





Review

Gestational Diabetes Mellitus—Recent Literature Review

Robert Modzelewski ¹, Magdalena Maria Stefanowicz-Rutkowska ^{2,*} , Wojciech Matuszewski ¹ 
and Elżbieta Maria Bandurska-Stankiewicz ¹

¹ Endocrinology, Diabetology and Internal Medicine Clinic, Department of Internal Medicine, University of Warmia and Mazury in Olsztyn, 10-719 Olsztyn, Poland

² Department of Endocrinology, Diabetes and Isotope Therapy, Wrocław Medical University, 50-367 Wrocław, Poland

* Correspondence: m.m.stefanowicz@gmail.com

Abstract: Gestational diabetes mellitus (GDM), which is defined as a state of hyperglycemia that is first recognized during pregnancy, is currently the most common medical complication in pregnancy. GDM affects approximately 15% of pregnancies worldwide, accounting for approximately 18 million births annually. Mothers with GDM are at risk of developing gestational hypertension, pre-eclampsia and termination of pregnancy via Caesarean section. In addition, GDM increases the risk of complications, including cardiovascular disease, obesity and impaired carbohydrate metabolism, leading to the development of type 2 diabetes (T2DM) in both the mother and infant. The increase in the incidence of GDM also leads to a significant economic burden and deserves greater attention and awareness. A deeper understanding of the risk factors and pathogenesis becomes a necessity, with particular emphasis on the influence of SARS-CoV-2 and diagnostics, as well as an effective treatment, which may reduce perinatal and metabolic complications. The primary treatments for GDM are diet and increased exercise. Insulin, glibenclamide and metformin can be used to intensify the treatment. This paper provides an overview of the latest reports on the epidemiology, pathogenesis, diagnosis and treatment of GDM based on the literature.

Keywords: gestational diabetes mellitus; insulin resistance; behavioral treatment



Citation: Modzelewski, R.; Stefanowicz-Rutkowska, M.M.; Matuszewski, W.; Bandurska-Stankiewicz, E.M. Gestational Diabetes Mellitus—Recent Literature Review. *J. Clin. Med.* **2022**, *11*, 5736. <https://doi.org/10.3390/jcm11195736>

Academic Editors: Katrien Benhalima and Yoav Yinon

Received: 5 August 2022

Accepted: 25 September 2022

Published: 28 September 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Gestational diabetes mellitus (GDM) is a state of hyperglycemia (fasting plasma glucose ≥ 5.1 mmol/L, 1 h ≥ 10 mmol/L, 2 h ≥ 8.5 mmol/L during a 75 g oral glucose tolerance test according to IADPSG/WHO criteria) that is first diagnosed during pregnancy [1]. GDM is one of the most common medical complications of pregnancy, and its inadequate treatment can lead to serious adverse health effects for the mother and child [1,2]. According to the latest estimates of the International Diabetes Federation (IDF), GDM affects approximately 14.0% (95% confidence interval: 13.97–14.04%) of pregnancies worldwide, representing approximately 20 million births annually [3]. Mothers with GDM are at risk of developing gestational hypertension, pre-eclampsia and termination of pregnancy via Caesarean section [4]. In addition, GDM increases the risk of complications, including cardiovascular disease, obesity, and impaired carbohydrate metabolism, leading to the development of type 2 diabetes (T2DM) in both mother and infant [5–7]. The increase in the incidence of GDM also leads to a significant economic burden and deserves greater attention and awareness [8].

Despite numerous studies, the pathogenesis of GDM remains unclear, and the results obtained so far indicate a complex mechanism of interaction of many genetic, metabolic and environmental factors [9]. The basic methods of treating GDM include an appropriate diet and increased physical activity, and when these are inadequate, pharmacotherapy, usually insulin therapy, is used. In developing countries, such as Brazil, oral hypoglycemic agents are also used, mainly metformin and glibenclamide (glyburide) [10]. The prevention

and appropriate treatment of GDM are needed to reduce the morbidity, complications and economic effects of GDM that affect society, households and individuals. Though it is well established that the diagnosis of even mild GDM and treatment with lifestyle recommendations and insulin improves pregnancy outcomes, it is controversial as to which type and regimen of insulin are optimal, and whether oral agents can be used safely and effectively to control glucose levels.

2. Aim of the Study

A review of current literature reports on epidemiology, pathogenesis, diagnosis and treatment of GDM.

3. Material and Methods

The study presents an analysis of data that are currently available in the literature that concern the epidemiology, pathogenesis, diagnosis and treatment of GDM. The study was based on reviews, original articles and meta-analyses published in English in the last 10 years.

A literature search was conducted from 1 January 2021 to 31 March 2022 using Web of Science, PubMed, EMBASE, Cochrane, Open Grey and Grey Literature Report. MeSH terms, including “gestational diabetes”, “pregnancy induced diabetes”, “hyperglycemia”, “glucose intolerance”, “insulin resistance”, “prevalence”, “incidence”, “GDM treatment” and “behavioral treatment”, were used alone or in combination.

4. Results and Discussion

4.1. Epidemiology

The growing problem of overweight and obesity around the world significantly contributes to the steady increase in the incidence of diabetes, including GDM in the population of women of reproductive age [11]. According to the 2019 report by the International Diabetes Federation (IDF), more than approximately 20.4 million women (14.0% of pregnancies) presented with disorders of carbohydrate metabolism, of which approximately 80% was GDM, i.e., about one in six births was affected by gestational diabetes [3]. Table 1 presents the analysis of the geographical distribution of GDM [3,12].

Table 1. The geographical distribution of GDM [3,12].

Occurrence of Gestational Diabetes Mellitus	
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%)

4.2. GDM Risk Factors

The incidence of hyperglycemia in pregnancy increases with age. According to Mosses et al., GDM was diagnosed in 6.7% of pregnancies in general, but in 8.5% of women over 30 years of age [13]. Lao et al. showed the highest risk of developing GDM at the ages of 35–39 compared with younger pregnant women (OR 95% CI: 10.85 (7.72–15.25) vs. 2.59 (1.84–3.67)) [14]. These observations were confirmed by IDF data showing the highest percentage of pregnancies with GDM reaching 37% at the ages of 45–49, which was also conditioned by a lower number of pregnancies with an accompanying general higher percentage of diabetes in this population [3]. The delivery of a macrosomic child is another important factor that may increase the risk of both GDM and DM2 by up to

20% [15]. Even after taking into account the age of the woman, pluriparity remains in a linear relationship to the incidence of GDM [16]. GDM in a previous pregnancy increases the risk of reoccurrence by more than six times [17]. In women with a BMI of at least 30 kg/m², the GDM frequency is 12.3%, and in women with first-line relatives that have a history of GDM, it is 11.6%. The combination of these two factors increases the risk of GDM up to 61% of cases [4,18,19]. More than twice the percentage of pregnancies with GDM was observed in women that were previously treated for polycystic ovary syndrome (PCOS) [20]. Recent studies indicated that the prevalence of GDM is related to the season and that GDM prevalence increases during the summer compared with winter [21–23]. Moreover, a 50% increase in the incidence of GDM in pregnancies resulting from in vitro fertilization was described [24].

4.3. Diagnosing GDM

The decades-long polemic about the diagnosis of GDM has covered two issues: whether to include all pregnant women or only those with risk factors, and whether to use one- or two-stage diagnostic procedures. A GDM diagnosis is only possible if a previous diagnosis of diabetes (i.e., type 1 or type 2 diabetes) had been excluded early in the pregnancy. Screening of only risk groups may result in GDM not being diagnosed in as many as 35–47% of pregnant women, which is certain to affect obstetric results [25]. The results of the Hyperglycemia Adverse Pregnancy Outcome (HAPO) study of 23,316 women gave a clear outcome that elevated glycemia (but below the threshold for overt diabetes mellitus) showed a linear relationship with the occurrence of maternal and neonatal complications expressed as large for gestational age (LGA) endpoints, the frequency of Caesarean sections, neonatal hypoglycemia and the concentration of the umbilical C-peptide [26]. The current criteria for the diagnosis of GDM introduced by The International Association of Diabetes and Pregnancy Study Groups (IADPSG), which were based on the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) results, found a threefold increase in GDM diagnoses, which suggests an earlier underestimation. The HAPO group sought to identify new screening values that would better identify pregnancies at risk for perinatal complications. The HAPO study demonstrated a positive linear relationship between screening glucose values and adverse perinatal outcomes. Moreover, the study authors found that perinatal risks began to increase in women with glucose values that were previously considered “normal” [27,28]. Therefore, nowadays, the basis of GDM diagnostics is the administration of 75 g of glucose between 24 and 28 weeks of pregnancy in all pregnant women without previously diagnosed diabetes. The treatment of even mild forms of glucose intolerance in GDM offers an added benefit, as demonstrated by the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) and Maternal-Fetal Medicine Units Network (MFMU). It was shown that the frequency of obstetric complications is reduced depending on hyperglycemia and pregnancy weight gain. In the ACHOIS study, the composite endpoint (neonatal death, perinatal injury, hyperbilirubinemia, neonatal hypoglycemia and hyperinsulinemia) was significantly reduced with antihyperglycemic intervention, and there was also a lower weight gain (by 1.7 kg on average) and a lower incidence of LGA. In the MFMU study, no changes were noted in the composite endpoint, but the incidence of LGA and shoulder dystocia decreased significantly [2,29,30]. The results of these studies showed that most scientific societies implement the recommendations of the IADPSG from 2010 and WHO from 2013 into their daily practice. The introduction of the IADPSG criteria for the screening of GDM increased the prevalence by threefold, albeit with no substantial improvements in GDM-related events for women without risk factors except for reduced risks for LGA, neonatal hypoglycemia and preterm birth [31]. This led to further research on a group of patients with GDM. In a large randomized trial (among 23,792 pregnant women), Hillier et al. showed that one-step screening, as compared with two-step screening, doubled the incidence of the diagnosis of GDM, but did not affect the risks of LGA, adverse perinatal outcomes, primary Caesarean section, or gestational hypertension or pre-eclampsia [32]. The GEMS Trial assessed two diagnostic thresholds

for GDM—namely, the currently used, higher diagnostic criteria and the IADPSG, lower diagnostic criteria—for their effects on fetal growth, perinatal morbidity, maternal physical and psychological morbidity, and health service utilization. The recently published results of the GEMS Trial showed that lower glycemic criteria (fasting plasma glucose level of at least 92 mg/dL, a 1 h level of at least 180 mg/dL or a 2 h level of at least 153 mg/dL) for the diagnosis of GDM did not result in a lower risk of a large-for-gestational-age infant than the use of higher glycemic criteria (fasting plasma glucose level of at least 99 mg/dL or a 2 h level of at least 162 mg/dL) [33]. This latest study is another important point in the discussion of the best diagnosis method for GDM. Table 2 presents the criteria for the diagnosis of GDM according to different scientific societies.

Table 2. The criteria for the diagnosis of GDM according to different scientific societies.

	Fasting	1 h	2 h	3 h	Number of Values for Diagnosis
Criteria	mg/dL (mmol/L)	mg/dL (mmol/L)	mg/dL (mmol/L)	mg/dL (mmol/L)	
ADA/ACOG ³ 2003, 2018	95 (5.3)	180 ¹ (10.0 ¹)	155 (8.6)	140 (7.8)	2
ADIPS 2014	92 (5.1)	180 (10.0)	153 (8.5)	- (-)	1
DCCPG 2018 ⁴	95 (5.3)	- (10.6)	- (9.0)	- (-)	1
DIPSI 2014 ⁵	- (-)	- (-)	140 (7.8)	- (-)	1
EASD 1991	110 ¹ /126 (6.1 ¹ /7.0)	- (-)	162 ¹ /180 (9.0 ¹ /10.0)	- (-)	1
FIGO 2015	92 (5.1)	180 (10.0)	153 (8.5)	- (-)	1
WHO 1998	110 ² /126 (6.1 ² /7.0)	- (-)	120 ² /140 (6.7 ² /7.8)	- (-)	1
WHO 2013	92 (5.1)	180 ¹ (10.0 ¹)	153 (8.5)	- (-)	1
IADPSG/WHO	92 (5.1)	180 ¹ (10.0 ¹)	153 (8.5)	- (-)	1
NICE	- (5.6)	- (-)	- (7.8)	- (-)	

Notes: ADA—American Diabetes Association, ACOG—American College of Obstetricians and Gynecologists, DCCPG—Diabetes Canada Clinical Practice Guidelines, DIPSI—Diabetes in Pregnancy Society Group India, EASD—European Association for the Study of Diabetes, FIGO—International Federation of Gynecology and Obstetrics, ADIPS—Australasian Diabetes in Pregnancy Society, WHO—World Health Organization, IADPSG—International Association of the Diabetes and Pregnancy Study Groups, NICE—National Institute for Health and Care Excellence. ¹ There are no established criteria for the diagnosis of diabetes mellitus in pregnancy based on a 1 h post-load value. ² Refers to the whole blood glucose level. ³ Recommends either the IADPSG one-step or two-step approach; initial screening by measuring plasma or serum glucose concentration 1 h after a 50 g oral glucose load (GCT). Those exceeding the cut-off perform either a 100 g OGTT or 75 g OGTT, requiring two or more venous plasma concentrations to be met or exceed the threshold. ⁴ Listed in the preferred approach, the alternate approach is the IADPSG, which uses a non-fasting 75 g OGTT. ⁵ Uses a non-fasting 75 g OGTT.

Many potential markers of GDM occurrence are being described more and more frequently. The greatest hopes are connected with afamine, adiponectin and 1,5-anhydroglucitol [34,35]. Due to the fact that in many countries, prenatal care is provided by gynecologists who can consult other specialists, it seems important to develop predictive models that allow for the identification of women at the highest risk for gestational diabetes in early pregnancy. The Benhalim-2 2020 model, which takes into account interview and biochemical data (propensity score model: history of GDM, FPG, height, triglycerides, age, ethnic origin, first trimester weight, family history of diabetes, HbA1c), showed the highest sensitivity [36].

4.4. Pathogenesis of Carbohydrate Metabolism Disorders in Pregnancy

Several factors may be responsible for the occurrence of GDM, the most important of which are insulin resistance and beta cell dysfunction, as well as genetic, environmental and dietary factors.

4.4.1. Insulin Resistance

In the pathogenesis of GDM, as in type 2 diabetes, a key role is played by insulin resistance and decreased insulin secretion relative to the patient's needs. We observe GDM in both obese and lean women [37]. Insulin resistance induced by pregnancy overlaps with the pre-pregnancy insulin resistance that is already present in obese women, while in lean women, an impaired first phase of insulin secretion is also dominant [38]. Insulin resistance in pregnancy is predisposed by the diabetogenic effect of placental hormones (human placental lactogen (hPL), human placental growth hormone (hPGH), growth hormone (GH), adrenocorticotrophic hormone (ACTH), prolactin (PRL), estrogens and gestagens), increased secretion of pro-inflammatory cytokines (tumor necrosis factor alpha (TNF- α), IL-6, resistin and C-reactive protein (CRP)), adiponectin deficiency, hyperleptinemia and central leptin resistance, impaired glucose transport in skeletal muscles, impaired insulin receptor signaling, and decreased expression and abnormal translocation of GLUT-4 to the cell membrane of adipocytes [39–41]. An increased secretion of insulin-antagonistic hormones (placental hormones, cortisol) during pregnancy results in an increased insulin resistance, which, at the end of the third trimester, reaches a value similar to full-blown type 2 diabetes [9,42]. Subclinical inflammation in pregnant women as a result of the synthesis of pro-inflammatory cytokines in the placenta and adipose tissue also leads to insulin resistance [43,44]. So far, the effects on the development of insulin resistance due to TNF- α , IL-6 and C-reactive protein have been best studied. Kirwan et al. stated that an increase in insulin resistance, which is characteristic of pregnancy, most strongly correlates with the increase in TNF- α concentration, considering that TNF- α as a marker of insulin resistance during pregnancy [45]. Furthermore, hyperleptinemia in the first weeks of pregnancy is a predictor of the development of gestational diabetes. According to Qui, the determination of the leptin concentration ≥ 31.0 ng/mL in the 13th week of pregnancy causes a 4.7-fold increase in the risk of GDM compared with the risk at the level of leptinemia of ≤ 14.3 ng/mL. For every 10 ng/mL increase in leptin concentration, the risk of GDM increases by 21% [46]. At the same time, GDM is characterized by elevated concentrations of leptin, which leads to hyperleptinemia [47]. However, pre-pregnancy BMI is a stronger predictor of leptinemia than GDM per se [48]. In women with gestational diabetes, the concentration of adiponectin is lower than in pregnant women without disturbances of carbohydrate metabolism, regardless of their pre-pregnancy BMI [49]. It was shown that a low adiponectin concentration in the first and second trimesters of pregnancy is a predictor of diabetes development in pregnancy [50]. In the Barbour study, a 1.5–2-fold increase in the level of the p85 α PI-3-kinase regulatory subunit was found in both the muscle and adipose tissue of obese pregnant and pregnant GDM women compared to obese non-pregnant women. In women with GDM, a 62% increase in the phosphorylation activity of IRS-1 serine residues was found in striated muscle cells compared with the control group of pregnant women without GDM, which points to insulin resistance post-receptor mechanisms [43].

4.4.2. β -Cell Dysfunction

The analysis of insulin secretion disorders in GDM gives inconclusive results. The mechanisms of β -cell hypertrophy and proliferation, resulting in a 300% increase in insulin secretion in the first two trimesters of physiological pregnancy, is insufficient to explain GDM [9,39]. In the pathogenesis of GDM, we also observed the influence of autoimmune and genetic factors, such as the presence of anti-insulin and/or anti-insulin antibodies, which are at risk of developing DM1 and latent autoimmune diabetes in adults (LADA) [51]. In cross-sectional studies, the prevalence of mutations in the gene variants GCK, HNF1A, HNF4A, HNF1B and INS in maturity-onset diabetes of the young (MODY) was 0–5% [52]. Great hopes in the search for the genetic causes of GDM are associated with research on the single nucleotide polymorphism (SNP) related to the cyclin-dependent kinase 5 (CDK5) regulatory subunit associated protein1-like1 gene (CKDAL1). Their presence is associated

with an impaired first phase of insulin secretion in DM2 and GDM and leads to a decrease in the mass of beta cells and impairment of their function, leading to GDM [53,54].

4.4.3. Other Factors

A study conducted in Spain showed that carriers of the gene rs7903146 T-allele who followed the Mediterranean diet in early pregnancy had a lower risk of developing GDM [55]. A growing body of research provides evidence of the importance of DNA methylation in the regulation of gene expression associated with metabolic disturbances in pregnant women and in the metabolic programming of the fetus in the setting of GDM-induced hyperglycemia [56–58]. In subcutaneous and visceral adipose tissue samples, the insulin receptor mRNA/protein expressions were significantly reduced in women with GDM ($p < 0.05$) [56]. Mothers with GDM displayed a significantly increased global placental DNA methylation (3.22 ± 0.63 vs. $3.00 \pm 0.46\%$ (\pm SD), $p = 0.013$) [57]. Additional light was shed on the pathogenesis of GDM by studies on disorders of the placental proteome, where the placental proteome was altered in pregnant women affected by GDM with large-for-gestational-age (LGA), with at least 37 proteins being differentially expressed to a higher degree ($p < 0.05$) as compared with those with GDM but without LGA [59]. In addition, Khosrowbeygi et al. showed that women with GDM had higher values of TNF- α (225.08 ± 27.35 vs. 115.68 ± 12.64 pg/mL, $p < 0.001$) and lower values of adiponectin (4.50 ± 0.38 vs. 6.37 ± 0.59 μ g/mL, $p = 0.003$) and the adiponectin/TNF- α ratio (4.31 ± 0.05 vs. 4.80 ± 0.07 , $p < 0.001$) than normal pregnant women. The ratio of adiponectin/TNF- α , which decrease significantly in GDM compared with normal pregnancy, might be an informative biomarker for the assessment of pregnant women at high risk of insulin resistance and dyslipidemia and for the diagnosis and therapeutic monitoring aims regarding GDM [60].

4.5. COVID-19 Pandemic and GDM

The second severe acute respiratory distress syndrome (SEA) coronavirus (SARS-CoV-2) causes an acute respiratory disease called coronavirus disease 2019 (COVID-19). There are limited data on the impact of SARS-CoV-2 infection on the onset and course of GDM. A living systematic review and meta-analysis of 435 studies reported the incidence of COVID-19 in pregnant women of approximately 10% (7–14%) [61]. The COVID-19 pandemic has caused organizational difficulties related to the correct diagnosis of GDM. In Anglo-Saxon countries, in order to minimize the risk of infection with SARS-CoV-2, replacement of the three-point OGTT was proposed and the assessment of fasting blood glucose and HbA1c were introduced. Postpartum screening postponement and the use of telemedicine were also offered [62]. However, simplifying the diagnosis of GDM in order to avoid the risk of COVID-19 infection was unfortunately associated with the risk of not diagnosing GDM by as much as 20–30%, which may affect obstetric outcomes [63–65]. This was confirmed by another study that showed that in the “COVID era”, diagnostics toward GDM cannot be abandoned and the procedures for its detection cannot be simplified [66]. The COVID-19 pandemic increased the incidence of GDM in 2020 compared with 2019 (13.5% vs. 9%, $p = 0.01$), especially in women in the first trimester of pregnancy. Experiencing lockdown during the first trimester of gestation increased the risk of GDM in these women by a factor of 2.29 ($p = 0.002$) compared with women whose pregnancies occurred before and after lockdown [67]. This is undoubtedly influenced by the sedentary lifestyle of women during the pandemic and reduced physical activity, most often caused by the fear of leaving their homes due to COVID-19 [68]. The “lockdown effect” caused a marked deterioration in glycemic control, an increase in the percentage of HbA1c, and weight/BMI gain in patients with DM2 and GDM [69,70].

4.6. Treatment of Gestational Diabetes

Regarding women with GDM, due to the lack of randomized clinical trials, it is extremely difficult to propose an unambiguous and uniform model of management in order

to achieve obstetric results similar to the population of healthy women. The treatment of GDM is based on consensus and expert opinion. Analyses of Cochrane Database Reviews showed the lack of unambiguous data on the correlation between the intensity of glycemic control and obstetric outcomes [71]. Based on a meta-analysis from 2014–2019, Mitanchez et al. indicated that the greatest impact on reducing the number of obstetric complications is achieved by combining dietary treatment with exercise [72].

4.6.1. Nutritional Treatment

Nutritional recommendations help women to achieve normoglycemia, optimal weight gain and proper development of the fetus, and the introduction of a pharmacological treatment does not release the mother from the obligation to follow the diet [73]. In GDM, it is necessary to develop an individual nutritional plan based on glycemic self-control, optimal weight gain based on pre-pregnancy BMI, and a calculation of energy requirements and macronutrient proportions, as well as taking into account the mother’s nutritional preferences, together with work, rest and exercise [73]. Chao et al. indicated better results when using individualized recommendations for a specific woman with GDM in contrast to general recommendations [74]. It is recommended to eat three main meals and 2–3 snacks a day, often with a snack around 9:30 pm to protect against nocturnal hypoglycemia and morning ketosis [6]. In a prospective observational study using the 24 h online diet and glycemic tool (“Myfood24 GDM”), better glycemic control was demonstrated with more frequent meals [75]. In women with GDM, carbohydrates are the most important macronutrient, and their high consumption can cause hyperglycemia. However, glucose is the main energy substrate of the placenta and fetus, and thus, is necessary for their proper growth and metabolism [76]. According to the ATA, the content of carbohydrates in the diet should constitute 40–50% of the energy requirement, not less than 180 g/day, and consist mainly of starchy foods with a low glycemic index (GI) [6,73]. The recommended dietary fiber intake is 25–28 g per day, which means a portion of about 600 g of fruit and vegetables per day with a minimum of 300 g of vegetables, whole grain bread, pasta and rice [73,77,78]. Protein should constitute about 30% of the caloric value, that is about 1.3 g/kg of b.w./d, with the minimum recommended daily intake of 71 g of protein [73]. Increased intakes of plant protein, lean meat and fish, and reduced intakes of red and processed meats are beneficial in the treatment of GDM and may improve insulin sensitivity [79,80]. A diet with a high fat content is contraindicated (20–30% of the caloric value is recommended, including < 10% saturated fat), as it leads to placental dysfunction and infant obesity, increased inflammation and oxidative stress, and impaired maternal muscle glucose uptake [80–82]. The consumption of saturated fat should be limited in favor of the consumption of the polyunsaturated fatty acids (PUFA) n-3 (linolenic acid) and n-6 (linoleic acid), which are the most important fatty acids for fetal growth and development. A total intake of n-3 in the amount of 2.7 g/day is considered safe during pregnancy [77], while additional fish oil supplementation gives inconclusive results [83]. The recommended weight gain in pregnancy amounts to on average 8–12 kg, depending on the initial body weight (Table 3) [78].

Table 3. Weight gain in relation to baseline body weight (BMI).

BMI	Weight Gain in Pregnancy
<18.5 kg/m ²	12.5–18 kg
18.5–24.9 kg/m ²	11.5–16 kg
25.0–29.9 kg/m ²	7–11.5 kg
≥30 kg/m ²	5–9 kg

A weight gain of over 18 kg is associated with a twice higher risk of macrosomia [84,85]. Many studies show an increase in the need for vitamins and minerals in pregnancy, mainly

folic acid, vitamin D and iron. All pregnant women are recommended to supplement daily with 400 µg of folic acid and 5.0 µg of vitamin D; additionally, depending on the dietary intake, 500–900 mg of calcium and 27–40 mg of iron are recommended [77]. The influence of gut microbiota on the development of GDM is interesting [86]. So far, it was shown that in women in the third trimester of pregnancy, GDM was associated with altered intestinal microflora [87]. However, in the conducted studies on the beneficial effects of probiotics in the prevention or treatment of GDM, the results are still inconclusive [88–91].

The main quality-oriented recommendations include the need to limit or eliminate processed products with a high content of salt, sugar and fats; avoiding unpasteurized milk, raw meat, alcohol and caffeine; and ensuring proper hydration of at least 2 L of water per day. In addition, the effect of the Dietary Approach to Stop Hypertension (DASH) diet on glycemic control was confirmed, and Sarathi et al. indicated that eating a high-protein diet based on soy products reduces insulin requirements in GDM patients [92,93]. Myoinositol (vitamin B8) supplementation or a diet rich in the MYO-INS isomer may improve glycemic control in GDM [94,95].

4.6.2. Exercise in GDM

In women with GDM, the quantitative and qualitative recommendations for exercise are ambiguous in terms of improving glycemic control [96]. Obstetric indications and contraindications should be followed. If there are no contraindications, the available observational studies indicate the safety of physical activity during pregnancy [97]. Activities that can be safely started and continued are walking, cycling, swimming, selected pilates and low-intensity fitness exercises. It is safe to continue with (but not initiate) the following after consulting with one's obstetrician: yoga, running, tennis, badminton and strength exercises. Pregnant people should avoid contact sports, horse riding, surfing, skiing and diving. The analysis of Aune et al. showed a reduction in the risk of GDM by 38% (RR 0.62, 95% CI 0.41–0.94) in physically active women [98]. An intervention study in overweight patients by Nasiri-Amiri et al. showed a 24% reduction in the risk of GDM in women exercising no more than three times a week [99]. In women with normal body weight, increased physical activity, according to an analysis by Ming et al., resulted in a lower weight gain in pregnancy without affecting the child's weight or the frequency of Caesarean sections and a 42% reduction in the risk of GDM (RR 0.58, 95% CI 0.37–0.90, $p = 0.01$) [100]. A meta-analysis by Harrison et al. of eight randomized trials showed a significant reduction in fasting and postprandial glucose levels in women with 20–30 min of activity 3–4 times a week [101].

4.6.3. Pharmacological Treatment

Patients who cannot achieve glycemic targets with a properly balanced diet and elimination of dietary errors should be treated pharmacologically [29]. Most studies indicate insulin therapy as the safest form of treatment, and OAD (orally administrated drugs) treatment should be introduced only in the case of the patient's lack of consent to insulin therapy or its unavailability [102]. Insulin therapy is carried out in the model of functional intensive insulin therapy (FIIT) with the use of subcutaneous injections. The safety of human insulin use in pregnancy was demonstrated [103]. The safety of the use of aspart and detemir analogs was confirmed in randomized trials [104–106] and the safety of lispro and glargine analogs was shown in observational studies [107]; none of the studies showed the passage of insulin analogs across the placenta [108,109]. Currently, metformin and glibenclamide are used as oral medications. Metformin and glibenclamide (glyburide) cross the placenta but are unlikely to be teratogenic [110,111]. The metformin in gestational (MiG) diabetes trial was a landmark study; it was one of the largest randomized controlled trials, in which 751 women with GDM prospectively assessed a composite of neonatal complications as the primary outcome and secondary outcome of neonatal anthropometry at birth. It was concluded that metformin alone, or with supplemental insulin, was not associated with increased perinatal complications. This trial was the basis of many subsequent studies to assess the safety and efficacy of metformin use in GDM [112].

Some studies showed that the use of metformin during pregnancy is associated with higher body weight, more visceral and subcutaneous tissue, and higher blood glucose levels when the offspring is 9 years old [113]. The use of glibenclamide, despite its high effectiveness, may result in a higher percentage of intrauterine deaths and neonatal complications, such as hypoglycemia, macrosomia and FGR (fetal growth restriction) [114]. Although there is an increasing amount of evidence that supports the use of glyburide or metformin for GDM, the American Diabetes Association (ADA) and American College of Obstetricians and Gynecologists (ACOG) still recommend insulin as the primary medical treatment if the glycaemic treatment goals are not achieved with lifestyle intervention due to the lack of evidence regarding the long-term safety of the alternatives [115]. Sodium-glucose cotransporter-2 (SGLT2) inhibitors block the transporter located in the proximal tubule of kidneys that promotes renal tubular reabsorption of glucose, which causes a decrease in blood glucose levels due to an increase in renal glucose excretion. Among women with diabetes, UTI during pregnancy can be associated with pyelonephritis and sepsis and potential long-term effects on the neonate [116]. There were some adverse events noted in animal reproductive studies, including adverse effects on renal development when SGLT2 inhibitors were used in the second and third trimesters, although there are no human data available. The use of SGLT2 inhibitors during pregnancy is not recommended [110]. Recently, some studies reported the use of GLP-1 agents in GDM. GLP-1 agents, including dipeptidyl peptidase-4 (DPP-4) inhibitor and glucagon-like peptide-1 receptor agonist (GLP-1 Ra), enhance insulin secretion in pancreatic b-cell and showed many benefits in treating diabetes mellitus type 2 but are not a common choice for GDM [117,118]. In a systematic review that included 516 patients and investigated the use of GLP-1 agents in GDM (at different time points, including the second trimester of pregnancy and after delivery), Chen et al. showed that the use of GLP-1 agents to normalize blood glucose and can improve insulin resistance, as well as reduce the rate of developing postpartum diabetes compared with a placebo. This systematic review suggested that a dipeptidyl peptidase-4 inhibitor and glucagon-like peptide-1 receptor agonist may be beneficial to GDM patients but need rigorously designed clinical trials to demonstrate this. In particular, whether it can be used during pregnancy to improve pregnancy outcomes or better used to prevent developing diabetes after delivery should be investigated [119]. The data of a randomized controlled trial, namely, The Treatment of Booking Gestational Diabetes Mellitus (TOBOGM), compared pregnancy outcomes among women with booking GDM receiving immediate or deferred treatment can provide new insights into the diagnosis and treatment of GDM [120].

5. Conclusions

GDM is one of the most common complications of pregnancy and confers lifelong risks to both women and their children. Observational data demonstrated a linear association between maternal glycemic parameters and risks for adverse pregnancy and offspring outcomes. SARS-CoV-2 infection will undoubtedly affect the risk of GDM. Many doubts regarding the diagnostic criteria and treatment of GDM are still under discussion. Treatment with insulin is effective, but costs and patient experiences limit its use in clinical practice. The use of metformin as a first-line agent for GDM remains controversial due to its transplacental passage and limited long-term follow-up data. Further clinical trials are necessary to use other oral hypoglycemic agents to treat GDM. It is very important for patients with GDM to receive behavioral therapy and to closely cooperate with the doctor. Future work in the field should include studies of both clinical and implementation outcomes, examining strategies to improve the quality of care delivered to women with GDM. The screening and treatment for GDM early in pregnancy are very controversial due to the lack of data from large randomized controlled trials. There is an urgent need for well-designed research that can inform decisions on the best practice regarding gestational diabetes mellitus screening and diagnosis.

Author Contributions: Conceptualization, R.M., M.M.S.-R. and E.M.B.-S.; methodology, R.M. and W.M.; formal analysis, E.M.B.-S.; investigation, R.M. and M.M.S.-R.; resources, R.M., M.M.S.-R. and W.M.; data curation, E.M.B.-S.; writing—original draft preparation, R.M. and M.M.S.-R.; writing—review and editing, E.M.B.-S.; visualization, R.M. and M.M.S.-R.; supervision, E.M.B.-S.; project administration, R.M. and W.M. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

- Buchanan, T.A.; Xiang, A.H.; Page, K.A. Gestational Diabetes Mellitus: Risks and Management during and after Pregnancy. *Nat. Rev. Endocrinol.* **2012**, *8*, 639–649. [[CrossRef](#)] [[PubMed](#)]
- Crowther, C.A.; Hiller, J.E.; Moss, J.R.; McPhee, A.J.; Jeffries, W.S.; Robinson, J.S.; 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*, 2477–2486. [[CrossRef](#)] [[PubMed](#)]
- Wang, H.; Li, N.; Chivese, T.; Werfalli, M.; Sun, H.; Yuen, L.; Hoegfeldt, C.A.; Elise Powe, C.; Immanuel, J.; Karuranga, S.; et al. 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. [[CrossRef](#)] [[PubMed](#)]
- Kondracki, A.J.; Valente, M.J.; Ibrahimou, B.; Bursac, Z. Risk of large for gestational age births at early, full and late term in relation to pre-pregnancy body mass index: Mediation by gestational diabetes status. *Paediatr. Perinat. Epidemiol.* **2022**, *36*, 566–576. [[CrossRef](#)] [[PubMed](#)]
- Lee, K.W.; Ching, S.M.; Ramachandran, V.; Yee, A.; Hoo, F.K.; Chia, Y.C.; Sulaiman, W.A.W.; Suppiah, S.; Mohamed, M.H.; Veettil, S.K. Prevalence and risk factors of gestational diabetes mellitus in Asia: A systematic review and meta-analysis. *BMC Pregnancy Childbirth* **2018**, *18*, 494. [[CrossRef](#)] [[PubMed](#)]
- McIntyre, H.D.; Catalano, P.; Zhang, C.; Desoye, G.; Mathiesen, E.R.; Damm, P. Gestational diabetes mellitus. *Nat. Rev. Dis. Primers* **2019**, *5*, 47. [[CrossRef](#)]
- Lenoir-Wijnkoop, I.; Van Der Beek, E.M.; Garssen, J.; Nuijten, M.J.C.; Uauy, R.D. Health economic modeling to assess short-term costs of maternal overweight, gestational diabetes, and related macrosomia—A pilot evaluation. *Front. Pharmacol.* **2015**, *6*, 103. [[CrossRef](#)]
- Xu, T.; Dainelli, L.; Yu, K.; Ma, L.; Zolezzi, I.S.; Detzel, P.; Fang, H. The short-term health and economic burden of gestational diabetes mellitus in China: A modelling study. *BMJ Open* **2017**, *7*, e018893. [[CrossRef](#)]
- Plows, J.F.; Stanley, J.L.; Baker, P.N.; Reynolds, C.M.; Vickers, M.H. The Pathophysiology of Gestational Diabetes Mellitus. *Int. J. Mol. Sci.* **2018**, *19*, 3342. [[CrossRef](#)]
- Oliveira, M.M.; Andrade, K.F.O.; Lima, G.H.S.; Rocha, T.C. Metformin versus glyburide in treatment and control of gestational diabetes mellitus: A systematic review with meta-analysis. *Einstein* **2022**, *20*, eRW6155. [[CrossRef](#)]
- Chen, C.; Xu, X.; Yan, Y. Estimated global overweight and obesity burden in pregnant women based on panel data model. *PLoS ONE* **2018**, *13*, e0202183. [[CrossRef](#)] [[PubMed](#)]
- Bucley, B.S.; Harreiter, J.; Damm, P.; Corcoy, R.; Chico, A.; Simmons, D.; Vellinga, A.; Dunne, F. Gestational diabetes mellitus in Europe: Prevalence, current screening practice and barriers to screening. *Diabet. Med.* **2012**, *29*, 844–854. [[CrossRef](#)] [[PubMed](#)]
- Moses, R.; Griffiths, R.; Daviess, W. Gestational diabetes: Do all women need to be tested? *Aust. N. Z. J. Obstet. Gynaecol.* **1995**, *35*, 387–389. [[CrossRef](#)]
- Lao, T.T.; Ho, L.-F.; Chan, B.C.P.; Leung, W.-C. Maternal Age and Prevalence of Gestational Diabetes Mellitus. *Diabetes Care* **2006**, *29*, 948–949. [[CrossRef](#)]
- Miller, C.; Lim, E. The risk of diabetes after giving birth to a macrosomic infant: Data from the NHANES cohort. *Matern. Health Neonatol. Perinatol.* **2021**, *7*, 12. [[CrossRef](#)] [[PubMed](#)]
- Schwartz, N.; Nachum, Z.; Green, S.M. The prevalence of gestational diabetes mellitus recurrence—Effect of ethnicity and parity: A metaanalysis. *Am. J. Obstet. Gynecol.* **2015**, *213*, 310–317. [[CrossRef](#)]
- Kim, C.; Berger, K.D.; Chamany, S. Recurrence of Gestational Diabetes Mellitus A systematic review. *Diabetes Care* **2007**, *30*, 1314–1319. [[CrossRef](#)]
- Torloni, M.R.; Betran, A.P.; Horta, B.L.; Nakamura, M.U.; Atallah, N.A.; Maron, A.F.; Valente, O. Prepregnancy BMI and the risk of gestational diabetes: A systemic review of literature with meta-analysis. *Obes. Rev.* **2009**, *10*, 194–203. [[CrossRef](#)]
- Song, X.; Chen, L.; Zhang, S.; Liu, Y.; Wei, J.; Wang, T.; Qin, J. Gestational Diabetes Mellitus and High Triglyceride Levels Mediate the Association between Pre-Pregnancy Overweight/Obesity and Macrosomia: A Prospective Cohort Study in Central China. *Nutrients* **2022**, *14*, 3347. [[CrossRef](#)]

20. Mikola, M.; Hillesmaa, V.; Halttunen, M.; Suhonen, L.; Tiitinen, A. Obstetric outcome in women with polycystic ovarian syndrome. *Hum. Reprod.* **2001**, *16*, 226–229. [[CrossRef](#)]
21. Katsarou, A.; Claesson, R.; Shaat, N.; Ignell, V.; Berntorp, V. Seasonal pattern in the diagnosis of gestational diabetes mellitus in southern Sweden. *J. Diabetes Res.* **2016**, *2016*, 8905474. [[CrossRef](#)]
22. Wang, P.; Wu, C.S.; Li, C.Y.; Yang, C.P.; Lu, M.C. Seasonality of gestational diabetes mellitus and maternal blood glucose levels: Evidence from Taiwan. *Medicine* **2020**, *99*, e22684. [[CrossRef](#)] [[PubMed](#)]
23. Chiefari, E.; Pastore, I.; Puccio, L.; Caroleo, P.; Oliverio, R.; Vero, A.; Foti, D.P.; Vero, R.; Brunetti, A. Impact of seasonality on gestational diabetes mellitus. *Endocr. Metab. Immune Disord.-Drug Targets* **2017**, *17*, 246–252. [[CrossRef](#)] [[PubMed](#)]
24. Bianchi, C.; Pelle, C.D.; Gennaro, G.D.; Aragona, M.; Cela, V.; Delprato, S.; Bertolotto, A. 1392-P: Assisted Reproduction Technology Treatment and Risk of Gestational Diabetes. *Diabetes* **2020**, *69* (Suppl. 1), 1392-P. [[CrossRef](#)]
25. Benhalima, K.; Hanssens, M.; Devlieger, R.; Verhaeghe, J.; Mathieu, C. Analysis of pregnancy outcomes using the new IADPSG recommendation compared with the Carpenter and Coustan criteria in an area with a low prevalence of gestational diabetes. *Int. J. Endocrinol.* **2013**, *2013*, 248121. [[CrossRef](#)] [[PubMed](#)]
26. HAPO Study Cooperative Research Group. Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study: Association with maternal body mass index. *BJOG* **2010**, *117*, 575–584. [[CrossRef](#)] [[PubMed](#)]
27. Werner, E.F.; Pettfer, C.M.; Zuckerwise, L.; Reel, M.; Funai, E.F.; Henderson, J.; Thung, S.F. Screening for gestational diabetes mellitus: Are the criteria proposed by the International Association of the Diabetes and Pregnancy Study Groups cost-effective? *Diabetes Care* **2012**, *35*, 529–535. [[CrossRef](#)] [[PubMed](#)]
28. Williams, C.B.; Iqbal, S.; Zawacki, C.M.; Yu, D.; Brown, M.B.; Herman, W.H. Effect of selective screening for gestational diabetes. *Diabetes Care* **1999**, *22*, 418–421. [[CrossRef](#)] [[PubMed](#)]
29. Landon, M.B.; Spong, C.Y.; Thom, E.; Carpenter, M.W.; Ramin, S.M.; Casey, B.; Wapner, R.J.; Varner, M.W.; Rouse, D.J.; Thorp, J.M., Jr.; et al. A multicenter, randomized trial of treatment for mild gestational diabetes. *N. Engl. J. Med.* **2009**, *361*, 1339–1348. [[CrossRef](#)]
30. Horvath, K.; Koch, K.; Jeitler, K.; Matyas, E.; Bender, R.; Bastian, H.; Lange, S.; Siebenhofer, A. Effects of treatment in women with gestational diabetes mellitus: Systemic review and meta-analysis. *BMJ* **2010**, *340*, c1395. [[CrossRef](#)]
31. Aubry, E.M.; Raio, L.; Oelhafen, S. Effect of the IADPSG screening strategy for gestational diabetes on perinatal outcomes in Switzerland. *Diabetes Res. Clin. Pract.* **2021**, *175*, 108830. [[CrossRef](#)] [[PubMed](#)]
32. Hillier, T.A.; Pedula, K.L.; Ogasawara, K.K.; Vesco, K.K.; Oshiro, C.E.S.; Lubarsky, S.L.; Van Marter, J. A Pragmatic, Randomized Clinical Trial of Gestational Diabetes Screening. *N. Engl. J. Med.* **2021**, *384*, 895–904. [[CrossRef](#)] [[PubMed](#)]
33. Crowther, C.A.; Samuel, D.; McCowan, L.M.; Edlin, R.; Tran, T.; McKinlay, C.J. Lower versus Higher Glycemic Criteria for Diagnosis of Gestational Diabetes. *N. Engl. J. Med.* **2022**, *387*, 587–598. [[CrossRef](#)] [[PubMed](#)]
34. Lorenzo-Almoros, A.; Hang, T.; Peiro, C.; Soriano-Guillen, L.; Egido, J.; Tunon, J.; Lorenzo, O. Predictive and diagnostic biomarkers for gestational diabetes and its associated metabolic and cardiovascular diseases. *Cardiovasc. Diabetol.* **2019**, *18*, 140. [[CrossRef](#)] [[PubMed](#)]
35. Corcoran, M.S.; Achamallah, N.; O'Loughlin, J.; Stafford, P.; Dicker, P.; Malone, D.F.; Breathnach, F. First trimester serum biomarkers to predict gestational diabetes in a high-risk cohort: Striving for clinically useful thresholds. *Eur. J. Obstet. Gynecol. Reprod. Biol.* **2018**, *222*, 7–12. [[CrossRef](#)]
36. Kotzaeridi, G.; Blätter, J.; Eppel, D.; Rosicky, I.; Mittlböck, M.; Yerlikaya-Schatten, G.; Schatten, C.; Husslein, P.; Eppel, W.; Huhn, E.A.; et al. Performance of early risk assessment tools to predict the later development of gestational diabetes. *Eur. J. Clin. Investig.* **2021**, *51*, e13630. [[CrossRef](#)]
37. Yong, H.Y.; Shariff, Z.M.; Yusof, B.N.M.; Rejali, Z.; Tee, Y.Y.S.; Bindels, J.; Van Der Beek, E.M. Independent and combined effects of age, body mass index and gestational weight gain on the risk of gestational diabetes mellitus. *Sci. Rep.* **2020**, *10*, 8486. [[CrossRef](#)]
38. Homko, C.; Sivan, E.; Chen, X.; Reece, E.A.; Boden, G. Insulin secretion during and after pregnancy in patients with gestational diabetes mellitus. *J. Clin. Endocrinol. Metab.* **2001**, *86*, 568–573. [[CrossRef](#)]
39. Baeyens, L.; Hindi, S.; Sorenson, R.L.; German, M.S. β -cell adaptation in pregnancy. *Diabetes Obes. Metab.* **2016**, *18* (Suppl. 1), 63–70. [[CrossRef](#)]
40. Baz, B.; Riverline, J.P.; Gautier, J.F. Endocrinology of pregnancy: Gestational Diabetes Mellitus: Definition, aetiological and clinical aspects. *Eur. J. Endocrinol.* **2016**, *174*, R43–R51. [[CrossRef](#)]
41. Barberoglu, Z. Pathophysiology of gestational diabetes mellitus. *EMJ Diabetes* **2019**, *7*, 97–106.
42. Buchanan, T.A.; Kijos, S.L.; Xiang, A.; Watanabe, R. What is Gestational Diabetes? *Diabetes Care* **2007**, *30* (Suppl. 2), 105–111. [[CrossRef](#)]
43. Barbour, L.A.; McCurdy CE Hernandez, T.L.; Kirwan, J.P.; Catalano, P.M.; Friedman, J.E. Cellular mechanism of insulin resistance in normal pregnancy and Gestational Diabetes. *Diabetes Care* **2007**, *30* (Suppl. 2), 112–119. [[CrossRef](#)] [[PubMed](#)]
44. Vrachins, N.; Belitsos, P.; Sifakis, S.; Dafopoulos, K.; Siristatidis, C.; Pappa, K.I.; Iliodromiti, Z. Role of adipokines and other inflammatory mediators in gestational diabetes mellitus and previous gestational diabetes mellitus. *Int. J. Endocrinol.* **2012**, *2012*, 549748. [[CrossRef](#)] [[PubMed](#)]
45. Kirwan, J.P.; Hauguel-De Mouzon, S.; Lepercq, J.; Challier, J.-C.; Huston-Presley, L.; Friedman, J.E.; Kalhan, S.C.; Catalano, P.M. TNF- α is a predictor of insulin resistance in human pregnancy. *Diabetes* **2002**, *51*, 2207–2213. [[CrossRef](#)]

46. Qiu, C.; Williams, M.A.; Vadachkoria, S.; Frederick, I.O.; Luthy, D.A. Increased maternal plasma leptin in early pregnancy and risk of gestational diabetes mellitus. *Obstet. Gynecol.* **2004**, *103*, 519–525. [[CrossRef](#)]
47. Honnorat, D.; Disse, E.; Millot, L.; Mathiotte, E.; Claret, M.; Charrié, A.; Drai, J.; Garnier, L.; Maurice, C.; Durand, E.; et al. Are third-trimester adipokines associated with higher metabolic risk among women with gestational diabetes? *Diabetes Metab.* **2015**, *41*, 393–400. [[CrossRef](#)]
48. Maple-Brown, L.; Ye, C.; Hanley, A.J.; Connelly, P.W.; Sermer, M.; Zinman, B.; Retnakaran, R. Maternal pregravid weight is the primary determinant of serum leptin and its metabolic associations in pregnancy, irrespective of gestational glucose tolerance status. *J. Clin. Endocrinol. Metab.* **2012**, *97*, 4148–4155. [[CrossRef](#)]
49. Miehle, K.; Stepan, H.; Fasshauer, M. Leptin, adiponectin and other adipokines in gestational diabetes and pre-eclampsia. *Clin. Endocrinol.* **2012**, *76*, 2–11. [[CrossRef](#)]
50. Valencia-Ortega, J.; González-Reynoso, R.; Ramos-Martínez, E.G.; Ferreira-Hermosillo, A.; Peña-Cano, M.I.; Morales-Ávila, E.; Saucedo, R. New Insights into Adipokines in Gestational Diabetes Mellitus. *Int. J. Mol. Sci.* **2022**, *23*, 6279. [[CrossRef](#)]
51. Kumar, A.d.L.A.; Corcoy, R. Autoimmunity in Gestational Diabetes A Decade after the HAPO Study. *Front. Diabetes* **2020**, *28*, 234–242. [[CrossRef](#)]
52. Gjesing, A.; Rui, G.; Launeborg, J.; Have, C.H.; Hollensted, M.; Andersson, E.; Grarup, N.; Sun, J.; Quan, S.; Brandslund, I. High Prevalence of Diabetes-Predisposing Variants in MODY Genes Among Danish Women With Gestational Diabetes Mellitus. *J. Endocr. Soc.* **2017**, *1*, 681–690. [[CrossRef](#)] [[PubMed](#)]
53. Mao, H.; Li, Q.; Gao, S. Meta-analysis of the relationship between common type 2 diabetes risk gene variants with gestational diabetes mellitus. *PLoS ONE* **2012**, *7*, e45882-6. [[CrossRef](#)] [[PubMed](#)]
54. Lowe, W.L.; Scholtens, D.M.; Sandler, V.; Hayes, M.G. Genetics of gestational diabetes mellitus and maternal metabolism. *Curr. Diabetes Rep.* **2016**, *16*, 15–24. [[CrossRef](#)]
55. Barabash, A.; Valerio, J.D.; de la Torre, N.G.; Jimenez, I.; del Valle, L.; Melero, V.; Assaf-Balut, C.; Fuentes, M.; Bordiu, E.; Durán, A.; et al. TCF7L2 rs7903146 polymorphism modulates the association between adherence to a Mediterranean diet and the risk of gestational diabetes mellitus. *Metab. Open* **2020**, *8*, 100069. [[CrossRef](#)] [[PubMed](#)]
56. Ott, R.; Melchior, K.; Stupin, J.H.; Ziska, T.; Schellong, K.; Henrich, W.; Rancourt, R.C.; Plagemann, A. Reduced insulin receptor expression and altered DNA methylation in fat tissue and blood of women with GDM and offspring. *J. Clin. Endocrinol. Metab.* **2019**, *104*, 137–149. [[CrossRef](#)]
57. Reichetzeder, C.; Dwi Putra, S.E.; Pfab, T.; Slovinski, T.; Neuber, C.; Kleuser, B.; Hocher, B. Increased global placental DNA methylation levels are associated with gestational diabetes. *Clin. Epigenet.* **2016**, *8*, 82. [[CrossRef](#)]
58. Zhang, Y.; Chen, Y.; Qu, H.; Wang, Y. Methylation of HIF3A promoter CpG islands contributes to insulin resistance in gestational diabetes mellitus. *Mol. Genet. Genom. Med.* **2019**, *7*, e00583. [[CrossRef](#)]
59. Assi, E.; D'Addio, F.; Mandò, C.; Maestroni, A.; Loretelli, C.; Ben Nasr, M.; Usuelli, V.; Abdelsalam, A.; Seelam, A.J.; Pastore, I.; et al. Placental proteome abnormalities in women with gestational diabetes and large-for-gestational-age newborns. *BMJ Open Diabetes Res. Care* **2020**, *8*, e001586. [[CrossRef](#)]
60. Khosrowbeygi, A.; Rezvanfar, M.R.; Ahmadvand, H. Tumor necrosis factor- α , adiponectin and their ratio in gestational diabetes mellitus. *Casp. J. Intern. Med.* **2018**, *9*, 71–79. [[CrossRef](#)]
61. Allotey, J.; Stallings, E.; Bonet, M. Clinical manifestations, risk factors, and maternal and perinatal outcomes of coronavirus disease 2019 in pregnancy: Living systematic review and meta-analysis. *BMJ* **2020**, *370*, 1–18. [[CrossRef](#)] [[PubMed](#)]
62. Noughjah, S.; Jahanfar, S.; Shahbazian, H. Temporary changes in clinical guidelines of gestational diabetes screening and management during COVID-19 outbreak: A narrative review. *Diabetes Metab. Syndr.* **2020**, *14*, 939–942. [[CrossRef](#)] [[PubMed](#)]
63. Van Gemert, E.T.; Moses, G.R.; Pape, V.A.; Morris, J.G. Gestational diabetes mellitus testing in the Covid19 pandemic: The problems with simplifying the diagnostic process. *Aust. N. Z. J. Obstet. Gynaecol.* **2020**, *60*, 671–674. [[CrossRef](#)] [[PubMed](#)]
64. Simmons, D.; Rudland, L.V.; Wong, V.; Flack, J.; Mackie, A.; Ross, P.G.; Coat, S.; Dalal, R.; Hague, M.B.; Cheung, W.N. Options for screening for gestational diabetes mellitus during the SARS-CoV-2 pandemic. *Aust. N. Z. J. Obstet. Gynaecol.* **2020**, *60*, 660–666. [[CrossRef](#)] [[PubMed](#)]
65. McIntyre, H.D.; Gibbons, S.K.; Ma, C.W.R.; Tam, H.W.; Sacks, A.D.; Lowe, J.; Madsen, R.L.; Catalano, M.P. Testing for gestational diabetes during the COVID-19 pandemic. An evaluation of proposed protocols for the United Kingdom, Canada and Australia. *Diabetes Res. Clin. Pract.* **2020**, *167*, 108353. [[CrossRef](#)]
66. McIntyre, H.D.; Moses, R.G. The diagnosis and management of gestational diabetes mellitus in the context of the COVID-19 pandemic. *Diabetes Care* **2020**, *43*, 1433–1434. [[CrossRef](#)]
67. Zanardo, V.; Tortora, D.; Sandri, A.; Severino, L.; Mesirca, P.; Straface, G. COVID-19 pandemic: Impact on gestational diabetes mellitus prevalence. *Diabetes Res. Clin. Pract.* **2022**, *183*, 109149. [[CrossRef](#)]
68. Hillyard, M.; Sinclair, M.; Murphy, M.; Casson, K.; Mulligan, C. The impact of COVID-19 on the physical activity and sedentary behaviour levels of pregnant women with gestational diabetes. *PLoS ONE* **2021**, *16*, e0254364. [[CrossRef](#)]
69. Eberle, C.; Stichling, S. Impact of COVID-19 lockdown on glycemic control in patients with type 1 and type 2 diabetes mellitus: A systematic review. *Diabetol. Metab. Syndr.* **2021**, *13*, 95. [[CrossRef](#)]
70. Ghesquière, L.; Garabedian, C.; Drumez, E.; Lemaître, M.; Cazaubiel, M.; Bengler, C.; Vambergue, A. Effects of COVID-19 pandemic lockdown on gestational diabetes mellitus: A retrospective study. *Diabetes Metab.* **2021**, *47*, 101201. [[CrossRef](#)]

71. Martis, R.; Brown, J.; Alsweiler, J.; Crawford, T.J.; Crowther, C.T. Different intensities of glycaemic control for women with gestational diabetes mellitus. *Cochrane Database Syst. Rev.* **2016**, *4*, CD011624. [[CrossRef](#)] [[PubMed](#)]
72. Mitanhez, D.; Ciangura, C.; Jacqueminet, S. How can maternal lifestyle interventions modify the effects of gestational diabetes in the neonate and the offspring? A systematic review of meta-analyses. *Nutrients* **2020**, *12*, 353. [[CrossRef](#)] [[PubMed](#)]
73. American Diabetes Association. 14. Management of Diabetes in Pregnancy: Standards of Medical Care in Diabetes—2020. *Diabetes Care* **2019**, *43*, S183–S192.
74. Chao, H.; Chen, G.; Wen, X.; Liu, J.; Zhang, J. Dietary control plus nutrition guidance for blood glucose and pregnancy outcomes in women with gestational diabetes. *Int. J. Clin. Exp. Med.* **2019**, *12*, 2773–2778.
75. Morris, M.A.; Hutchinson, J.; Gianfrancesco, C.; Alwan, N.A.; Carter, M.C.; Scott, E.M.; Cade, J.E. Relationship of the frequency, distribution, and content of meals/snacks to glycaemic control in gestational diabetes: The myfood24 GDM pilot study. *Nutrients* **2020**, *12*, 3. [[CrossRef](#)]
76. Hay, W.W. Placental-Fetal Glucose Exchange and Fetal Glucose Metabolism. *Trans. Am. Clin. Clim. Assoc.* **2006**, *117*, 321–340.
77. Nordic Nutrition of Ministers. *Nordic Nutrition Recommendations 2012*, 5th ed.; Norden: Copenhagen, Denmark, 2014; pp. 1–629.
78. Yaktine, A.L.; Rasmussen, K.M.; Youth, F.; National Research Council; Institute of Medicine; Board on Children; Committee to Reexamine IOM Pregnancy Weight Guidelines. *Weight Gain During Pregnancy: Reexamining the Guidelines (2009)*; Rasmussen, K.M., Yaktine, A.L., Eds.; The National Academies Press: Washington, DC, USA, 2009.
79. Jamilian, M.; Asemi, Z. The Effect of Soy Intake on Metabolic Profiles of Women with Gestational Diabetes Mellitus. *J. Clin. Endocrinol. Metab.* **2015**, *100*, 4654–4661. [[CrossRef](#)]
80. Rasmussen, L.; Poulsen, C.W.; Kampmann, U.; Smedegaard, S.B.; Ovesen, P.G.; Fuglsang, J. Diet and Healthy Lifestyle in the Management of Gestational Diabetes Mellitus. *Nutrients* **2020**, *12*, 3050. [[CrossRef](#)]
81. Hernandez, T.L.; Van Pelt, R.E.; Anderson, M.A.; Daniels, L.J.; West, N.A.; Donahoo, W.T.; Friedman, J.E.; Barbour, L.A. A Higher-Complex Carbohydrate Diet in Gestational Diabetes Mellitus Achieves Glucose Targets and Lowers Postprandial Lipids: A Randomized Crossover Study. *Diabetes Care* **2014**, *37*, 1254–1262. [[CrossRef](#)]
82. Danielewicz, H.; Myszczyzyn, G.; Debinska, A.; Myszkal, A.; Boznanaski, A.; Hirnle, L. Diet in pregnancy—More than food. *Eur. J. Pediatr.* **2017**, *176*, 1573–1579. [[CrossRef](#)]
83. Elshani, B.; Kotori, V.; Daci, A. Role of omega-3 polyunsaturated fatty acids in gestational diabetes, maternal and fetal insights: Current use and future directions. *J. Matern.-Fetal Neonatal Med.* **2019**, *34*, 124–136. [[CrossRef](#)] [[PubMed](#)]
84. Kiel, D.; Dodson, E.; Artal, R.; Boehmer, T.; Leet, T. Gestational Weight Gain and Pregnancy Outcomes in Obese Women How Much Is Enough? *Obstet. Gynecol.* **2007**, *110*, 752–758. [[CrossRef](#)] [[PubMed](#)]
85. Sun, Y.; Shen, Z.; Zhan, Y. Effects of pre-pregnancy body mass index and gestational weight gain on maternal and infant complications. *BMC Pregnancy Childbirth* **2020**, *20*, 390. [[CrossRef](#)] [[PubMed](#)]
86. Bouter, K.E.; Van Raalte, D.H.; Groen, A.K.; Nieuwdorp, M. Role of the Gut Microbiome in the Pathogenesis of Obesity and Obesity-Related Metabolic Dysfunction. *Gastroenterology* **2017**, *152*, 1671–1678. [[CrossRef](#)] [[PubMed](#)]
87. Crusell, M.K.W.; Hansen, T.H.; Nielsen, T.S.; Allin, K.H.; Rühlemann, M.C.; Damm, P.; Vestergaard, H.; Rørbye, C.; Jørgensen, N.R.; Christiansen, O.B.; et al. Gestational diabetes is associated with change in the gut microbiota composition in third trimester of pregnancy and postpartum. *Microbiome* **2018**, *6*, 89. [[CrossRef](#)] [[PubMed](#)]
88. Pellonperä, O.; Mokkala, K.; Houuttu, N.; Vahlberg, T.; Koivuniemi, E.; Tertti, K.; Rönnemaa, T.; Laitinen, K. Efficacy of Fish Oil and/or Probiotic Intervention on the Incidence of Gestational Diabetes Mellitus in an At-Risk Group of Overweight and Obese Women: A Randomized, Placebo-Controlled, Double-Blind Clinical Trial. *Diabetes Care* **2019**, *42*, 1009–1017. [[CrossRef](#)]
89. Callaway, L.K.; McIntyre, H.D.; Barrett, H.L.; Foxcroft, K.; Tremellen, A.; Lingwood, B.E.; Tobin, J.M.; Wilkinson, S.A.; Kothari, A.; Morrison, M.; et al. Probiotics for the Prevention of Gestational Diabetes Mellitus in Overweight and Obese Women: Findings From the SPRING Double-blind Randomized Controlled Trial. *Diabetes Care* **2019**, *42*, dc182248. [[CrossRef](#)]
90. Pan, J.; Pan, Q.; Chen, Y.; Zhang, H.; Zheng, X. Efficacy of probiotic supplement for gestational diabetes mellitus: A systematic review and meta-analysis. *J. Matern.-Fetal Neonatal Med.* **2017**, *32*, 317–323. [[CrossRef](#)]
91. Kijmanawat, A.; Panburana, P.; Reutrakul, S.; Tangshewinsirikul, C. Effects of probiotic supplements on insulin resistance in gestational diabetes mellitus: A double-blind randomized controlled trial. *J. Diabetes Investig.* **2018**, *10*, 163–170. [[CrossRef](#)]
92. Asemi, Z.; Samimi, M.; Tabassi, Z.; Esmailzadeh, A. The effect of DASH diet on pregnancy outcomes in gestational diabetes: A randomized controlled clinical trial. *Eur. J. Clin. Nutr.* **2014**, *68*, 490–495. [[CrossRef](#)]
93. Sarathi, V.; Kolly, A.; Chaithanya, H.B.; Dwarakanath, C.S. Effect of soya based protein rich diet on glycaemic parameters and thyroid function tests in women with gestational diabetes mellitus. *Rom. J. Diabetes Nutr. Metab. Dis.* **2016**, *23*, 201–208. [[CrossRef](#)]
94. Guardo, F.D.; Curro, J.M.; Valenti, G.; Rossetti, P.; Di Gregorio, L.M.; Conway, F.; Chiofalo, B.; Garzon, S.; Bruni, S.; Rizzo, G. Non-pharmacological management of gestational diabetes: The role of myo-inositol. *J. Complement. Integr. Med.* **2019**, *17*. [[CrossRef](#)] [[PubMed](#)]
95. Brown, J.; Crawford, T.J.; Alsweiler, J.; Crowther, C.A. Dietary supplementation with myo-inositol in women during pregnancy for treating gestational diabetes. *Cochrane Database Syst. Rev.* **2016**, *9*, CD012048. [[CrossRef](#)] [[PubMed](#)]
96. Brown, J.; Ceysens, G.; Boulvain, M. Exercise for pregnant women with gestational diabetes for improving maternal and fetal outcomes. *Cochrane Database Syst. Rev.* **2017**, *6*, CD012202. [[CrossRef](#)] [[PubMed](#)]

97. American College of Obstetricians and Gynecologists. ACOG Committee Opinion Number 650, December 2015. Physical Activity and Exercise During Pregnancy and the Postpartum Period. Available online: <http://www.acog.org/Resources-And-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Physical-Activity-and-Exercise-During-Pregnancy-and-the-Postpartum-Period> (accessed on 1 December 2015).
98. Aune, D.; Sen, A.; Henriksen, T.; Saugstad, O.D.; Tonstad, S. Physical activity and the risk of gestational diabetes mellitus: A systemic review and dose-response meta-analysis of epidemiological studies. *Eur. J. Epidemiol.* **2016**, *31*, 967–997. [[CrossRef](#)]
99. Nasiri-Amiri, F.; Sepidarkish, M.; Shirvani, M.A.; Habibipour, P.; Tabari, N.S. The effect of exercise on the prevention of gestational diabetes in obese and overweight pregnant women: A systemic review and meta-analysis. *Diabetol. Metab. Syndr.* **2019**, *11*, 72. [[CrossRef](#)]
100. Ming, W.K.; Ding, W.; Zhang, C.J.; Zhong, L.; Long, Y.; Li, Z.; Sun, C.; Wu, Y.; Chen, H.; Chen, H.; et al. The effect of exercise during pregnancy on gestational diabetes mellitus in normal-weight women: A systemic review and meta-analysis. *BMC Pregnancy Childbirth* **2018**, *18*, 440. [[CrossRef](#)]
101. Harrison, A.L.; Shields, N.; Taylor, N.; Frawley, H.C. Exercise improves glycaemic control in women diagnosed with gestational diabetes mellitus: A systematic review. *J. Physiother.* **2016**, *62*, 188–196. [[CrossRef](#)]
102. Nguyen, L.; Chan, S.Y.; Teo, A.K. Metformin from mother to unborn child—are there unwarranted effects? *EbioMedicine* **2018**, *35*, 394–404. [[CrossRef](#)]
103. Blum, A.K. Insulin Use in Pregnancy: An Update. *Diabetes Spectr.* **2016**, *29*, 92–97. [[CrossRef](#)]
104. Hod, M.; Mathiesen, E.R.; Jovanović, L.; McCance, D.R.; Ivanisevic, M.; Duran-Garcia, S.; Brøndsted, L.; Nazeri, A.; Damm, P. A randomized trial comparing perinatal outcomes using insulin detemir or neutral protamine Hagedorn in type 1 diabetes. *J. Matern.-Fetal Neonatal Med.* **2014**, *27*, 7–13. [[CrossRef](#)] [[PubMed](#)]
105. Mathiesen, E.R.; Andersen, H.; Kring, S.I.; Damm, P. Design and rationale of a large, international, prospective cohort study to evaluate the occurrence of malformations and perinatal/neonatal death using insulin detemir in pregnant women with diabetes in comparison with other long-acting insulins. *BMC Pregnancy Childbirth* **2017**, *17*, 38. [[CrossRef](#)] [[PubMed](#)]
106. Hod, M.; Damm, P.; Kaaja, R.; Visser, G.H.; Dunne, F.; Demidova, I.; Pade Hansen, A.-S.; Mersebach, H. Fetal and perinatal outcomes in type 1 diabetes pregnancy: A randomized study comparing insulin aspart with human insulin in 322 subjects. *Am. J. Obstet. Gynecol.* **2007**, *198*, 186–e1. [[CrossRef](#)] [[PubMed](#)]
107. Pantalone, K.M.; Failman, C.; Olansky, L. Insulin Glargine Use During Pregnancy. *Endocr. Pract.* **2011**, *17*, 448–455. [[CrossRef](#)] [[PubMed](#)]
108. Brown, J.; Grzeskowiak, L.; Williamson, K.; Downie, M.R.; Crowther, C.A. Insulin for the treatment of women with gestational diabetes. *Cochrane Database Syst. Rev.* **2017**, *11*, CD012037. [[CrossRef](#)] [[PubMed](#)]
109. Norgaard, K.; Sukumar, N.; Raffnson, S.B.; Saravanan, P. Efficacy and safety of rapid-acting insulin analogs in special populations with type 1 diabetes or gestational diabetes: Systemic review and meta-analysis. *Diabetes Ther.* **2018**, *9*, 891–917. [[CrossRef](#)]
110. Mukerji, G.; Feig, D.S. Advances in Oral Anti-Diabetes Drugs in Pregnancy. *Pract. Man. Diabetes Pregnancy* **2017**, *15*, 189–201. [[CrossRef](#)]
111. Lee, H.Y.; Wei, D.; Loeken, M.R. Lack of metformin effect on mouse embryo AMPK activity: Implications for metformin treatment during pregnancy. *Diabetes/Metab. Res. Rev.* **2014**, *30*, 23–30. [[CrossRef](#)]
112. Rowan, J.A.; Hague, W.M.; Gao, W.; Battin, M.R.; Moore, M.P. Metformin versus insulin for the treatment of gestational diabetes. *N. Engl. J. Med.* **2008**, *358*, 2003–2015. [[CrossRef](#)]
113. Rowan, J.; Rush, C.E.; Plank, L.D.; Lu, J.; Obolonkin, V.; Coat, S.; Hague, W.M. Metformin in gestational diabetes: The offspring follow-up (MiG TOFU): Body composition and metabolic outcomes at 7–9 years of age. *BMJ Open Diabetes Res. Care* **2018**, *6*, e000456. [[CrossRef](#)]
114. Zeng, Y.; Li, M.; Chen, Y.; Jiannig, L.; Wang, S.; Mo, X.; Li, B. The use of glyburide in the management of gestational diabetes mellitus: A meta-analysis. *Adv. Med. Sci.* **2014**, *59*, 95–101. [[CrossRef](#)] [[PubMed](#)]
115. Yu, D.-Q.; Xu, G.-X.; Teng, X.-Y.; Xu, J.-W.; Tang, L.-F.; Feng, C.; Rao, J.-P.; Jin, M.; Wang, L.-Q. Glycemic control and neonatal outcomes in women with gestational diabetes mellitus treated using glyburide, metformin, or insulin: A pairwise and network meta-analysis. *BMC Endocr. Disord.* **2021**, *21*, 199. [[CrossRef](#)] [[PubMed](#)]
116. Schneeberger, C.; Kazemier, B.M.; Geerlings, S.E. Asymptomatic bacteriuria and urinary tract infections in special patient groups: Women with diabetes mellitus and pregnant women. *Curr. Opin. Infect. Dis.* **2014**, *27*, 108–114. [[CrossRef](#)] [[PubMed](#)]
117. White, W.B.; Cannon, C.P.; Heller, S.R.; Nissen, S.E.; Bergenstal, R.M.; Bakris, G.L.; Perez, A.T.; Fleck, P.R.; Mehta, C.R.; Kupfer, S.; et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N. Engl. J. Med.* **2013**, *369*, 1327–1335. [[CrossRef](#)] [[PubMed](#)]
118. Marso, S.P.; Daniels, G.H.; Brown-Frandsen, K.; Kristensen, P.; Mann, J.F.E.; Nauck, M.A.; Nissen, S.E.; Pocock, S.; Poulter, N.R.; Ravn, L.S.; et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N. Engl. J. Med.* **2016**, *375*, 311–322. [[CrossRef](#)] [[PubMed](#)]
119. Chen, C.; Huang, Y.; Dong, G.; Zeng, Y.; Zhou, Z. The effect of dipeptidyl peptidase-4 inhibitor and glucagon-like peptide-1 receptor agonist in gestational diabetes mellitus: A systematic review. *Gynecol. Endocrinol.* **2020**, *36*, 375–380. [[CrossRef](#)]
120. Simmons, D.; Nema, J.; Parton, C.; Vizza, L.; Robertson, A.; Rajagopal, R.; Ussher, J.; Perz, J. The treatment of booking gestational diabetes mellitus (TOBOGM) pilot randomised controlled trial. *BMC Pregnancy Childbirth* **2018**, *18*, 151. [[CrossRef](#)]