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REVIEW

Gestational diabetes mellitus: an updated overview

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Abstract The clinical and public health relevance of gestational diabetes mellitus (GDM) is widely debated due to its increasing incidence, the resulting negative economic impact, and the potential for severe GDM-related pregnancy complications. Also, effective prevention strategies in this area are still lacking, and controversies exist regarding diagnosis and management of this form of diabetes. Different diagnostic criteria are currently adopted worldwide, while recommendations for diet, physical activity, healthy weight, and use of oral hypoglycemic drugs are not always uniform. In the present review, we provide an update of current insights on clinical aspects of GDM, by discussing the more controversial issues.

Keywords Gestational diabetes mellitus · Peripheral insulin resistance · Pancreatic β-cell dysfunction · Universal screening · Selective screening

Introduction

Gestational diabetes mellitus (GDM), the most common metabolic disorder of pregnancy, is defined as "the type of glucose intolerance that develops in the second and third trimester of pregnancy, resulting in hyperglycemia of variable severity" [1]. As a consequence of increasing obesity prevalence and advancing maternal age, the incidence of GDM is increasing worldwide, constituting a major economic burden for the public health care system [1, 2]. In fact, GDM confers an increased risk for severe pregnancy complications for both mother and child, including cesarean delivery, shoulder dystocia, macrosomia, and neonatal hypoglycemia [3]. In addition, women with GDM have a substantially increased risk to develop type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) after pregnancy [4, 5], while their offspring are at increased risk for the development of obesity and T2DM early in life [6]. Therefore, strategies addressed to optimize management of GDM are mandatory. These should include effective prevention, and proper diagnosis and treatment.

Epidemiology

As reported before, the prevalence of GDM in a population of pregnant women usually reflects the prevalence of T2DM in that population [2]. As a consequence of the unfavorable global shift toward a western lifestyle of overeating and sedentary living, a pandemic diffusion of T2DM is occurring today throughout the entire world [1], which contributes importantly to the dramatic increase in the incidence of GDM rate [2]. Nevertheless, the exact worldwide prevalence of GDM remains unknown, as systematically synthesized data on this are lacking [2], and the only available information is that GDM prevalence is largely variable among countries and even among regions within a country, ranging from 0.6 to 15%, depending on the race/ethnicity and socio-economic status of individuals [2]. Aboriginal in Australia, Middle Eastern (Syrian, Lebanese, Iraqi, Iranian, or Afghanistan) and Pacific Islanders women are the major at risk-groups for GDM [2]. Recent epidemiological

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studies indicate that the prevalence of GDM is over 9% in the United States of America [7], whereas native Americans, Asians, Hispanics, and African-American women are at higher risk for GDM than non-Hispanic white women [7]. In Asian countries, GDM ranges from 3.0 to 21.2% [7], while in India, GDM is more common in women living in urban areas than in those living in rural areas [7]. On the other hand, recent evidence indicates that the prevalence of GDM may vary according to seasons, with higher values during the summer season than in the winter season [8].

Also, it must be considered that a further push toward the increasing prevalence of GDM is derived from the adoption of tighter diagnostic criteria for GDM, which have been recently introduced by the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) [9]. These new criteria recommend a universal 75-g oral glucose tolerance test (OGTT) screening for pregnant women, which employs more rigorous cut-offs of glucose level. The adoption of these newer criteria resulted in a considerable increase in GDM prevalence [10], reaching 27.5% in Southern Italy [11] and 41.9% in North Indian women [12].

Etiology

There are significant changes in maternal metabolism during the course of pregnancy [13]. During the first phase, these changes are mostly anabolic changes with the progressive increase of maternal adipose tissue, whereas in late pregnancy the catabolic changes prevail with increased lipolysis and an increase in glycemia, insulinemia, postprandial fatty acid levels, and decreased maternal fat stores. These alterations are induced, at least in part, by hormones and other mediators secreted by placenta, which facilitate the occurrence of a physiological condition of peripheral insulin resistance [13] that can be worsen by both advanced maternal age and pre-pregnancy overweight (Table 1), two conditions that have become typical in Western countries. The effects of pregnancy on glucose homeostasis are generally alleviated following delivery of the placenta, so that glycemia returns to normal levels within 6–12 weeks postpartum. The negative influence of pre-pregnancy overweight or obesity on GDM is underlined by the observation that physical activity, both before pregnancy and in early pregnancy, by ameliorating body weight loss and insulin resistance, is inversely associated with the risk of GDM [14]. When insulin secretion does not increase adequately to counterbalance the insulin-resistant state of the second half of pregnancy, maternal glucose intolerance appears and may contribute to the increased risk for developing GDM (Fig. 1) [13]. Thus, β-cell secretory impairment represents a critical defect in the pathophysiology of GDM.

Table 1 Risk factors for GDM

Modifiable factors	Unmodifiable factors
High pre-pregnant BMI	Advanced maternal age
Poor dietary quality	Personal history of GDM or prediabetes
Sedentary lifestyle	Family history of diabetes
Vitamin D deficiency	Ethnicity (Asian, Hispanic, Native American and African American)
PCOS	Maternal history of low birth weight
High total bile acid in the first trimester	Low stature
	Twin pregnancy
	Genetic susceptibility

PCOS polycystic ovary syndrome

The defect in β-cell function is not specific to pregnancy as it may exist before and after pregnancy, and in most cases is progressive, conferring a high risk of overt diabetes after the index pregnancy [15]. Thus, as already pointed out, GDM could be seen as an early stage of T2DM which appears during pregnancy [15].

To date, many evidences exist pointing to a link between genetics and GDM (Fig. 1). Among these: the fact that GDM recurs in at least 30% of women with a previous history of GDM [16]; the growing body of epidemiological research showing some ethnic-group differences in the risk for GDM, independently of the living place [7]; and the identification of numerous genetic variants in many genes that are involved in insulin secretion and insulin resistance, as well as in lipid and glucose metabolism, which have been associated with GDM risk [17]. In particular, about this latter point, many of the variants identified are associated with increased risk for T2DM [18], thereby supporting the notion for a continuum between GDM and T2DM. Table 2 shows examples of gene variants whose association with susceptibility to GDM has been reported in several meta-analysis studies, in which most of the genes involved were found to be related to the regulation of insulin secretion and peripheral insulin resistance. Because of these pathophysiological similarities between GDM and T2DM, metabolomic studies of GDM have been recently designed to identify biomarkers of diseases [25]. Although further studies are necessary in larger, ethnically different populations [25, 26], many metabolites that are known to be implicated in impaired glucose homeostasis or are specific for inflammation and altered redox-balance have been associated with GDM [27–29].

On the other hand, studies have been reported emphasizing the relevance of epigenetic modification of placental DNA in GDM, independently of other well-known risk factors (Fig. 1) [30]. Furthermore, increasing evidence indicates that dysregulation of immune and inflammatory activation may play a role

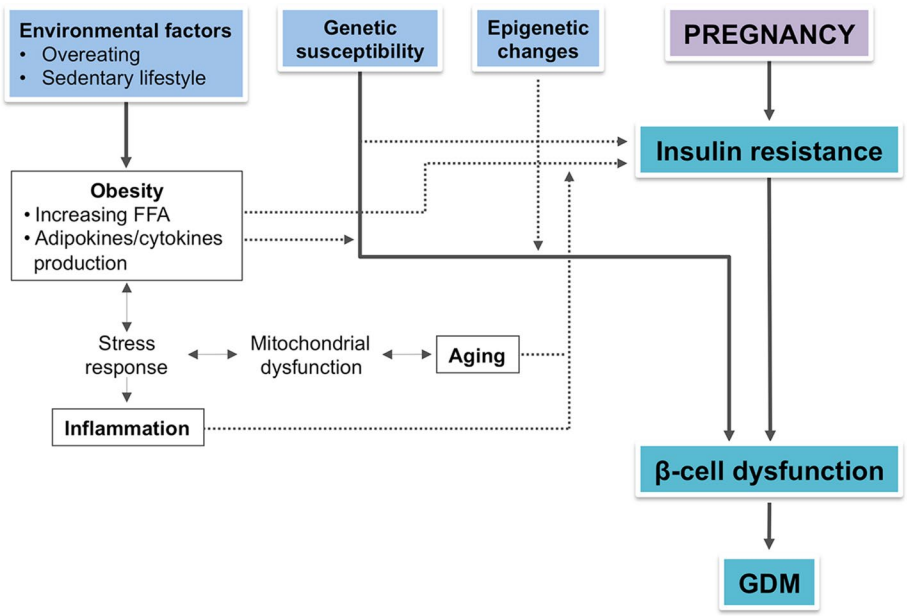

Fig. 1 Pathogenic factors underlying GDM. As woman gains weight and reduces physical activity during pregnancy, peripheral insulin resistance develops and glucose intolerance may occur. This in turn undermines pancreatic β-cell function and may contribute to the increased risk of GDM

Table 2 Gene variants associated with GDM

Gene	Variant	Function	References
Transcription factor 7-like 2 (*TCF7L2*)	*rs7903146* *rs5030952* *rs7903146* *rs12255372* *rs4506565*	β-Cell function	[17, 19–21]
Melatonin receptor 1B (*MTNR1B*)	*rs10830963* *rs1387153*	β-Cell function	[17, 19, 22]
Glucokinase (*GCK*)	*rs1799884*	β-Cell function	[17]
Potassium inwardly rectifying channel, subfamily J, member 11 (*KCNJ11*)	*rs5219*	β-Cell function	[17]
CDK5 regulatory subunit associated protein 1-like 1 (*CDKAL1*)	*rs7754840*	β-Cell function	[17, 22]
Insulin-like growth factor 2 mRNA-binding protein 2 (*IGF2BP2*)	*rs4402960*	β-Cell function	[17]
Insulin receptor substrate 1 (*IRS1*)	*rs1801278*	Insulin action	[17, 19]
Peroxisome proliferator-activated receptor gamma (*PPARG*)	*rs1801282*	Insulin action	[19]
Hexokinase domain containing 1 (*HKDC1*)	*rs10762264* *rs4746822*	β-Cell function?	[23]
C–C motif chemokine ligand 2 (*CCL2*)	*rs1024611* *rs4586*	β-Cell function?	[24]

in the pathogenesis of GDM, as an impairment of antioxidant defense and reduction in molecular oxygen have been reported in women with GDM (Fig. 1) [31]. There is also the increasing use of endocrine disrupting chemicals, which may be a risk factor for GDM [32].

GDM and long-term health consequences

GDM not only increases the risk for maternal and fetal complications during pregnancy, but it also raises the risk of long term complications in both mother and offspring.

Once GDM is diagnosed, the risk for both T2DM and CVD in the mother increases. In particular, the risk of T2DM increases by sevenfold, with a cumulative incidence of 60% at 10 years from GDM diagnosis [4]. The rate of T2DM increases rapidly during the first months after delivery, continuing to increase thereafter without signs of a plateau [33]. Also, women with prior GDM have a significantly higher rate of obesity, hypertension and metabolic syndrome, together with altered levels of circulating inflammatory markers, all of which are risk factors for CVD [34, 35]. While several protocols have been proposed in the postpartum follow-up phase to counteract and prevent T2DM [36], further studies are needed to identify and validate biomarkers for CVD, and to determine whether lifestyle and drug interventions can reduce the risk for CVD in these women [35].

As said above, long-term complications related to GDM may also affect the offspring of GDM mothers. In this regard, children of GDM women are more often overweight or obese [37, 38], show greater central adiposity [38–40], high blood pressure [40, 41], insulin resistance and impaired glucose tolerance and dyslipidemia [41], thereby indicating that the offspring of GDM pregnancies are at increased risk of developing T2DM and CVD later in life [40, 41], thus emphasizing the importance of a more rigorous management and prevention of GDM.

Diagnosis

Prompt identification of pregnant women with GDM is a critical need, as an early appropriate treatment can reduce both mild and severe pregnancy-related complications. Neverthless, there is no universal uniformity on issues concerning screening time, diagnostic test and the appropriate glycemic cut-offs that should be used to define GDM. Until 2010, the most widely employed criteria for GDM included those of the World Health Organization (WHO) and the American Diabetes Association (ADA). In particular, to predict GDM, a 100-g OGTT was recommended by ADA in early pregnancy (14–18 weeks of gestation) for high risk women and in late pregnancy (28–32 weeks) for women at medium risk, following the Carpenter and Coustan cut-offs [42]. These ADA criteria were later revised following the demonstration, by the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, that increasing levels of maternal glycemia were linearly associated with maternal and fetal adverse events [3], so that new, more rigorous criteria, have been elaborated by the International Association Diabetes Pregnancy Study Groups (IADPSG) [9], which recommend fasting plasma glucose (FPG), glycosylated hemoglobin (HbA1c), or random plasma glucose in all women at the first prenatal visit. The revised guidelines state that a diagnosis of GDM is made when the results, not diagnostic of overt diabetes, indicate a FPG ≥92 mg/dL; on the contrary, if FPG is <92 mg/dL, a 2-h 75-g OGTT should be performed at 24–28 weeks' gestation (Table 3). Gestational glycemic cut-off values during OGTT are lower compared to previous guidelines [42], and only one abnormal value of glycemia during OGTT is sufficient to make diagnosis of GDM (Tables 3, 4). Given this, it is not surprising that IADPSG criteria drastically increased the number of GDM cases, compared to previously adopted criteria [10].

These recommendations have been adopted by the ADA as well as the WHO [1, 43] and the American Association of Clinical Endocrinologists (AACE) [44] (Table 3). Instead, the Canadian Diabetes Association (CDA) recommends that all women be screened with a 1-h glucose measurement after a 50-g oral glucose load between 24 and 28 week's gestation, followed by the 2-h 75-g OGTT only if the threshold has been surpassed (Table 3) [45]. This two-step approach, commonly used in USA, is supported by the American College of Obstetricians and Gynecologists (ACOG) [46], and recommended by the NIH consensus development conference (Table 3) [47]. On the other hand, selective screening based on individual risk assessment has been proposed by several international medical societies (Table 3) [47–50]. Therefore, up to date, a variety of different criteria are routinely used worldwide to diagnose GDM, with disparity among and within countries, mainly due to the need to reconcile better health care quality for pregnant women and their newborns with public finances. In this respect, adoption of the IADPSG's recommendations has led to an increase in the diagnosis of GDM [10], which has profoundly impacted on the health care system. It has been calculated that the overall cost of care for a woman with GDM is ~35% greater than for a woman without GDM [51]. Overall, the one-step approach should be preferred because of its simplicity in execution with more patient adherence, its accuracy in diagnosis of GDM, and also its closeness to international consensus [52]. Alternatively, to contain the costs, selective screening could be performed only in women at risk for GDM (i.e. women who are overweight or obese, women of advanced maternal age, women with previous GDM or macrosomic infant, women of high-risk ethnic groups or those with a family history of diabetes among first-degree relatives), although studies have been able to show that selective screening would miss a significant proportion of cases of GDM with minimal cost saving [11, 53, 54]. The International Diabetes Federation (IDF) gives some attention to this aspect by suggesting that selective screening should be considered only in particular epidemiological and clinical conditions, and local cost-effectiveness [55].

Table 3 Current protocols for the diagnosis of GDM

	Step 1						Step 2						
	Women	Time	Test	Fasting	1 h after	2 h after	Women	Time	Test	Fasting	1 h after	2 h after	3 h after
ADA [1], AACE [30] IADPSG [9], WHO [29]	All	24–28 weeks	75gr OGTT[a]	92 mg/dL (5.1 mmol/L)	≥180 mg/dL (≥10.0 mmol/L)	153 mg/dL (8.5 mmol/L)	–	–	–	–	–	–	–
ACOG [32]	All		50 gr OCGT	Not required	≥130–140	Not required	Positive women	24–28 weeks	100gr OGTT[b]	≥95 mg/dL (5.3 mmol/L)	≥180 mg/dL (≥10.0 mmol/L)	155 mg/dL (8.6 mmol/L)	≥140 mg/dL (7.8 mmol/L)
DIPSI [44]	All	First visit	75gr OGTT[c]	Not required	Not required	≥140 mg/dL (7.8 mmol/L)	–	24–28 weeks	75gr OGTT[c]	Not required	Not required	≥140 mg/dL (7.8 mmol/L)	Not required
CDA [59] (preferred)	All	24–28 weeks	50 gr OCGT	Not required	≥140 mg/dL (≥7.8 mmol/L)	Not required	Positive women	24–28 weeks	75gr OGTT[b]	≥95 mg/dL (≥5.3 mmol/L)	≥191 mg/dL (≥10.6 mmol/L)	≥162 mg/dL (≥9.0 mmol/L)	Not required
CDA [59] (alternative)	All	24–28 weeks	75gr OGTT[a]	92 mg/dL (5.1 mmol/L)	≥180 mg/dL (≥10.0 mmol/L)	153 mg/dL (8.5 mmol/L)	–	–	–	–	–	–	–
NICE [34]	At high risk[a]	As soon as possible	75gr OGTT[a]	≥101 mg/dL (≥5.6 mmol/L)	Not required	≥140 mg/dL (≥7.8 mmol/L)	Step 1 negative and at risk women[b]	24–28 weeks	75gr OGTT[a]	≥101 mg/dL (≥5.6 mmol/L)	Not required	≥140 mg/dL (≥7.8 mmol/L)	Not required
ADIPS [adips.org/]	At high risk[a]	As soon as possible	75gr OGTT[a]	92 mg/dL (5.1 mmol/L)	≥180 mg/dL (≥10.0 mmol/L)	153 mg/dL (8.5 mmol/L)	Step 1 negative and at risk women[b]	24–28 weeks	75gr OGTT[a]	92 mg/dL (5.1 mmol/L)	≥180 mg/dL (≥10.0 mmol/L)	153 mg/dL (8.5 mmol/L)	92 mg/dL (5.1 mmol/L)
Italian Minister [36]	At high risk[a]	14–16 weeks	75gr OGTT[a]	92 mg/dL (5.1 mmol/L)	≥180 mg/dL (≥10.0 mmol/L)	153 mg/dL (8.5 mmol/L)	Step 1 negative and at risk women[b]	24–28 weeks	75gr OGTT[a]	92 mg/dL (5.1 mmol/L)	≥180 mg/dL (≥10.0 mmol/L)	153 mg/dL (8.5 mmol/L)	Not required

ADA, American Diabetes Association; AACE, American Association of Clinical Endocrinologists; IADPSG, International Association of the Diabetes and Pregnancy Study Groups

WHO World Health Organization, *ACOG* American Congress of Obstetricians and Gynecologists, *DIPSI* Diabetes in Pregnancy Study Group India, *CDA* Canadian Diabetes Association, *NICE* National Institute for health and Clinical Excellence, *ADIPS* Australasian Diabetes in Pregnancy Society

[a]One value is sufficient for diagnosis; *OGTT* oral glucose tolerance test, *OCGT* oral glucose challenge test

[b]Two or more values are required for diagnosis

[c]Irrespective to last meal

Table 4 Glycemic targets for GDM women

Society	Fasting	1 h after starting a meal	2 h after starting a meal
ADA [1]	90–99 mg/dL (5.0–5.5 mmol/L)	<140 mg/dL (<7.8 mmol/L)	<120–127 mg/dL (<6.7–7.1 mmol/L)
NICE [34]	63 and 106 mg/dL (3.5 and 5.9 mmol/L)	<140 mg/dL (<7.8 mmol/L)	
CDA [59]	95 mg/dL (<5.3 mmol/L)	<140 mg/dL (<7.8 mmol/L)	<120 mg/dL (<6.7 mmol/L)
ADIPS [*adips.org/*]	≤90 mg/dL (≤5.0 mmol/L)	≤133 mg/dL (≤7.4 mmol/L)	≤120 mg/dL (≤6.7 mmol/L)

ADA American Diabetes Association, *NICE* National Institute for health and Clinical Excellence, *CDA* Canadian Diabetes Association, *ADIPS* Australasian Diabetes in Pregnancy Society

Additionally, doubts have emerged concerning the threeshold values indicated by the IADPSG to define internationally accepted criteria for the diagnosis of GDM [56, 57]. In fact, the HAPO study, on which the IADPSG criteria are largely based, examined mainly Caucasian women, and findings may not apply to all populations. As a consequence of this, the Indian health care system continues to adopt the Diabetes in Pregnancy Study Group India (DIPSI) guidelines that recommend universal screening twice during pregnancy by following the one step 2-h 75-g OGTT, irrespective of the last meal timings (Table 3) [58]. However, challenging data have been reported on the cost-effectiveness of this approach compared to IADPSG [59]. In addition, although several studies confirmed that IADPSG criteria allow to identify more at-risk women, the major efficacy of these criteria in identifying pregnancies at risk for severe adverse outcomes is still controversial, compared to other guidelines [60, 61], while 25% of pregnant women could be reclassified in view of the poor reproducibility of OGTT [47].

Hence, although the IADPSG criteria is the only outcome-based criteria, some authors suggest a combined strategy that would consider the ethnic and regional characteristics of women with GDM, and the different resources available [56, 57, 61]. In this context, by adopting the OGTT threesholds recommended by IADPSG, we recently proposed the new Capula's index that increases the accuracy of selective screening by reducing both the number of potential false negatives and the number of women to be screened [62], thereby reducing the impact of GDM on pregnancy and on health care costs. Based on universal predictors of GDM and pregnancy complications, Capula's index allows a better correlation with the risk for maternal and neonatal adverse events [62].

Treatment

Pregnant women with untreated GDM have a greater risk of developing many adverse maternal, fetal and neonatal outcomes [63]. Also, a strong association between maternal glucose concentrations and perinatal complications has been reported in the HAPO study, in women with milder forms of GDM, at glucose levels below those usually considered diagnostic of GDM. Thus, early and efficacious treatment of these women is decisive to reduce perinatal and obstetrical complications [64, 65].

Most GDM women can be effectively managed with a programme of lifestyle intervention comprising dietary counseling and enhanced physical activity, together with self-monitoring of blood glucose [63], that is essential for verifying the effectiveness of treatment and reduce risk of complications. Although no randomised trial has been conducted to define the optimal treatment targets, a substantial uniformity exists on the importance of self-monitoring blood glucose (Table 3). Current general guidelines, in this regard, recommend to assess postprandial glucose levels at 1- and 2-h (Table 3), given that several studies have demonstrated that treatment decisions based on these parameters resulted in fewer complications [66], thus suggesting that postprandial glucose excursion is of major importance in pregnant women with less elevated HbA1c levels [67].

Appropriate nutrition therapy in GDM women becomes effective to meet the maternal and fetal nutritional needs, and to achieve and maintain glycemic control, which is essential to improve pregnancy outcomes, thereby resulting in cost savings for more intensive medical care, including insulin treatment and other medications. This aspect is of particular relevance in the light of the recent increase in the prevalence of GDM. General guidelines, in this respect, emphasize the choice of nutrients that will promote proper weight gain and euglycemia without ketonuria, and moderate calorie restriction for obese pregnants [63]. Based on the observation that elevated postprandial glucose concentrations are often associated with adverse pregnancy outcomes in GDM [66], diet therapy for GDM has been historically based on carbohydrate restriction in order to blunt postprandial hyperglycemia [63]. Nevertheless, as underlined elsewhere [68, 69], a minimum of 175 g carbohydrate/day should be provided to avoid nutritional deficiencies and ketosis, which can lead to negative consequences for the neonate. However, although larger-controlled randomized prospective studies are needed to define the better nutritional intervention in GDM, recent evidences in this

direction indicate that diets containing greater amounts of complex carbohydrate and fiber and lower amounts in glycemic index carbohydrates and saturated fat can be effective in blunting postprandial glucose excursions and in improving maternal insulin resistance and fetal fat accumulation [70].

Similarly to what occurs in the case of T2DM, with which GDM shares the same pathogenetic mechanisms, sedentary lifestyle is a risk factor for GDM, whereas regular physical activity can help reduce this risk [71]. The beneficial effect of exercise is mainly explained by the increase in insulin sensitivity that commonly occurs from exercise and its beneficial impact on body weight. Although specific guidelines on exercise prescription (the type, frequency and intensity of exercise) are lacking, some practical recommendations are made concerning physical activity in GDM women as an initial step in combination with diet [63]. In particular, a minimum of 30 min of moderate exercise per day is recommended for normal pregnancy, taking into account that preferable activities are those that avoid excessive and inappropriate abdominal muscle contraction [63]. If these measures do not ensure optimal glycemic control, subcutaneous insulin injection therapy must be considered. As insulin does not cross the placental barrier, it is considered harmless to the foetus. Nevertheless, as already reported [72], insulin therapy has many disadvantages, including the initial fear and anxiety and the need for education and skills in injection and dose adjustment, as well as the risk of hypoglycemia and more weight gain.

In the last years, many studies have investigated the safety and effectiveness of oral hypoglycemic drugs in the treatment of GDM. Recently, results of a large randomized controlled trial demonstrated no significant increase in perinatal complications among women with GDM who were randomly treated with metformin, as compared with GDM women who were treated with insulin [73]. Accordingly, both CDA and the National Institute for health and Clinical Excellence (NICE) recommend metformin as an option for the treatment of GDM [45, 74], although, caution should be used given the ability of metformin to cross the placenta and the lack of long-term follow-up data from both mother and child. Also, metformin has not yet been approved for GDM treatment in all countries.

Glyburide (glibenclamide) is a sulfonylurea largely investigated in pregnant women with GDM. Safety and effectiveness of glyburide in GDM were recognized and confirmed [75, 76]. According to more recent studies, however, glyburide is inferior to either insulin or metformin and therefore should not be employed for treating women with GDM if insulin or metformin is available [77].

The importance of vitamin D in GDM has been raised in recent studies showing a relation between hypovitaminosis D and altered glucose homeostasis during pregnancy [78]. However, if from one side there is evidence that the administration of vitamin D can ameliorate insulin resistance and glucose tolerance by acting on pancreatic β-cells and attenuating insulin resistance-associated systemic inflammation [79], on the other hand further randomized studies are necessary to see whether vitamin D supplementation effectively improves glycemic control in women with GDM.

Prevention

Based on the above information underlining the adverse impact of GDM on pregnancy and on health care system, approaches aimed at preventing or minimize GDM are mandatory. As overweight and obesity are strong predictors of GDM [80], while diet and exercise are effective in preventing and controlling the disease, most of the studies undertaken so far on this issue have investigated the role of these interventions in the prevention of GDM [81]. However, no significant effect of diet or combined diet and exercise was found in trials enrolling women with no defined risk factors for GDM [81]. In overweight and obese pregnant women, only one trial indicated a reduction of GDM risk [82], while another trial revealed the reduction of macrosomia incidence in the absence of effects on GDM risk and gestational weight gain [83]. In a recent European multicentre, randomised controlled trial, enrolling consecutive pregnant women with a BMI $\geq$29 kg/m^2, it was demonstrated that a healthy eating intervention combined with physical exercise resulted in less gestational weight gain with no impact, however, on reducing fasting plasma glucose [84]. In contrast with these findings, the effectiveness of physical activity before and in early pregnancy for the prevention of GDM has been proven in a recent meta-analysis [14], and supported by a recent randomized controlled trial in a Chinese population [85]. Certainly, the heterogeneity of the studies examined can account for much of this disparity, so that no definitive conclusions can be made and more trials with larger populations and longer follow-up periods are needed [81].

Metformin decreases the incidence of T2DM in adults with impaired glucose homeostasis [86], as well as it reduces the incidence of T2DM in women with previous GDM [87]. However, no specific effect of metformin on the incidence of GDM has been observed so far [88], except for women with polycystic ovary syndrome (PCOS), a condition of insulin resistance among women of reproductive age. In a prospective cohort study of women with PCOS, metformin use before conception was associated with a reduced risk of developing GDM and pre-eclampsia [89]. Neverthless, this was not confirmed in another trial, in which metformin was initiated during pregnancy and not in the preconception period [90].

Instead, promising results in this direction have come from use of nutritional supplements and probiotic products [81]. In particular, trials were carried out to analyze the effect of myoinositol, an insulin sensitizer belonging to the Vitamin B complex group, in women with a single defined risk factor for GDM [91]. Results from these studies are encouraging as a significant reduction was observed in the incidence of GDM, macrosomia, and neonatal hypoglycaemia. Even here, caution has to be used as all clinical trials had a limited sample size and were performed solely in Italy. Thus, trials in other populations with larger sample size are necessary to confirm and extend these results [92]. Similar considerations can also be applied to the use of probiotic supplements, which are a combination of micro-organisms designed to modify maternal gut microbiota. There is some evidence that probiotics may ameliorate insulin resistance in the pre- and post-partum periods, and decrease the woman's risk of developing GDM especially when combined with a diet intervention program [93].

An emerging issue in this area relates to bariatric surgery and its effectiveness in the management of obesity and associated metabolic conditions [94]. Several studies have been reported concerning the effect of weight loss surgery in preventing GDM and its related negative outcomes in obese women [95]. Results from these studies support the association of bariatric surgery with reduced risk of weight gain during pregnancy, GDM, and gestational hypertension [95, 96], even though this positive impact is counterbalanced by the occurrence of surgical complications and nutritional and vitamin deficiencies during and after pregnancy [95]. Also, controversial data exist about the risks and benefits of bariatric surgery in the obstetric population [95, 96], so that further and larger prospective studies are necessary before bariatric surgery's efficacy in GDM and GDM-related complications can be established.

Conclusions

Similarly to obesity and T2DM, the management of women with GDM is a major emerging challenge for the health care system around the world, which is magnified by the lack of globally shared guidelines for GDM. Thus, further efforts are necessary to identify effective prevention strategies that would facilitate clinical management of GDM and would likely improve health and cost-effectiveness.

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Compliance with ethical standards

Conflict of interest We declare no competing interests.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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