama, E. (2022). Prevalence and factors associated to gestational diabetes mellitus among pregnant women in Libreville: a cross-sectional study. *The Pan African Medical Journal, 41*, 129. https://doi.org/10.11604/pamj.2022.41.129.28710

Li, H., Shen, L., Song, L., Liu, B., Zheng, X., Xu, S., and Wang, Y. (2017). Early age at menarche and gestational diabetes mellitus risk: Results from the Healthy Baby Cohort study. *Diabetes & Metabolism, 43*(3), 248–252. https://doi.org/10.1016/j.diabet.2017.01.002

Louie, J. C., Brand-Miller, J. C., Markovic, T. P., Ross, G. P., and Moses, R. G. (2010). Glycemic index and pregnancy: a systematic literature review. *Journal of Nutrition and Metabolism, 2010, 282464*. https://doi.org/10.1155/2010/282464

Markovic TP, Muirhead R, Overs S, et al. (2016). Randomized controlled trial investigating the effects of a low–glycemic index diet on pregnancy outcomes in women at high risk of gestational diabetes mellitus: the GI Baby 3 Study. *Diabetes Care,* 39:31–38

Maslova, E., Hansen, S., Grunnet, L. G., Strøm, M., Bjerregaard, A. A., Hjort, L., Kampmann, F. B., Madsen, C. M., Baun Thuesen, A. C., Bech, B. H., Halldorsson, T. I., Vaag, A. A., and Olsen, S. F. (2017). Maternal protein intake in pregnancy and offspring metabolic health at age 9-16 y: results from a Danish cohort of gestational diabetes mellitus pregnancies and controls. *The American Journal of Clinical Nutrition, 106*(2), 623–636. https://doi.org/10.3945/ajcn.115.128637

Metzger B.E., Gabbe, S.G., Persson, B., *et al* (2010). International Association of Diabetes and Pregnancy Study Groups consensus panel. International Association of Diabetes and Pregnancy Study Groups recommendations on the diagnosis and classification of hyperglycemia in pregnancy. *Diabetes Care*, 33:676–82.

Mdoe, M. B., Kibusi, S. M., Munyogwa, M. J., and Ernest, A. I. (2021). Prevalence and predictors of gestational diabetes mellitus among pregnant women attending antenatal clinic in Dodoma region, Tanzania: an analytical cross-sectional study. *BMJ Nutrition, Prevention and Health, 4*(1), 69–79. https://doi.org/10.1136/bmjnph-2020-000149

Moreno-Castilla, C., Mauricio, D., and Hernandez, M. (2016). Role of Medical Nutrition Therapy in the Management of Gestational Diabetes Mellitus. *Current Diabetes Reports, 16*(4), 22. https://doi.org/10.1007/s11892-016-0717-7

Mousa, A., Naqash, A., and Lim, S. (2019). Macronutrient and Micronutrient Intake during Pregnancy: An Overview of Recent Evidence. *Nutrients, 11*(2), 443. https://doi.org/10.3390/nu11020443

Nasiri-Amiri, F., Sepidarkish, M., Shirvani, M. A., Habibipour, P., and Tabari, N. S. M. (2019). The effect of exercise on the prevention of gestational diabetes in obese and overweight pregnant women: a systematic review and meta-analysis. *Diabetology & Metabolic Syndrome, 11*, 72. https://doi.org/10.1186/s13098-019-0470-6

National Institute for Health and Care Excellence. (2015). Diabetes in pregnancy management from perception to postnatal period. NICE guideline (NG3).. www.nice.org.uk/guidance/ng3. 12th March, 2023, 6:14am.

Nayak, Prasanta & Mitra, Subarna & Sahoo, Jayaprakash & Daniel, Mary & Mathew, Agnes & Padma, Alaganandam. (2013). Feto-maternal outcomes in women with and without gestational diabetes mellitus according to the International Association of Diabetes and Pregnancy Study Groups (IADPSG) diagnostic criteria. *Diabetes & Metabolic Syndrome.* 7. 206-9. 10.1016/j.dsx.2013.10.017.

Ozgu-Erdinc, A.S. (2020). Two criteria of oral glucose tolerance test to diagnose gestational diabetes mellitus. Revista da *Associação Médica Brasileira*, 66:234-235. https://doi.org/10.1590/1806-9282.66.2.234

Pang, W. W., Colega, M., Cai, S., Chan, Y. H., Padmapriya, N., Chen, L. W., Soh, S. E., Han, W. M., Tan, K. H., Lee, Y. S., Saw, S. M., Gluckman, P. D., Godfrey, K. M., Chong, Y. S., van Dam, R. M., and Chong, M. F. (2017). Higher Maternal Dietary Protein Intake Is Associated with a Higher Risk of Gestational Diabetes Mellitus in a Multiethnic Asian Cohort. *The Journal of Nutrition*, *147*(4), 653–660. https://doi.org/10.3945/jn.116.243881

Plows, J. F., Stanley, J. L., Baker, P. N., Reynolds, C. M., and Vickers, M. H. (2018). The Pathophysiology of Gestational Diabetes Mellitus. *International Journal of Molecular Sciences*, *19*(11), 3342. https://doi.org/10.3390/ijms19113342

Position Statement American Diabetes Association (2010). Diagnosis and classification of diabetes mellitus. *Diabetes Care*, 33(Suppl. 1):S62–9.

Rammah, A., Whitworth, K. W., and Symanski, E. (2020). Particle air pollution and gestational diabetes mellitus in Houston, Texas. *Environmental Research, 190,* 109988. https://doi.org/10.1016/j.envres.2020.109988

Richter, E. A., Derave, W., and Wojtaszewski, J. F. (2001). Glucose, exercise and insulin: emerging concepts. *The Journal of Physiology, 535* (pt2): 313-322 https://doi.org/10.1111/j.1469-7793.2001.t01-2-00313.x

Rogozińska, E.; Chamillard, M.; Hitman, G. A.; Khan, K.S. (2015). Thangaratinam, S. Nutritional manipulation for the primary prevention of gestational diabetes mellitus: a meta-analysis of randomised studies. *PLoS One*, 10(2), e0115526. https://doi.org/10.1371/journal.pone.0115526.

Saeedi M., Cao Y., Fadl H., Gustafson H., Simmons D. (2021). Increasing prevalence of gestational diabetes mellitus when implementing the IADPSG criteria: A systematic review and meta-analysis. *Diabetes Research and Clinical Practice,* 172:108642. doi: 10.1016/j.diabres.2020.108642.

Santangelo, C., Zicari, A., Mandosi, E., Scazzocchio, B., Mari, E., Morano, S., and Masella, R. (2016). Could gestational diabetes mellitus be managed through dietary bioactive compounds? Current knowledge and future perspectives. *The British Journal of Nutrition, 115*(7), 1129–1144. https://doi.org/10.1017/S0007114516000222

Schenk, S., Cook, J. N., Kaufman, A. E., and Horowitz, J. F. (2005). Postexercise insulin sensitivity is not impaired after an overnight lipid infusion. American journal of physiology. *Endocrinology and Metabolism, 288*(3), E519–E525. https://doi.org/10.1152/ajpendo.00401.2004

Society of Maternal-Fetal Medicine (SMFM) Publications Committee. (2018). SMFM Statement: Pharmacological treatment of gestational diabetes. *American Journal of Obstetrics and Gynecology*, 218(5), B2-B4. https://doi.org/10.1016/j.ajog.2018.01.041.

Sorensen, A. E., van Poppel, M. N. M., Desoye, G., Simmons, D., Damm, P., Jensen, D. M., Dalgaard, L. T., and The Dali Core Investigator Group (2022). The Temporal Profile of Circulating miRNAs during Gestation in Overweight and Obese Women with or without Gestational Diabetes Mellitus. *Biomedicines, 10*(2), 482. https://doi.org/10.3390/biomedicines10020482

Sparks, J. R., Ghildayal, N., Hivert, M. F., and Redman, L. M. (2022). Lifestyle interventions in pregnancy targeting GDM prevention: looking ahead to precision medicine. *Diabetologia*, *65*(11), 1814–1824. https://doi.org/10.1007/s00125-022-05658-w

Suman Rao PN, Shashidhar A, Ashok C. (2013). In utero fuel homeostasis: Lessons for a clinician. *Indian Journal of Endocrinology and Metabolism,* 17(1):60-8.

Wang, C., Wei, Y., Zhang, X., Zhang, Y., Xu, Q., Su, S., Zhang, L., Liu, C., Feng, Y., Shou, C., Guelfi, K. J., Newnham, J. P., and Yang, H. (2016). 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, 39*(10), e163–e164. https://doi.org/10.2337/dc16-1320

Wang, H., Li, N., Chirese, T., Weifalli, M., Sun, H., Yuen, Li, Hoegfeldt, C. A., Powe, C. E., Immanuel, J., Karuranga, S., Divakar, H., Levitt, N., Li, C., Simmons, D. and Yang, C. (2020). IDF Diabetes Atlas: Estimation of Global and Regional Diabetes Mellitus Prevalance for 2021 by International Association of Diabetes in Pregnancy Study Groups Criteria. *Diabetes Research and Clinical Practice, 183*:109050. Doi: https://doi.org/10.1016/j.diabres2021.109050

Yamamoto, J. M., Kellett, J. E., Balsells, M., García-Patterson, A., Hadar, E., Solà, I., *et al.* (2018). Gestational Diabetes Mellitus and Diet: A Systematic Review and Meta-analysis of Randomized Controlled Trials Examining the Impact of Modified Dietary Interventions on Maternal Glucose Control and Neonatal Birth Weight. *Diabetes Care, 41*(7), 1346–1361. https://doi.org/10.2337/dc18-0102

Zhang, C., Schulze, M. B., Solomon, C. G., and Hu, F. B. (2006). A prospective study of dietary patterns, meat intake and the risk of gestational diabetes mellitus. *Diabetologia, 49*(11), 2604–2613. https://doi.org/10.1007/s00125-006-0422-1

Zheng, J., Wang, H., and Ren, M. (2017). Influence of exercise intervention on gestational diabetes mellitus: a systematic review and meta-analysis. *Journal of Endocrinological Investigation*, *40*(10), 1027–1033. https://doi.org/10.1007/s40618-017-0673-3

World Health Organisation (1999). Definition, diagnosis, and classification of diabetes mellitus and its implications: report of a WHO consultation. Geneva: WHO Document Production Services.

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