Supplement Article

Maternal nutrition: opportunities in the prevention of gestational diabetes

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Gestational diabetes mellitus (GDM) is currently defined as glucose intolerance that is of variable severity with onset or first recognition during pregnancy. The Hyperglycemia and Adverse Pregnancy Outcome Study, including 25 000 nondiabetic pregnant women in 15 centers across the world, reported that an average of 17.8% of pregnancies are affected by GDM and its frequency can be as high as 25.5% in some countries, based on the International Association of Diabetes and Pregnancy Study Groups criteria. Nevertheless, true global prevalence estimates of GDM are currently lacking due to the high level of heterogeneity in screening approaches, diagnostic criteria, and differences in the characteristics of the populations that were studied. The presence of systemic high blood glucose levels in pregnancy results in an adverse intrauterine environment, which has been shown to have a negative impact on short- and long-term health outcomes for both the mother and her offspring, including increased risks for the infant to develop obesity and for both mother and child to develop type 2 diabetes mellitus later in life. Epigenetic mechanisms that are directly influenced by environmental factors, including nutrition, may play a key role in shaping these future health risks and may be part of this vicious cycle. This article reviews the burden of GDM and the current evidence that supports maternal nutritional interventions as a promising strategy to break the cycle by addressing risk factors associated with GDM.

INTRODUCTION

Diabetes mellitus is one of the most prevalent noncommunicable diseases worldwide, affecting over 370 million people and resulting in 4.8 million deaths annually.[1] The current trend indicates that the age of onset of type 2 diabetes mellitus (T2DM) is rapidly decreasing, with a growing proportion of young people becoming affected. Among women of reproductive age, an estimated 28 million have T2DM. Of great concern is the fact that the majority of these cases (80%) are concentrated in low- and middle-income countries.[1]

Pregnancy is associated with a certain degree of insulin resistance and hyperinsulinemia in order to ensure appropriate nutrient supply to the fetus; however, in some women this progresses to gestational diabetes mellitus (GDM).[2] According to the World Health Organization, hyperglycemia that is first detected during pregnancy is classified as GDM.[3] Systematically synthesized data on global prevalence estimates of GDM are lacking, particularly among developing countries. It is also challenging to directly compare the GDM burden across countries or regions, considering the high level of heterogeneity in

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screening approaches, diagnostic criteria, and differences in the characteristics of the populations that were studied. A recent review reports wide variations in the prevalence estimates of GDM, with prevalence as high as 25.1% in some countries, based on the new International Association of Diabetes and Pregnancy Study Groups criteria.[4] Although a variety of genetic and environmental factors may contribute to an individual's propensity for developing GDM, maternal obesity and nutritional deficiencies are key contributors, making GDM one of the most commonly encountered clinical complications of pregnancy.[5] It is becoming increasingly clear that GDM, like obesity and other metabolic diseases, is a result of suboptimal lifestyle and nutrition.[6] Not surprisingly, the proportion of GDM in a given population parallels that of T2DM. African women, Hispanic women, and some populations of Asian women are at greater risk of developing GDM compared to Caucasian women.[7–11]

GDM not only has a tremendous impact on the health of the mother, it also has long-lasting consequences on the health of the child. Pregnant women with GDM and their unborn children have a higher risk of complications, including pre-eclampsia, preterm birth, miscarriage, macrosomia, and intrauterine growth retardation.[1] Women with GDM are also at risk of postpartum complications, including the development of overt diabetes and GDM in subsequent pregnancies.[12] The effects on the children born to women with GDM are of utmost concern due to the increased risk of a range of short- and long-term morbidities. In the postnatal period and depending on the severity of the maternal hyperglycemia, these can range from high birth weight, serum C-peptide, and newborn percent body fat above the 90th percentile, neonatal hypoglycemia, macrosomia to shoulder dystocia and trauma during delivery, hyperbilirubinemia, respiratory distress syndrome, hypocalcemia, polycythemia, and hypertrophic cardiomyopathy.[13] In later childhood and adulthood, these individuals are at risk of T2DM, obesity, and metabolic syndrome,[14] an observation that supports the tenets of the developmental origins of health and disease hypothesis. The adverse intrauterine environment created by GDM is hypothesized to result in epigenetic changes that predispose the offspring to developing metabolic disease later in life. In turn, these traits are transmitted to the following generation, thereby perpetuating the vicious cycle of metabolic diseases.[15] A recent US study estimated that the economic burden associated with adult diabetes, gestational diabetes, and prediabetes exceeded $322 billion in 2012 (combining excess medical costs and reduced productivity).[16] This national estimate is 48% higher than the $218 billion estimate for 2007.[16,17] These findings underscore the importance of the economic burden of GDM, and in low- to middle-income countries where GDM is more prevalent, the burden is likely to be proportionally even higher.

Against this backdrop of rising GDM prevalence and adverse outcomes for the following generations, nutritional interventions are moving to the forefront as effective strategies to address the lifestyle and dietary issues contributing to the development of GDM. This article reviews the burden of GDM and the current evidence that supports maternal nutritional interventions for reducing the risk of developing GDM, and thereby addressing related noncommunicable diseases such as obesity.

GESTATIONAL DIABETES DIAGNOSIS

Moderate levels of peripheral insulin resistance and hyperinsulinemia are normal occurrences during pregnancy and are accompanied by increasing levels of the hormones prolactin, lactogen, and estrogen.[18] These processes ensure a sufficient nutrient supply to the fetus and prevent low maternal blood glucose levels by counteracting the actions of insulin.[18] Insulin secretion increases early on in pregnancy, although insulin sensitivity may or may not change during this time. By mid-pregnancy, and until the end of the third trimester, insulin sensitivity begins to decline.[2] A normal response by the maternal pancreatic islets is to augment insulin production. In GDM, the balance between the increased insulin resistance and maternal insulin production is disrupted, and the pancreas cannot meet the increased insulin requirements of pregnancy.[2]

Until recent international efforts to standardize diagnosis and screening of GDM,[3] there was a complete lack of consensus that led to significant differences in the reported prevalence, which posed a challenge for the application of research findings obtained using different criteria.[15] Currently, the World Health Organization formally recognizes the criteria defined by the International Association of Diabetes and Pregnancy Study Groups (Table 1). Since the presence of only 1 of these criteria is sufficient to reach a diagnosis, the overall prevalence of GDM will increase significantly from the current estimates, if these criteria are applied.[12]

RISK FACTORS FOR GESTATIONAL DIABETES

There are several risk factors associated with developing GDM. A genetic component is likely to be involved, with some populations being more susceptible than others. There is evidence associating variants in several key genes with the pathogenesis of insulin resistance during pregnancy, including the adipokines,[19,20] the prolactin receptor,[21] and the melatonin receptor.[22,23] Not surprisingly, all of these genes are known to play a

Table 1 **Most widely accepted diagnostic criteria for diabetes in pregnancy and GDM[3,16]**

Diagnosis	Criteria
Diabetes (WHO)	Recorded at any time during the course of pregnancy; one or more of the following criteria:
	Fasting plasma glucose levels ≥7 mmol/L (126 mg/dL)
	2-h OGTT values ≥11.1 mmol/L (200 mg/dL) after a 75 g oral glucose load
	Random plasma glucose levels ≥11.1 mmol/L (200 mg/dL)
GDM (WHO and IADPSG)	When 1 or more of the following results are recorded during routine testing between 24 and 28 wks of pregnancy or at any other time during the course of pregnancy:
	Fasting plasma glucose levels 5.1–6.9 mmol/L (92–125 mg/dL)
	1-h OGTT values ≥10.0 mmol/L (180 mg/dL) after a 75 g oral glucose load
	2-h OGTT values between 8.5 and 11.0 mmol/L (153–199 mg/dL) after a 75 g oral glucose load

Abbreviations: GDM, gestational diabetes mellitus; IADPSG, International Association of Diabetes and Pregnancy Study Groups; OGTT, oral glucose tolerance test; WHO, World Health Organization.

role in the regulation of glucose homeostasis and metabolism. Polycystic ovarian syndrome, another medical condition that results in metabolic and hormonal dysfunction, also increases the risk of developing GDM.[24] Finally, the high concordance of T2DM in monozygotic twins and evidence from family studies further support the importance of genetic background in an individual's propensity for developing GDM.[25–28]

However, several lines of evidence point to the complex and multifactorial nature of this health condition. First, there are no defining genetic factors that can be exemplified as the hallmark of GDM; thus, lifestyle factors in early pregnancy, including nutritional factors, are moving to the forefront as key forces that drive the pathogenesis of GDM.[29,30] Indeed, among the strongest risk factors is prepregnancy obesity (defined as body mass index [BMI] $>30\,kg/m^2$).[28,31] Other risk factors are excessive gestational weight gain (GWG),[32] advanced maternal age,[33] and a previous pregnancy with GDM.[34] The presence of these factors can propel an individual toward developing GDM, particularly in the case of a genetic predisposition.[35–37] Not surprisingly, there is significant overlap between GDM and T2DM, in terms of risk factors (elevated BMI, family history, ethnic background),[38] genetic variants,[27] and pathogenesis (peripheral insulin resistance alongside pancreatic B-cell insufficiency).[27,36] Women with GDM are also at high risk of developing T2DM after pregnancy (Table 2), suggesting that GDM is an environmental stressor in its own right and can drive the progression toward a diabetic state in some individuals.[39] Altogether, the striking connections between GDM and T2DM highlight the importance of the gestation period as a pivotal window of time that can tip the balance in favor of obesity and other noncommunicable diseases in the mother and the offspring.

CONSEQUENCES OF GESTATIONAL DIABETES FOR OFFSPRING

Although there is no evidence for increased congenital abnormalities in the offspring of women with GDM, poor glycemic control has been shown to increase the incidence of stillbirths.[40] Women with type 1 or 2 diabetes mellitus are more likely to experience miscarriages compared to their healthy counterparts.[28] In response to high maternal glucose levels, the fetus increases insulin secretion. Due to the growth-promoting properties of insulin, a large proportion of these fetuses are macrosomic,[41] or large for gestational age (LGA).[13] Macrosomia, defined as a weight of more than 4 kg at birth or a weight above the 95th percentile for the gestational age, is the most frequently seen effect of GDM in neonates.[42] Due to their higher innate insulin levels, infants born to mothers with GDM frequently experience marked hypoglycemia after birth when they are no longer in a high-glucose environment, necessitating additional medical care.[43] Compared to the children of mothers without GDM, the offspring of women diagnosed with this condition have increased rates of cognitive and motor abnormalities, including attention deficit hyperactivity disorder, learning difficulties, and autism.[35]

Among all the consequences of GDM, the most insidious effects are on the long-term health of the child. There is now substantial data highlighting the importance of prenatal and early postnatal nutrition in determining an individual's susceptibility to noncommunicable diseases in adulthood.[30,37] Historical evidence for this comes from studies in wartime birth cohorts that demonstrated that individuals exposed to undernutrition in utero were at increased risk of metabolic, cardiovascular, and cognitive disorders.[44–46] Recent studies have shown that the offspring of obese women with GDM are not only LGA, they also have higher adipose tissue mass[13] and a greater incidence of T2DM in later childhood (Table 2).[14,47,48] GWG during pregnancy is emerging as a critical predictor of childhood obesity (Table 2), foreshadowing not only body weight but also antioxidant status, immunity, and metabolic function in the offspring.[49]

Studies in animal models and in humans have shown that the maternal nutritional environment exerts its effects on the phenotype of the offspring by

Table 2 **Risks of subsequent outcomes in mother and offspring exposed to prepregnancy overweight and/or obesity, or GDM, or the combination of both conditions**

Outcome	OR or RR (95% CI) vs women without the condition(s)		
	Overweight and/or obesity	GDM	Overweight and/or obesity and GDM
Postpartum T2DM (mother)[43]	3.89 (2.53–6.00)	7.43 (4.79–11.51)	8.66 (2.27–32.94)
High birth weight (>90th percentile)[17]	1.73 (1.50–2.00)	2.19 (1.93–2.47)	3.62 (3.04–4.32)
High neonatal adiposity (>90th percentile)[17]	1.65 (1.41–1.93)	1.98 (1.73–2.27)	3.69 (3.06–4.44)
Childhood obesity (girls with BMI >85th percentile at age 6–8 yrs)[92]	1.71 (1.08–2.72)	3.56 (1.28–9.92)	5.6 (1.70–18.2)
T2DM later in life (offspring)[51]	2.5 (1.3–5.0)	3.9 (1.1–14.5)	19.2 (6.1–60.8)

Abbreviations: CI, confidence interval; GDM, gestational diabetes mellitus; OR, odds ratio; RR, relative risk; T2DM, type 2 diabetes mellitus.

influencing the methylation pattern of the fetal DNA or histones.[37] Studies in rats have revealed that vitamin D deficiency in pregnant dams affects insulin action in the offspring, and this is thought to occur via methylation of the gene encoding nuclear factor κB inhibitor α.[50] Other animal studies have shown that periconceptional supplementation (or deprivation) of choline, folic acid, methionine, or vitamin B^{12} can affect the DNA methylation patterns and phenotype of the offspring.[51] In humans, low maternal vitamin D status has been shown to affect bone mineral content in the offspring via methylation of the retinoid-X receptor-alpha, an essential cofactor in facilitating the actions of vitamin D.[52] Individuals from the Dutch famine birth cohort had, even after 60 years, less deoxyribonucleic acid (DNA) methylation of the Insulin-like growth factor 2 (*IGF2*) gene compared to their gender-matched siblings who were not exposed to the famine in utero.[53] This association reinforces the hypothesis that early development is a critical period for establishing and maintaining the epigenetic signature.[53] Under certain circumstances, epigenetic modifications in key genes can predispose the offspring's propensity for developing obesity and type 2 diabetes.[54] Maternal lifestyle factors such as overfeeding and obesity can act in concert with the genetic background to control the expression of central regulators of the metabolic phenotype of the offspring.

INTERVENTIONS AIMING AT THE PREVENTION OF GESTATIONAL DIABETES

Currently, the key factor in the management of GDM is strict glycemic control, including frequent self-monitoring of blood glucose levels throughout the day.[2] Target levels are 5.0–5.3 mmol/L or lower (90–95 mg/dL) for fasting glucose, 7.8 mmol/L or lower (140 mg/dL) 1 hour after a meal, or 6.7 or lower mmol/L (120 mg/dL) 2 hours after a meal.[2] Dietary control is normally the first line of treatment and generally involves limiting carbohydrate intake to between 35% and 45% of total calories, distributed in 3 small- to moderate-sized meals and 2–4 snacks.[55] If nutritional control is not successful in the first 2 weeks, pharmacotherapy is initiated. To date, many guidelines using blood glucose-lowering pharmacological therapy exist, and depending on the country, different oral hypoglycemic agents, specifically metformin or glyburide, and/or insulin and insulin analogs, are used.[56]

Although the monitoring of glucose levels is essential in women with GDM, additional primary care interventions are needed that target the fundamental causes of GDM. Of note, weight loss is not recommended during pregnancy (even for obese women), underscoring the importance of addressing body weight and nutritional status before conception and between pregnancies.[57] In this sense, metformin has been used as a prevention strategy against pregnancy complications such as GDM, typically among women with specific conditions such as polycystic ovarian syndrome, whereby a 10-fold reduction in GDM and a reduction in insulin resistance and insulin secretion were demonstrated.[58] However, among nondiabetic pregnant obese women, daily administration of 3 g of metformin from the first trimester until delivery did not result in a decrease in GDM incidence, although significant beneficial effects were observed on gestational weight gain and incidence of pre-eclampsia.[59] Positioning metformin as a prevention strategy could be challenging because studies have reported increased incidence of side effects as it can easily cross the placenta. Hence, it is important to understand its effect on fetal insulin sensitivity, hepatic gluconeogenesis, and long-term fetal programming.[60] Given the key role played by nutrition in defining the long-term consequences of GDM on women and their offspring, nutrition appears to be the prime target for addressing prevention of GDM.

The current approaches in GDM prevention are focused on interventions such as diet, physical activity, or even a combined approach of dietary modification with lifestyle and behavioral changes. More recently, interventions using nutritional supplements incorporating bioactive agents with positive effects on insulin

sensitivity, such as myo-inositol and probiotics, have shown promising results.[61] In addition, some micronutrients have been proposed as potentially modulating glucose tolerance in pregnancy. The results are from observational studies showing associations between low levels of specific micronutrients (e.g., vitamin D, iron, selenium) and glucose tolerance.[62–65]

Following is an overview of the efficacy and/or effectiveness of diet, physical activity, combined diet and physical activity, and nutrient-based interventions in the prevention of GDM and the impact on other key related pregnancy and infant outcomes based on recent systematic reviews and meta-analyses (Table 3). The maternal outcomes include: GWG, hypertensive disorders of pregnancy (gestational hypertension and/or pre-eclampsia and/or eclampsia), and Caesarian section (C-section). The infant outcomes are: small for gestational age, LGA, macrosomia, birth weight, preterm birth, and neonatal hypoglycemia.

Diet-based interventions, including dietary counseling

Various dietary interventions including diet counseling, low glycemic index (GI) diet, energy restriction diet (~33% reduction in caloric intake), and low carbohydrate content diet (carbohydrate intake lower than 45% of energy) have been studied in relation to pregnancy and infant outcomes. Dietary counseling vs standard prenatal care was shown to reduce the risk for GDM and to significantly lower GWG; however, no benefits on any of the infant outcomes were reported.[66] The interventions included in this systematic review were diverse, randomized control trials (RCTs), were of poor quality, and the inclusion criteria were heterogeneous. Dietary interventions specifically targeted at preventing excessive GWG or reducing pregnancy-related complications such as low-fat, low-carbohydrate, or low-energy diets, as well as dietary education about healthy eating and nutritional advice on how to stay within the GWG guidelines, significantly reduced GWG and the incidence of C-section. However, the results need to be interpreted with caution since no common standard was applied in these studies for the calculations of GWG.[67] Comparisons for efficacy have also been performed for low-moderate GI vs high-moderate GI diets, low-GI vs high-fiber moderate-GI diets, energy-restricted vs no energy restriction diets, low- vs high-carbohydrate diets, high-monounsaturated fats vs high-carbohydrate diets, and diets with 20 gram fiber per day vs 80 gram fiber per day among pregnant women with GDM or pre-existing diabetes mellitus, but not among women who were healthy or at risk of GDM.[68] None of these diets showed any beneficial effect on either pregnancy or infant outcomes, and it is impossible to recommend any particular types of dietary advice that would be most suitable for women with GDM considering that data were only available from single studies, thereby limiting the possibility to make any reliable conclusions for comparing the efficacy or effectiveness of different dietary interventions. A striking example is the recommendation of carbohydrate restriction (40% of calories) to blunt postprandial glucose excursions, whereby, women are substituting fat for carbohydrates. But there is an increasing recognition that replacing dietary carbohydrates with fat may be detrimental to maternal insulin resistance and may result in excess fetal fat accretion.[60] A study of the CHOICE diet, which is rather high in carbohydrates (60% complex carbohydrates and 25% fat), found that it was able to maintain a 24-hour glucose area under the curve well below targets. The postprandial free fatty acids were 20% lower compared to the conventional low-carbohydrate/higher-fat diet (40% carbohydrates and 45% fat). Such a diet strategy may have important implications for preventing infant complications such as macrosomia[69]; however, further research is needed to confirm this hypothesis.

Physical activity-based interventions

Meta-analyses of RCTs show a 28%–31%[70,71] reduction in risk for GDM and also a mean difference of approximately 1.1 kg in GWG between the intervention and control groups[71,72] using structured physical exercise programs of low to moderate intensity and including an aerobic component. In addition, when the exercise program is conducted throughout pregnancy, the reduction in risk of GDM appears to be even greater (36%).[71] Interestingly, structured and supervised prenatal exercises have also shown a 31% reduction in the odds of having an LGA baby, with no simultaneous risk of having an small for gestational age baby.[72] However, a Cochrane systematic review of 5 randomized or cluster randomized trials did not show any beneficial effect of supervised exercise sessions or exercise advice compared to standard antenatal care among pregnant women and their infants.[73] All the above findings have to be interpreted in the light of important limitations such as using different diagnostic criteria for GDM assessment, failure to assess physical activity that was performed outside the program, lack of standardized interventions, high heterogeneity in the data for reduction of GWG due to variations in exercise duration, volume, and adherence between trials, differences in study design and intervention content, the overall limited number of studies, and very low adherence to intervention protocols in some studies. In addition, 1 of the biggest challenges in any physical activity intervention is identifying and addressing barriers that may reduce adherence.

Table 3 **Diet-, physical activity-, combined diet and physical activity-, and nutrient-based interventions on prevention of GDM and their impacts on related pregnancy and infant outcomes, based on recent systematic reviews and meta-analyses**

Reference	Study design	Study population	Description of intervention	Effect of intervention on pregnancy outcomes	Effect of intervention on infant outcomes	Limitations and comments
Dietary interventions including dietary advice						
Tanentsapf et al. (2011)[67]	Systematic review of 13 RCTs and quasi-RCTs	Healthy normal weight or overweight and obese women with a singleton pregnancy	Intervention: any dietary intervention aiming at preventing excessive GWG or reducing pregnancy-related complications, including low-fat, low-carbohydrate, or low-energy diets, dietary education about healthy eating, and nutritional advice on how to stay within the GWG guidelines. Control: standard of care	Reduction in GWG (10 RCTs, n = 1434) (WMD = −1.92 kg; 95% CI: −3.65, −0.19). Reduction in C-section incidence (6 RCTs, n = 609) (RR = 0.75; 95% CI: 0.60–0.94). No significant difference on pre-eclampsia and GDM	No significant difference on birth weight, preterm birth, and macrosomia LGA, SGA, and neonatal hypoglycemia not reported	Comparison of GWG is of concern as no common standard for calculations was applied: some studies calculated GWG based on self-reported prepregnancy weight, some did not report the means of data collection when calculating GWG, and in some the final weight was taken at the day of delivery while in some at the last clinic visit prior to delivery. There was a lack of statistical power to capture small intervention effects on some clinical outcomes. There was a high risk of bias in 7 out of 13 studies
Physical activity interventions						
Sanabria-Martinez et al. (2015)[71]	Meta-analysis of 13 RCTs	Healthy pregnant women who were sedentary or had low levels of physical activity	Intervention: structured physical exercise programs of low to moderate intensity. Control: standard prenatal care with no physical exercise received	Decreased risk of GDM (8 RCTs, n = 2501) (RR = 0.69; 95% CI: 0.52–0.91). Decreased GWG (13 RCTs, n = 2873) (WMD = −1.14 kg; 95% CI: − 1.50, −0.78). Outcomes on pre-eclampsia and C-section not reported	Infant outcomes including birth weight, LGA, SGA, macrosomia, and neonatal hypoglycemia not reported	Studies were of medium to low quality with a high risk of bias. Physical activity performed outside the program was not assessed. Different diagnostic criteria for GDM were used in each of the studies. Pregnant women participating in these studies were volunteers and may have had a higher level

(continued)

Table 3 **Continued**

Reference	Study design	Study population	Description of intervention	Effect of intervention on pregnancy outcomes	Effect of intervention on infant outcomes	Limitations and comments
						of adherence than the general population
Wiebe et al. (2015)[72]	Meta-analysis of 28 RCTs	Pregnant women who were at low risk for GDM and women without specific pregnancy complications	Intervention: structured and supervised prenatal exercises. Control: standard care	Reduced GWG (15 RCTs, n = 5322) (WMD = −1.1 kg; 95% CI: −1.61, −0.62). Reduced odds of cesarean delivery (17 RCTs, n = 5322) (OR = 0.81; 95% CI: 0.68–0.96). Outcomes on preeclampsia and GDM not reported	32% reduction in the odds of having an LGA baby (15 RCTs, n = 5322) (OR = 0.68; 95% CI: 0.54–0.87). No simultaneous risk of having an SGA baby (9 RCTs, n = 5322) (OR = 1.10; 95% CI: 0.73–1.66). Reduction in newborn birth weight (26 RCTs, n = 5215) (WMD, −28.35 g; 95% CI, −56.04, −0.66 g) Outcomes on macrosomia and neonatal hypoglycemia not reported	High heterogeneity was reported for reduction in GWG that could be explained by variability in exercise duration, volume, and adherence between trials
Russo et al. (2015)[70]	Meta-analysis of 10 RCTs	Pregnant women without GDM at baseline	Intervention: exercise interventions that included an aerobic component Control: standard care	28% reduced risk of GDM (10 RCTs, n = 3401) (RR = 0.72; 95% CI: 9%–42%) Outcomes on GWG, preeclampsia, and C-section not reported	Infant outcomes on LGA, macrosomia, birth weight, SGA, and neonatal hypoglycemia not reported	There was wide variation in adherence to an intervention protocol, and in some studies it was as low as 16%. There was a high loss to follow-up of 33%, reducing power, and potentially introducing differential bias. Differences in study design and intervention

(continued)

Table 3 **Continued**

Reference	Study design	Study population	Description of intervention	Effect of intervention on pregnancy outcomes	Effect of intervention on infant outcomes	Limitations and comments
						content, overall limited number of studies, and general null findings in individual studies limit the ability to detect the effectiveness of specific interventions and their application to practice. Variable GDM diagnosis criteria was used between studies. Possible underestimation of the association between participation in an exercise intervention and risk of GDM due to an inconsistent classification/misclassification of GDM
Han et al. (2012)[73]	Cochrane systematic review of 5 RCTs or cluster RCTs	Pregnant women, regardless of age, gestation, parity, or plurality, all without pre-existing type 1 or T2DM	Intervention: supervised exercise sessions and exercise advice. Control: standard antenatal care with normal daily activities	No significant difference in GDM incidence, GWG, C-section, or pre-eclampsia	No significant differences in birth weight, macrosomia, and SGA LGA and neonatal hypoglycemia not reported	No trial reported on the primary outcomes for the review of LGA. Many of the trials were of small sample size. All the trials were conducted in high-income countries
Combined diet and physical activity interventions						
Bain et al. (2015)[75]	Cochrane systematic review of 13 RCTs and cluster-RCTs	Pregnant women, regardless of age, gestation, parity, or plurality	Intervention: combined diet (dietary advice, including low-GI and high-fiber diet) and exercise interventions (exercise advice, providing exercise sessions). Control: standard care	A trend observed toward reduced GWG (8 RCTs, n = 2707) (MD = −0.76 kg; 95% CI: −1.55, 0.03). No significant differences in the risk of GDM, pre-eclampsia, or C-section	Reduced risk of preterm birth (5 RCTs, n = 2713) (RR = 0.71; 95% CI: 0.55–0.93). No significant difference in risk of LGA, macrosomia, birth weight, SGA, or	Huge variations in the quality of trials, characteristics of the interventions, populations assessed, reporting of outcomes, and outcome definitions (GDM diagnosis criteria) between trials Majority of studies were conducted in western population and therefore have limited applicability

(continued)

Table 3 **Continued**

Reference	Study design	Study population	Description of intervention	Effect of intervention on pregnancy outcomes	Effect of intervention on infant outcomes	Limitations and comments
					neonatal hypoglycemia	in low- and middle-income countries
Muktabhant et al. (2015)[76]	Cochrane systematic review of 49 RCTs	Pregnant women of any BMI (normal BMI or overweight and/or obese women)	Intervention: any diet or exercise, or both, intervention (e.g., healthy eating plan, low glycemic diet, exercise intervention, health education, lifestyle counseling). Control: standard or routine care	Reduced risk of excessive GWG by 20% (24 RCTs, n = 7096) (RR = 0.80; 95% CI: 0.73–0.87). GWG not analyzed due to substantial heterogeneity No significant difference in C-section and preeclampsia GDM not reported	No significant difference in preterm birth, macrosomia, LGA, birth weight, SGA, or neonatal hypoglycemia	Most studies included were carried out in developed countries, and it is not clear whether these results are widely applicable to lower-income settings. Interventions were often multifaceted and were quite heterogeneous in approach, e.g., in the timing, duration, intensity, content, and delivery
Thangaratinam et al. (2012)[74]	Systematic review of 40 RCTs and 48 non-randomized and observational studies	Healthy pregnant women or those who were overweight or obese	Intervention: combination of dietary and physical activity, interventions with the potential to influence weight change in pregnant women (dietary interventions: balanced diet of carbohydrates, fat,and protein, moderate energy and caloric restriction based on individual requirements, low-fat and low-cholesterol diets and the use of a food diary for monitoring; physical activity interventions: weight-bearing sessions, walking for 30 min a day, and low-intensity resistance training or behavioral counseling intervention).Control:standard of care	Reduction in GWG in the intervention group of 0.97 kg (30 RCTs, n = 4503) (95% CI: −1.60, −0.34 kg) The largest reduction in GWG was observed in the dietary intervention studies, with an MD of −3.36 kg (95% CI: −4.73, −1.99 kg), followed by mixed approach, with an MD of −0.57 kg (95% CI: −1.60, 0.65 kg). Significant reduction in the incidence of preeclampsia of 26% (10 RCT, n = 3072) (RR = 0.74; 95% CI: 0.59– 0.92) No significant differences in incidence of C-section or GDM	Reduction in the mean birth weight (28 RCTs, n = 4573) of 0.07 kg (95% CI: −0.14, −0.01 kg) Reduced risk of LGA (12 RCTs, n = 3021) (RR, 0.73; 95% CI: 0.54–0.99) No differences in SGA, preterm birth, or neonatal hypoglycemia	There was a lack of detail about the components of the intervention in some of the included studies, gestational age at which the intervention was commenced, its frequency, and the method of delivery. The estimate of reduced GWG with diet was associated with significant heterogeneity

(continued)

Table 3 **Continued**

Reference	Study design	Study population	Description of intervention	Effect of intervention on pregnancy outcomes	Effect of intervention on infant outcomes	Limitations and comments
Han et al. (2012)[77]	Cochrane systematic review of 4 RCTs and cluster RCTs	Pregnant women with hyperglycemia not meeting diagnostic criteria for GDM and T2DM regardless of gestation, age, parity, or plurality	Intervention: any type of dietary advice (standard or individualized) with metabolic monitoring. Control: standard antenatal care	No significant difference in C-section, GWG, insulin, or oral hypoglycemic agent required for hyperglycemia or pre-eclampsia Outcome on GDM not reported	Reduced risk for macrosomia (3 RCTs, n = 438) (RR = 0.38; 95% CI: 0.19–0.74) Reduced risk for LGA (3 RCTs, n = 438) (RR = 0.37; 95% CI: 0.20–0.66) Significantly lower birth weight (4 RCTs, n = 521) (MD = −117.33 g; 95% CI: −198.72, −35.94) No significant differences in preterm birth, SGA, or neonatal hypoglycemia	Results of this review were based on 4 small RCTs with moderate to high risk of bias without follow-up outcomes for both women and their babies. Due to the inconsistencies existing in GDM diagnosis around the world, the review included women with various degrees of pregnancy hyperglycemia and may have included some women who could be diagnosed with GDM when using a different set of criteria
Interventions with specific nutrients Long-chain polyunsaturated fatty acids (LC-PUFA)						
Szajewska et al. (2006)[82]	Meta-analysis of 6 RCTs	Healthy pregnant women	Intervention: LCPUFA supplementation, but not the precursor essential FAs such as α-linolenic and linoleic acids. Control: placebo or no supplementation	Greater duration of pregnancy (6 RCTs, n = 1278) (WMD = 1.57 d; 95% CI: 0.35–2.78 d). No significant difference in the rate of pre-eclampsia, C-section, or GDM Outcomes on GWG not reported	No significant difference in birth weight and preterm birth. Macrosomia, LGA, SGA, and neonatal hypoglycemia not reported	Small sample sizes as well as limited number of trials. There was marked variability among study populations and baseline n-3 LCPUFA status, and the interventions tested that may have decreased the sensitivity for detecting possible effects
Zhou et al. (2012)[81]	Double-blind, multicenter RCT	Healthy women with singleton pregnancies		No significant difference in the relative risk for	Increased macrosomia in the	Fish oil supplements in the trial began in the

(continued)

Table 3 **Continued**

Reference	Study design	Study population	Description of intervention	Effect of intervention on pregnancy outcomes	Effect of intervention on infant outcomes	Limitations and comments
		and ≤21 wks of gestation at study entry	Intervention: 3500 mg capsules of DHA-rich fish-oil concentrate daily from trial entry to birth. Control: 3500 mg vegetable oil capsules without DHA from trial entry to birth	GDM and pre-eclampsia. Outcomes on GWG and C-section not reported	fish oil-supplemented group than in the control group (16.3% vs 12.8%). No significant difference in birth weight, SGA, LGA, or neonatal hypoglycemia Preterm birth not reported	second half of pregnancy, so not known whether supplementation initiated earlier could lower the risk of GDM or pre-eclampsia
Vitamin D						
De Regil et al. (2016)[83]	Cochrane systematic review of 15 RCTs, quasi-RCTs, or cluster RCTs	Pregnant women of any gestational or chronological age, parity, and number of fetuses; pregnant women with pre-existing conditions (i.e., GDM) were excluded	Intervention: daily, weekly, or monthly oral supplementation with vitamin D (D2, D3, or not specified) alone or in combination with calcium. Control: no intervention or placebo	Reduced risk of pre-eclampsia (3 RCTs, n = 1114) (RR = 0.51; 95% CI: 0.32–0.80) for vitamin D + calcium No significant differences observed for GDM and C-section incidence GWG and fasting glucose not included in the analysis	Reduced risk of preterm birth in (3 RCTs, n = 477) (RR = 0.36; 95% CI: 0.14–0.93), for vitamin D, but increased risk of preterm birth (3 RCTs, n = 798) (RR = 1.57; 95% CI: 1.02–2.43) for vitamin D + calcium. No significant difference was observed for birth weight. SGA, LGA, macrosomia, neonatal hypoglycemia, and shoulder dystocia not	Across RCT, the doses and types of vitamin D supplements, gestational age at first administration, and outcomes were very heterogeneous Heterogeneity probably due to methodological differences to assess serum 25-hydroxyvitamin D. GDM diagnosis was included in only 2 out of the 15 trials

(continued)

Table 3 **Continued**

Reference	Study design	Study population	Description of intervention	Effect of intervention on pregnancy outcomes	Effect of intervention on infant outcomes	Limitations and comments
					included in the analysis	
Perez Lopez et al. (2015)[86]	Systematic review and meta-analysis of 13 RCTs	Pregnant women of any gestational or chronologic age and parity without previous disease history	Intervention: Any dose of vitamin D_2/D_3 supplementation, alone or in combination with multivitamin, calcium, or iron. Control: a control (placebo or active)	No significant differences were observed for GDM, hypertensive disorders of pregnancy, or C-section incidence. GWG, insulin sensitivity, and fasting glucose not included in the analysis	Increased birth weight (10 RCTs, n = 1489) (mean difference = 107.60; 95% CI: 59.86–155.33). No significant difference observed for SGA LGA, macrosomia, neonatal hypoglycemia, preterm birth, and shoulder dystocia not included in the analysis	Across RCTs, the doses and types of vitamin D supplements, gestational age at first administration, and outcomes were very heterogeneous GDM diagnosis was only included in 3 out of the 13 trials
Myo-inositol						
Crawford et al. (2015)[91]	Cochrane systematic review of 4 RCTs	Healthy pregnant women at high risk of GDM, including those who were obese or had a family history of T2DM, all without pre-existing type 1 or type 2 diabetes	Intervention: 2 g of myo-inositol + 200 μg of folic acid twice a day, or 2 g of myo-inositol + 400 μg of D-chiro-inositol + 400 μg of folic acid + 10 mg of manganese once a day. Control: 200 μg of folic acid twice a day or placebo (not specified)	Reduced risk of GDM (3 RCTs, n = 502) (RR = 0.43; 95% CI: 0.29–0.64) Reduced fasting glucose (OGTT) (3 RCTs, n = 502) (mean difference = −0.20 mmol/L; 95% CI: −0.28–0.12) No significant differences were observed for hypertensive disorders of pregnancy and C-section rate, and GWG	No significant differences were observed for birth weight, macrosomia, neonatal hypoglycemia, preterm birth, or shoulder dystocia LGA not reported in any study SGA not included in the analysis	All RCTs were conducted in Italy. The trials had small sample sizes, and 2 trials were open-label
Zheng et al. (2015)[92]	Systematic review and meta-analysis of 5 RCTs	Healthy pregnant women at high risk of GDM, including those who were	Intervention: 2 g of myo-inositol + 200 μg of folic acid twice a day, or a daily dose	Reduced risk of GDM (4 RCTs, n = 444) (RR = 0.29; 95% CI: 0.19–0.44)	Reduced birth weight (3 RCTs, n = 353) (mean difference	All RCTs included were open-label and conducted in Italy. One of the trials included is a

(continued)

Table 3 **Continued**

Reference	Study design	Study population	Description of intervention	Effect of intervention on pregnancy outcomes	Effect of intervention on infant outcomes	Limitations and comments
		obese and had a family history of T2DM or who had PCOS, all diagnosed with GDM and all without pre-existing type 1 or type 2 diabetes	of 4 g of myo-inositol + 400 μg of folic acid Control: 200 μg of folic acid twice a day, or a daily dose of 400 μg of folic acid + 1.5 g of metformin	Reduced fasting glucose (OGTT) (4 RCTs, n = 444) (mean difference = −0.36 mmol/L; 95% CI: −0.51, −0.21). Hypertensive disorders of pregnancy, C-section, and GWG not included in the analysis	= −116.98 g; 95% CI: −208.87, −25.09) Reduced risk of neonatal hypoglycemia in 1 RCT, n = 73 (OR = 0.04; 95% CI: 0.00–0.68). No significant differences observed for macrosomia, preterm birth, and shoulder dystocia LGA not reported in any study SGA not included in the analysis	retrospective case–control study and may have increased the likelihood of random assignments. Inclusion criteria were heterogeneous, and there were variations in the components of the intervention. Only in the analysis of the fasting glucose outcome was 1 study with women already diagnosed with GDM included
Rogozinska et al. (2015)[61]	Systematic review and meta-analysis of 20 RCTs	Low- and high-risk women, including those with at least 1 of the following: obesity, previous history of GDM or fetal macrosomia, advanced maternal age, and family history of diabetes	Intervention: Myo-inositol (2 g of myo-inositol + 200 μg of folic acid twice a day) or diet with probiotics. Control: 200 μg of folic acid twice a day, or a daily dose of 400 μg of folic acid + 1.5 g of metformin	Reduced risk of GDM (1 RCT, n = 220) (RR = 0.40; 95% CI: 0.16–0.99) No significant differences observed for hypertensive disorders of pregnancy and C-section GWG and fasting glucose (OGTT) not included in the analysis	Reduced birth weight (1 RCT, n = 220) (mean difference = −0.51 g; 95% CI: −0.79, −0.22). No significant difference was observed for shoulder dystocia and preterm birth LGA not reported in any study SGA, macrosomia, and neonatal	Only 1 study using myo-inositol as intervention was included in this analysis. Variable definition of GDM between studies

(continued)

Table 3 **Continued**

Reference	Study design	Study population	Description of intervention	Effect of intervention on pregnancy outcomes	Effect of intervention on infant outcomes	Limitations and comments
					hypoglycemia not included in the analysis	
Probiotics						
Barrett et al. (2014)[94]	Cochrane systematic review of 1 RCT	Pregnant women not previously diagnosed with diabetes mellitus, including those with GDM in a previous pregnancy but no evidence of diabetes mellitus or GDM in the current before entering the trial	Intervention: diet + probiotics (a mix of *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* Bb12 in a dose of 10^{10} colony-forming units each + intensive dietary counseling) Control: placebo (microcrystalline cellulose and dextrose anhydrate) + intensive dietary counseling	Reduced risk of GDM (1 RCT, n = 225) (RR = 0.38; 95% CI: 0.20–0.70) No significant difference was observed for C-section Fasting glucose (OGTT), hypertensive disorders of pregnancy, and GWG not reported	Reduced birth weight (1 RCT, n = 256) (mean difference = −127.1 g; 95% CI: −320.46, 32.46) No significant difference was observed for preterm birth SGA, LGA, macrosomia, neonatal hypoglycemia, and shoulder dystocia not reported	Of 5 RCTs identified, only 1 had reported results; all other were ongoing studies
Rogozinska et al. (2015)[61]	Systematic review and meta-analysis of 20 RCTs	Low-risk and high-risk women, including those with at least 1 of the following: obesity, previous history of GDM or fetal macrosomia, advanced maternal age, and family history of diabetes	Intervention: diet + probiotics (mix of *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* Bb12 in a dose of 10^{10} colony-forming units each + intensive dietary counseling). Control: placebo + intensive dietary counseling	Reduced risk of GDM (1 RCT, n = 170) (RR = 0.40; 95% CI: 0.20–0.78) No significant difference observed for C-section. Hypertensive disorders of pregnancy not reported. Fasting glucose (OGTT) and GWG not included in the analysis	Birth weight, SGA, LGA, macrosomia, neonatal hypoglycemia, preterm birth, and shoulder dystocia not reported	Just 1 study in Finnish population was included in this analysis. Variable definitions of GDM between studies

Abbreviations: CI, confidence interval; GDM, gestational diabetes mellitus; GWG, gestational weight gain; LGA, large for gestational age; OGTT, oral glucose tolerance test; PCOS, polycystic ovarian syndrome; RCT, randomized control trial; RR, relative risk; SGA, small for gestational age.

Combined diet and physical activity-based interventions

The combination of diet- and lifestyle-based interventions appears to show a consistent reduction in GWG, although the effect estimates varied widely, with some meta-analyses showing small differences between the intervention and control groups,[74,75] others reporting a larger difference of 2.2 kg between the intervention and control groups,[66] and yet others showing a reduction in risk for excessive GWG of approximately 20%.[76] Such differences may be partly due to differences in the trials included, variations in the quality of the trials, characteristics of the interventions, populations assessed, reporting of outcomes, and outcome definitions. A combination of dietary and physical activity interventions was shown to significantly reduce the incidence of pre-eclampsia by 26% and the risk of having an LGA baby by 27% among healthy pregnant women or those who were overweight or obese compared to normal-weight women receiving standard care.[74] A Cochrane systematic review also showed that any type of dietary advice (standard or individualized) with metabolic monitoring reduced the risk of macrosomia by 62% and LGA by 63% compared to standard antenatal care among pregnant women with hyperglycemia who did not meet the diagnostic criteria for GDM and T2DM.[77] However, the result of this review was only based on 4 small RCTs with moderate to high risk of bias. The studies included women with various degrees of pregnancy hyperglycemia and may also have included some women who could be diagnosed with GDM when using a different set of criteria.

Long-chain polyunsaturated fatty acids

There is some evidence that n-3 long-chain polyunsaturated fatty acids (LCPUFA) may be beneficial in enhancing insulin action[78] and improving glucose tolerance in both animals and humans. However, epidemiologic studies examining the association between n-3 LCPUFA intake and risk of GDM have reported conflicting results,[79,80] and very few RCTs have investigated the effect of n-3 LCPUFA supplementation in pregnancy on the risk of GDM. A double-blind multicenter RCT of 3 500 mg capsules of DHA-rich fish-oil supplementation from trial entry to birth among healthy women with singleton pregnancies did not show a beneficial effect on the risk for GDM or any other relevant maternal or infant outcomes.[81] However, in this trial, fish oil supplementation began in the second half of pregnancy, and it is not known whether supplementation earlier may have had any additional benefits. A meta-analysis of 6 RCTs of LCPUFA supplementation in healthy pregnant women failed to show a beneficial effect on the risk for GDM or any other maternal or infant outcomes, other than a significant increase in the duration of pregnancy.[82] However, this analysis was based on a limited number of trials with small sample sizes, and there was a high variability among study populations, baseline n-3 LCPUFA status, and the interventions tested that may have limited the possibility to detect any beneficial effects.

Vitamin D

Maternal vitamin D deficiency in early pregnancy has been associated with increased risk for GDM.[62,63] In the most recent meta-analysis of 20 observational studies (n = 16 515), low vitamin D levels increased the risk of gestational diabetes in 45% of participants (relative risk = 1.45; 95% confidence interval [CI]: 1.15–1.83),[62] which is consistent with previous findings.[64,65] In a recent Cochrane review of vitamin D interventions including 15 RCTs, no clear difference was found for GDM,[83] but a 49% risk reduction for pre-eclampsia was observed for interventions combining vitamin D and calcium. For preterm risk, results are difficult to interpret because vitamin D supplementation appears to reduce the risk of preterm birth by 64%, but the risk increased by 57% when vitamin D and calcium were combined.[83] It is important to note that GDM was reported in 2 trials (n = 219),[84,85] while pre-eclampsia was reported in 3 trials (n = 1114). One additional recent systematic review and meta-analysis found no difference for GDM, and only 1 found an increase in birth weight (mean difference, 107.60; 95% CI: 59.86–155.33).[86] Important to consider is that most trials included were of low methodological quality, were highly heterogenous, and had inconsistent results for serum 25-hydroxyvitamin D levels, most probably due to methodological differences.[87] To generate recommendations, additional rigorous high-quality and larger randomized trials are required that evaluate the effect of vitamin D supplementation on glucose tolerance and related outcomes in pregnancy.

Other micronutrients

A recent systematic review and meta-analysis of 15 observational studies found a positive correlation between ferritin levels and GDM (relative risk = 1.53; 95% CI: 1.17–2.00).[88] The elevated ferritin may reflect elevated body iron stores, but it could also be due to inflammation as ferritin is an acute-phase reactant. Considering this, the study concluded that the results did not constitute definitive proof that dietary total iron or serum transferrin levels are related to GDM and that more

research needs to be done. Another recent systematic review and meta-analysis of 6 studies comparing the levels of selenium in pregnant women with and without GDM revealed that serum selenium concentrations were lower in women with GDM (Hedges, −1.34; 95% CI: −2.33, −0.36) and in women showing subclinical levels of glucose intolerance (Hedges, −0.85; 95% CI: −1.18, −0.52).[89] Due to the limitations of observational studies, it is still unclear whether reduced serum selenium levels are a risk factor for GDM and impaired glucose tolerance (IGT). Finally, some negative associations seem to exist for micronutrient vitamin B^{12} deficiencies[90] during pregnancy and metabolic outcomes such as insulin resistance, adiposity, and/or increased risk for GDM.

Myo-inositol

Although the evidence is still limited and based mainly on 3 small trials conducted in healthy women at high risk of developing GDM, a daily dose of 2 gram myo-inositol twice per day has been shown to reduce the risk of developing GDM by approximately 60%–70% and to have a positive effect on birth weight.[61,91,92] Most maternal and neonatal outcomes included in this review were not reported in the systematic reviews and meta-analyses available to date. One additional study in overweight (BMI, ≥25 and <30) pregnant women in Italy has been recently published[93] that shows a 67% risk reduction of GDM, which is consistent with previous findings (Table 3). Additional evidence should be generated in larger trials in diverse settings, including participants of different ethnicities and varying risk factors, to confirm these promising results.

Probiotics

The clinical trial consistently reported in the cited reviews (Table 3)[61,94] was conducted in Finland and used a double-blind design from the first trimester to the end of exclusive breastfeeding in which 2 intervention groups were compared: 1 received intensive dietary counseling promoting a healthy diet and another received the same dietary advice plus daily administration of *Lactobacillus rhamnosus* GG and *Bifidobacterium lactis* Bb12 (dosed at 10^{10} colony-forming units each).[95–97] The combination of dietary advice with the probiotic intervention reduced the rate of GDM, while dietary counseling alone had no effect compared with no intervention.[97] The risk of larger birth size in participants with GDM who received the combination therapy was also reduced.[96] Although this study used a different criterion for GDM diagnosis compared to most others, blood glucose concentrations were also significantly reduced in the probiotics-supplemented group.[96] Interestingly, the beneficial effect of probiotics appeared to extend beyond the risk of developing GDM, with the group receiving them also demonstrating reduced maternal central adiposity 6 months after delivery[95] and lower blood glucose concentrations 12 months after delivery.[97] These data suggest that this probiotic intervention independently modulates the maternal metabolic state when the diet is well balanced. More recently, a double-blind placebo-controlled trial[98] assessed the impact of a different probiotic, *Lactobacillus salivarius* UCC118, in obese pregnant women. In this study, 138 women were examined between weeks 24 and 28 of gestation with fasting glucose as the main outcome and GDM as the secondary outcome after 4 weeks of intervention. The study did not identify a benefit with regard to the maternal fasting glucose level, the metabolic profile, or pregnancy outcomes among obese women. These discrepancies could be related to differences in the length of the 2 study interventions, the probiotic strains used, or the specificity of the probiotic effects.[99] Regarding the role of probiotics in glucose tolerance modulation, probiotics have been proposed to act through 1 or more of the following mechanisms: (1) balancing the properties of gut microbiota, (2) normalizing increased intestinal permeability; and (3) controlling systemic and local low-grade inflammation.[100] More insight is expected when the results of 3 additional ongoing trials are published.[94]

CONCLUSION

The power of nutrition to influence health from one generation to the next is a fundamental concept that has transformed our understanding of health and disease. The health legacy of an individual is predetermined by a series of factors that occur long before birth and during the earliest days of life. The growing prevalence of GDM, particularly in low- and middle-income countries, is of great concern, especially with respect to its impact on the health of the next generation, the cost burden on health systems, and the loss of societal productivity. Maintaining a healthy prepregnancy body composition, diet, and lifestyle is the most effective solution in many settings, particularly in low- and middle-income countries.[6] Considering that there is a high level of controversy with regards to the dietary prevention of GDM, it is imperative to carefully design and conduct RCTs that are sufficiently powered to better elucidate the optimum diet that could help control glycemia, reduce pregnancy complications such as preeclampsia, and improve neonatal and infant outcomes such as by reducing risk for LGA or macrosomia.

Although physical activity programs appear to be an effective and safe strategy to prevent excessive GWG and to reduce the risk of GDM, well-designed trials with sufficient power to demonstrate clear effects on

both short- and long-term outcomes in pregnant women and their offspring should be conducted. These are needed because of the limitations of previous studies with regard to the types and intensities of the exercise utilized. In addition, novel strategies to improve adherence should be explored, such as the use of technology-assisted lifestyle interventions that are practical, interactive, and easily integrated in day-to-day practice. The great effort required to deliver complex interventions based on diet, or diet and physical activity, make nutritional supplements based on micronutrients and simple bioactives such as probiotics and myo-inositol a potentially convenient and cost-effective complement, or even an alternative. Nevertheless, in order to provide better recommendations and incorporate nutritional interventions as part of the clinical practice, there is a need to evaluate nutritional supplements' effectiveness by performing large randomized intervention trials involving a range of healthy women with and without the major known risk factors, such as overweight/obesity, family risk of diabetes, and advanced age. Understanding the potential benefits of combining specific nutritional supplements, as well as dietary and lifestyle advice, and identifying receptive subpopulations represent a great opportunity to develop strategies that aim to break the cycle and abate the burden of metabolic disease by reducing the risk of GDM in populations.

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