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Dietary Interventions, Lifestyle Changes, and Dietary Supplements in Preventing Gestational Diabetes Mellitus: A Literature Review

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Gestational diabetes mellitus (GDM) is associated with increased rates of fetal morbidity and mortality, both during the pregnancy and in the postnatal life. Current treatment of GDM includes diet with or without medications, but this management is expensive and poorly cost-effective for the health care systems. Strategies to prevent such condition would be preferable with respect to its treatment. The aim of this literature review was to evaluate studies reporting the efficacy of the most used approaches to prevent GDM as well as evidences of efficacy and safety of dietary supplementations. Systematic literature searches were performed in electronic databases, covering the period January 1983 to April 2014. Randomized controlled clinical trials were included. Quality of the articles was evaluated with the Jadad scale. We did not evaluate those articles that were already entered in the most recent systematic reviews, and we completed the research with the trials published thereafter. Of 55 articles identified, 15 randomized controlled trials were eligible. Quality and heterogeneity of the studies cannot allow firm conclusions. Anyway, trials in which only intake or expenditure has been targeted mostly reported negative results. On the contrary, combined lifestyle programs including diet control (orienting food intake, restricting energy intake) associated with moderate but continuous physical activity exhibit better efficacy in reducing GDM prevalence. The results from dietary supplements with myo-inositol or probiotics are promising. The actual evidences provide enough arguments for implementing large-scale, high-quality randomized controlled trials looking at the possible benefits of these new approaches for preventing GDM.

Target Audience: Obstetricians and gynecologists, family physicians

Learning Objectives: After completing this CME activity, physicians should be better able to summarize the benefits of myo-inositol during pregnancy because it is a safe insulin sensitizer substance able to improve glucose homeostasis and insulin sensitivity, also during pregnancy; therefore, it seems reasonable to implement its assumption starting, if possible, in the preconceptional period (ie, in women with polycystic ovary syndrome); to take into account the possibility of supplying probiotics for preventing GDM in women at risk for GDM development; as well as to encourage preconceptional weight loss in obese women focused to decrease weight-related infertility and pregnancy complications.

All authors and staff in a position to control the content of this CME activity and their spouses/life partners (if any) have disclosed that they have no financial relationships with, or financial interests in, any commercial organizations pertaining to this educational activity.

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Gestational diabetes mellitus (GDM) is defined as an impairment of any degree of glucose tolerance or as hyperglycemia with either onset or first recognition during pregnancy. It is common knowledge that GDM develops when insulin (over)secretion becomes inadequate for the physiological degree of insulin resistance, ascertained in pregnant women.[1]

As reported in the last Cochrane Review, the prevalence of GDM is estimated between 1% and 14% of the population.[2] However, figures are changing, and we cannot estimate exactly its prevalence, namely, after the introduction of the new criteria of the International Association of Diabetes and Pregnancy Study Groups for GDM diagnosis.[3] It could be expected that the prevalence of GDM will undergo an increase because of both the introduction of new risk factors (often recognized in the general population) and the lowering of thresholds (just a value outside the cutoff is enough for the GDM diagnosis) requested for the diagnosis.

Gestational diabetes mellitus is associated with increased rates of fetal morbidity and mortality, both during the pregnancy and in the postnatal life.[4] Moreover, women with GDM and their infants are at increased risk for diabetes mellitus and metabolic dysfunction later in life.[5]

Current treatment of GDM includes diet with or without medications (metformin or insulin). Unfortunately, this management is expensive and poorly cost-effective for the health care systems, either in the short-term or in the long-term period.[6]

Strategies to prevent such condition would be preferable with respect to its treatment. Current approaches to prevent GDM have focused on lifestyle interventions such as diet and physical activity (PA), whereas recently, some supplements are emerging as additional options.

The aim of this literature review was 2 fold: (*a*) to evaluate studies reporting the efficacy of the most used approaches to prevent GDM before and during pregnancy as well as (*b*) to evaluate evidences of efficacy and safety of inositols and probiotics supplementation on glucose/insulin homeostasis in pregnancy.

METHODS

A literature search was performed in May 2014 in the MEDLINE electronic database, looking at randomized controlled trials (RCTs) published in the period January 1983 to April 2014.

The following search terms, words and combinations of words, were used: *pregnancy*, *fertility*, *gestational diabetes*, *prevention gestational diabetes*, *obesity*, *pregnancy outcome*, *prenatal care*, *prenatal/antenatal/pre pregnancy intervention*, *life-style*, *exercise/sport*, *diet*, *weight loss*, *glucose regulation*, *Inositol*, and *probiotics*.

We found many trials regarding lifestyle, diet, exercise, and weight loss during pregnancy. We did not evaluate those articles that were already entered in the most recent systematic reviews published during 2011 and 2012,[7–10] while we completed the research looking at RCTs published thereafter.

The search was limited to articles published in the English language and that were easily retrievable via the home library. For inclusion, an article had to be performed in humans and contain original data, whereas data from animal and in vitro investigations were excluded.

We attempted to obtain hard copies of every article listed through our own university library or interlibrary loans.

In the first section, we analyzed the efficacy of the most common approaches to prevent GDM either before or during pregnancy, whereas in the second one, we examined efficacy and safety of inositols or probiotics supplementation on glucose/insulin homeostasis in pregnancy.

We evaluated the quality of RCTs with the Jadad method,[11] considered reliable for such assessment.[12] The parameters considered by this method are the following:

(1) Was the study described as randomized?
(2) Was the study described as double blind?
(3) Follow-up: adequate (number and reasons for dropouts and withdrawals described) or inadequate (number or reasons for dropouts and withdrawals not described)
(4) Generation of the allocation sequence: adequate (computer-generated random numbers, table of random numbers…) or inadequate
(5) Double blinding: adequate (taking placebo, or similar) or inadequate (not intervened or different)

For each positive answer, 1 point is assigned, the overall score going from 0 to 5. Studies scoring 3 or higher were considered of good quality.

Moreover, we filled in the trasparent reporting of systematic reviews and meta-analyses (PRISMA) checklist.[13]

All sources of information were read and evaluated by one of the authors (G.D.) and later independently checked by another author (E.P.).

RESULTS

A decision tree is reported in Figure 1. Nineteen RCTs were considered eligible for this review; 1 was excluded because of duplicate publication,[14] and 3 were excluded because these referred to ongoing study protocols.[15–17]

Only 1 study pertained to the effects of a prepregnancy approach (diet and exercise) to prevent GDM,[18] 5 trials described the effects of exercise,[19–23] 1 reported the effects of dietary counseling,[24] and 3 evaluated lifestyle intervention.[25–27] Moreover, 3 studies reported supplementation with myo-inositol (MYO),[28–30]

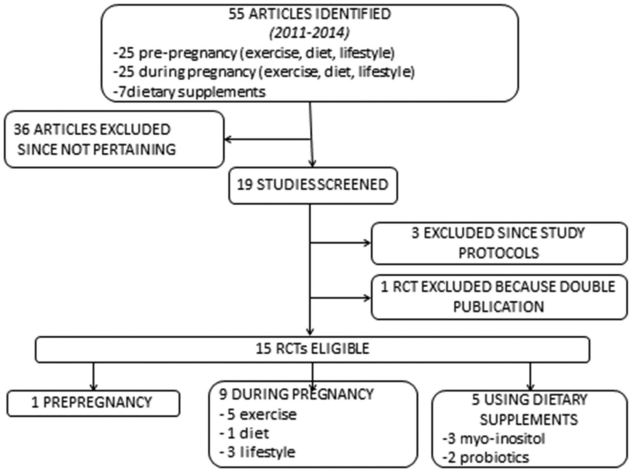

FIG. 1. Decision tree.

whereas 2 used probiotics.[31,32] No study reported the use of D chiro-inositol (DCI).

The study design, inclusion and exclusion criteria, Jadad score, as well as the main results of the RCTs are described in Tables 1 to 5.

EXERCISE, DIET, AND LIFESTYLE INTERVENTIONS

During the past few decades, obesity has become a global health challenge. The prevalence of overweight and obesity among women of childbearing age is rapidly increasing.

Maternal obesity and GDM are independently associated with perinatal complications, whereas obesity is an independent risk factor of GDM. The combined adverse effect of these 2 risk factors on the frequency of adverse obstetric outcomes is greater than that of either one alone.[33–35]

Prepregnancy body size may be a stronger predictor than gestational weight gain (GWG) for adverse obstetric and perinatal outcomes.[8,11,12,36–38] Because pregnancy is a relatively brief period in life, PA and diet interventions should optimally be initiated already before pregnancy and continue after delivery to prevent the development of overt diabetes.

Prepregnancy Interventions

Some studies described a relationship between obesity and infertility; modest preconception reductions in weight (5% to 10%) through diet or lifestyle interventions increase spontaneous or assisted reproductive technology (ART) conceptions and reduce miscarriage rates.[39–42]

The only RCT[18] carried out in the preconceptional period was done in overweight/obese women undergoing in vitro fertilization with gonadotropin-releasing hormone agonist protocols. Women were approached after their initial medical consultation and randomized to lifestyle or standard treatment before commencement of their in vitro fertilization cycle. All dietary and exercise advices were provided by a qualified dietitian.

There was a greater reduction in GWG for lifestyle intervention (–3.8 ± 3.0 kg, $p < 0.001$) compared with standard treatment (–0.5 ± 1.2 kg, $p = 0.092$). Both the intervention (–5.3 ± 4.6 cm) and control (–3.5 ± 3.5 cm) groups had similar reductions in waist circumference. The overall pregnancy rate was 53% for the intervention and control groups combined. No data are available on GDM prevalence or pregnancy outcome.

Interventions During Pregnancy

Exercise

The last Cochrane Review evaluated the effects of physical exercise for pregnant women for preventing glucose intolerance or GDM.[2] Literature searches were performed by using 3 Trials Registers, and the searches were unlimited by time up to April 2012.

Interventions included any type of exercise and lifestyle management reported in RCTs and cluster RCTs. Five articles were included in which women receiving additional exercise intervention were compared with those receiving routine antenatal care.

There was no significant difference in GDM incidence (relative risk (RR), 1.10; 95% confidence interval [CI], 0.66 to 1.84) between the 2 study groups, and none of the 5 trials found significant differences in insulin sensitivity. Babies born to women receiving exercise interventions had a nonsignificant trend to a lower ponderal index (mean difference (MD), –0.08 g × 100 m^3; 95% CI, –0.18 to 0.02).[42] No significant differences were seen in birth weight (MD, –102.87; 95% CI, –235.34 to 29.60), macrosomia (RR, 0.91; 95% CI, 0.68 to 1.22), small for gestational age (RR, 1.05; 95% CI, 0.25 to 4.40), gestational age at birth (MD, 0.04 weeks; 95% CI, –0.37 to 0.29), or Apgar score of lower than 7 at the fifth minute (RR, 1.00; 95% CI, 0.27 to 3.65).

After the publication of such meta-analysis, additional 5 RCTs were published between April 2012 and April 2014.

In the study published by Barakat et al,[19] healthy pregnant women were randomly assigned to either an exercise group or a control group. Maternal glucose screen (50 g), GWG, and several pregnancy outcomes were recorded. The physical conditioning program was a 35- to 45-minute session performed 3 times a week, with 2 land aerobic sessions and 1 aquatic

TABLE 1
Prepregnancy Interventions

RCT Design, Reference	Timing/Duration of Treatment	No. of Subjects/Jadad' Score	Inclusion Criteria	Exclusion Criteria	Main Findings
Open label[18]	Since prior to the in vitro fertilization (IVF) to embryo transfer	Active group: 18 Control group: 21 Jadad: 3	Women with body mass index (BMI) ≥28 and <45 kg/m^2, 18–40 y who underwent IVF with GnRH agonist protocols	Acute cerebrovascular, cardiovascular, renal, gallbladder, and hepatic disease; diabetes; malabsorptive disorders; and current use of lithium therapy or a weight loss program	There was a significant effect of treatment on change in weight and BMI ($P < 0.001$) such that active intervention showed weight or BMI reductions ($P < 0.001$), whereas the control group showed no weight ($P = 0.092$) or BMI ($P = 0.097$) changes

activity session from the beginning of the pregnancy to the end of the third trimester. No cases of GDM were reported, while no differences in GWG were found between groups. No exercise-related injuries were experienced during pregnancy.

In the RCT published by Price et al,[20] inactive women were randomized at 12 to 14 weeks' gestation to a group that remained sedentary or to a group that performed aerobic exercise (45- to 60-minute duration, performed 4 times per week, at moderate intensity). Gestational diabetes mellitus was slightly less common among the active group (9.6% vs 12.9% in controls), although absolute numbers (3 vs 4) were too small to achieve significance.

In the RCT by Ruchat et al,[21] women either at low or at high risk for GDM were randomized between 16 and 20 weeks' gestation into a low-intensity versus vigorous-intensity exercise program consisting of walking sessions 3 or 4 times a week, gradually increasing time from 25 to 40 minutes per session, associated with nutritional control.

Capillary glucose responses to exercise were strongly influenced by an interaction between GDM risk, exercise duration, and exercise intensity. Decreases in glucose concentrations were observed after 25 (4% [13%]), 35 (21% [12%]), and 40 minutes (15% [18%]) of walking in the high-risk group. In low-risk women, decreases in glucose concentrations were significant, regardless of exercise intensity and duration.

In the RCT by Oostdam et al,[22] overweight/obese women at risk for GDM since the 15th week of gestation were enrolled until 12 weeks after delivery. Normal cares were compared with an exercise training program consisting of 60 minutes of aerobic and strength exercises, 2 times per week. Intention-to-treat analysis showed that the exercise program did not reduce maternal fasting blood glucose levels at 24 and 32 weeks of gestation, insulin sensitivity, or mean glycosylated hemoglobin. No adverse events (AEs) resulting from the intervention were reported.

In the RCT by Barakat et al,[23] healthy women were randomly assigned to either an exercise intervention or usual care. The exercise program focused on moderate-intensity resistance and aerobic exercises 3 times per week, with duration of 50 to 55 minutes per session. The intervention did not reduce the risk for developing GDM (odds ratio [OR], 0.84; 95% CI, 0.50 to 1.40).

Diet

A recent systematic review and meta-analysis published in 2011 selected RCTs from January 1980 until March 2011 in several electronic databases. The

TABLE 2
Exercise

RCT Design, Reference	Timing/Duration of Treatment	No. of Subjects/Jadad' Score	Inclusion Criteria	Exclusion Criteria	Main Findings
Open label[19]	Since 10–12 wk to 38–38 wk	Exercise group: 210 Control group: 218 Jadad: 3	Exercise <20 min, 3 d/wk; singleton uncomplicated pregnancy; not at high risk for preterm birth	Any medical condition that could affect exercise Plan to deliver outside their birth center	No cases of GDM in exercise group vs 3 in the control group were found.
Open label[20]	Since 12–14 wk to 6 wk postpartum	Active group: 31 Control group: 31 Jadad: 2	Exercise less than once per week for at least the past 6 mo; singleton pregnancy at 12–14 wk; BMI <39 kg/m^2	Chronic heart or lung diseases, poorly controlled diabetes, hypertension, epilepsy, hyperthyroidism, severe anemia, orthopedic diseases, history of premature delivery, previous small-for-gestational-age infant, unexplained fetal death	GDM was slightly less common among the active group.
Open label[21]	Since 16–20 wk	Low-intensity group: -Low risk for GDM: 12 -High risk for GDM: 11 Vigorous-intensity group: -Low-risk for GDM: 12 -High-risk for GDM: 11 Jadad: 3	History of polycystic ovary syndrome and/or GDM, macrosomia, diabetes in the immediate family, early GWG ≥9 kg, prepregnancy BMI ≥25 kg/m^2; nonsmokers; aged 20–40 y, regular prenatal care, no other medications than prenatal vitamins	Multiple pregnancy; chronic diseases; contraindications to practice exercise	Capillary glucose responses to exercise were strongly influenced by an interaction between GDM risk, exercise duration, and exercise intensity. Decreases in glucose concentrations were observed after 25, 35, and 40 min of walking in high-risk low-intensity group. In the high-risk vigorous-intensity group, glucose concentrations decreased significantly only after 25 and 35 min and increasing the exercise time attenuated glucose concentrations decline. In low-risk women, regardless of exercise intensity and duration, decreases in glucose concentrations were significant and similar.
Open label[22]	From 15 wk of gestation until 12 wk after delivery	Intervention: 62 Control: 59 Jadad: 3	BMI ≥30 or BMI ≥25 kg/m^2 and at least: history of macrosomia or history of GDM or first grade relative with type 2 DM	Recruitment after 20 wk; aged <18 y; inadequate knowledge of the Dutch language; GDM before randomization; hypertension; alcohol/drug abuse; use of any medication that affect insulin secretion or sensitivity; serious pulmonary, cardiac, hepatic, or renal impairment; malignant disease; serious mental or physical impairment	No differences on GDM diagnosis were found between groups. Also the exercise program did not reduce maternal fasting blood glucose levels or insulin sensitivity at 24–32 wk.
Open label[23]	From 6–9 wk to 38–39 wk	Exercise: 40 Control: 43 Jadad: 2	Healthy women, uncomplicated and singleton pregnancies	Any type of absolute obstetric contraindication to practice exercise	Significant differences were not found between study groups in GDM cases. Values corresponding to the exercise group were better than those of the control group.

TABLE 3
Diet

RCT Design, Reference	Timing/Duration of Treatment	No. of Subjects/Jadad' Score	Inclusion Criteria	Exclusion Criteria	Main Findings
Open label[24]	Since the beginning of pregnancy (within 18th wk)	Intervention: 372 Control: 387 Jadad: 2	II Gravida who previously delivered a macrosome (>4000 g)	Any medical disorder, previous GDM, drugs, aged <18 y, gestation >18 wk, multiple pregnancy	No significant difference existed in the incidence of GDM; the rate of glucose intolerance was lower in the intervention group.

search strategy focused on pregnant women and outcomes related to GDM as well as possible interventions to prevent or treat GDM.[9] We consider only the results about dietary counseling.

Nine studies compared any form of dietary counseling with usual care; 3 of them showed no statistical difference in maternal fasting glucose (weighted mean differences, –0.21; 95% CI, –0.45 to –0.02 mmol/L) between groups. Seven studies reported the incidence of GDM. Dietary counseling was more effective than usual care in reducing the risk for GDM (reducing the risk, –0.05; 95% CI, –0.10 to –0.01). According to the authors, the studies were of low quality.

Three trials showed no statistical difference in maternal fasting glucose (weighted mean differences, –0.13; 95% CI, –0.3 to –0.04 mmol/L) between pregnant women who received low glycemic index diet advice (carbohydrates that break down more slowly during digestion) and those who received high glycemic index diet advice (carbohydrates that break down quickly). Still, this evidence was of low quality.

After this review, only 1 other trial was published. In this study,[24] nondiabetic women who previously delivered an infant weighing more than 4 kg were randomized to receive low glycemic index diet early in pregnancy or no dietary intervention. No significant differences were found in the incidence of GDM or in birth weight, whereas the rate of glucose intolerance was lower in the intervention group. The latter also reported a significantly lower GWG (12.2 vs 13.7 kg; MD, –1.3; 95% CI, –2.4 to –0.2).

Lifestyle Interventions

A systematic review and meta-analyses of RCTs and non-RCTs on the efficacy of antenatal dietary, activity, behavior, or lifestyle interventions in overweight and obese pregnant women was published in 2012.[8] Literature searches were performed using 5 electronic databases and 8 other databases; the searches were unlimited by time up to January 2012. Maternal outcome measures included GWG and GDM.

Thirteen RCTs and 6 non-RCTs were identified and included in the meta-analysis. The evidence suggests that antenatal dietary and lifestyle interventions in obese pregnant women reduce GWG (–2.21 kg; 95% CI, –2.86 to –1.59 kg) and suggests a trend toward a reduction in the prevalence of GDM (OR, 0.80; 95% CI, 0.58 to 1.10).

After the publication of these data, we found 3 more RCTs published until April 2014.

In the RCT by Harrison et al,[25] pregnant women at risk for developing GDM were enrolled and allocated

TABLE 4
Lifestyle

RCT Design, Reference	Timing/Duration of Treatment	No. of Subjects/Jadad' Score	Inclusion Criteria	Exclusion Criteria	Main Findings
Open label[27]	Since the diagnosis of GDM until 3 y after delivery	Intensive therapy group: 40 Standard therapy group: 41 Jadad: 1	Pregnant women affected by GDM	Not reported	Patients receiving intensive treatment had lower 30-min glucose levels after 75-g glucose load
Open label[26]	Since 12th–36th week	Therapeutic Lifestyle Changes (TLC) group: 33 Control group: 28 Jadad: 4	BMI ≥25 kg/m^2, aged >18 y, single pregnancy	Twin pregnancy, chronic disease, GDM in previous pregnancies, smoking during pregnancy, previous bariatric surgery, regular physical activity, dietary supplements or herbal products known to affect body weight, other medical conditions that might affect body weight, and plans to deliver outside our birth center	Lower incidence of GDM in the TLC group
Open label[25]	Since 12–15 wk to 26–28 wk	Intervention:106 Controls: 97 Jadad: 3	BMI ≥25 or 23 kg/m^2 if high-risk ethnicity for GDM; obesity; high risk of GDM	Multiple pregnancy; type 1/2 diabetes mellitus; BMI ≥45 kg/m^2; preexisting chronic diseases; non–English speaking	GDM prevalence was 22%, with a trend toward less cases in the intervention group

to control or to receive an individual 4-session behavior change lifestyle intervention. The sessions provided pregnancy-specific dietary advices in addition to simple healthy eating and PA messages. All women received standard maternal care. At 28 weeks, GDM prevalence was 22%, with a trend to be lower in the intervention group ($P = 0.1$). Gestational weight gain was significantly lower in the intervention versus control group (6.0 ± 2.8 kg vs 6.9 ± 3.3 kg).

In the RCT by Petrella et al,[26] women with a prepregnancy body mass index (BMI) of greater than 25 were randomized at first trimester to no intervention or a Therapeutic Lifestyle Changes (TLC) program including diet and mild PA consisting of 30 minutes of moderate-intensity activity at least 3 days a week. Significant changes in eating habits occurred in the TLC group, which increased the number of snacks, the intake of fruits and vegetables, and decreased the consumption of sugar. Gestational diabetes mellitus in women randomized to the TLC group was significantly lower versus those receiving standard care (23.3% vs 57.1%, $P = 0.009$).

In the RCT by Xiaopei et al,[27] pregnant women with GDM were randomly selected to receive an intensive treatment regimen that included one-to-one education, lifestyle intervention, clinic visits, strict glucose control, and frequent glucose self-monitoring. The standard therapeutic regimen included group education on the importance of proper diet, exercise, and self-monitoring of glucose level. Patients receiving intensive treatment had lower 30-minute glucose levels after 75-g glucose load (8.26 [1.85] vs 9.46 [2.74] mmol/L), a smaller waist circumference (75.8 [3.1] vs 78.3 [4.2] cm), and healthier outcomes for the neonates as reduced preterm delivery (2.4% vs 8.3%) and neonatal care admission (21.3% vs 33.3%).

DIETARY SUPPLEMENTS

Inositols

Inositol belongs to vitamin B complex, and its main source comes from the diet. Epimerization of the 6-hydroxyl groups of inositol leads to the formation of 9 stereoisomers, including MYO and DCI, both applied as insulin sensitizer drugs.

Biochemical studies have suggested that impairment in insulin message could be due to a defect in the inositol phosphoglycans (IPGs) second messengers.[43,44] Inositol phosphoglycans are known to have a role in activating enzymes that control glucose metabolism.[45,46]

Most tissues through a membrane-associated sodium-dependent inositol cotransporter take up circulating

TABLE 5
Dietary Supplementation

RCT Design, Reference	Timing/Duration of Treatment	No. of Subjects/ Jadad' Score	Inclusion Criteria	Exclusion Criteria	Main Findings
Open label[28]	Since 12th–13th wk, for 16 wk	MYO: 99 Control: 98 Jadad: 3	First-degree relatives affected by type 2 diabetes mellitus, single pregnancy, white race	Prepregnancy BMI ≥30 kg/m^2, previous GDM, pregestational diabetes mellitus, first-trimester glycosuria, corticosteroids	Prevalence of GDM significantly reduced in MYO group
Double-blind[29]	Since 13–14.7 wk (range, 7–27 wk) until delivery	MYO: 35 Control: 33 Jadad: 3	Single pregnancy, fasting glucose levels between 92–126 mg/dL	Pregestational BMI ≥35 kg/m^2	Prevalence of GDM significantly reduced in MYO group
Open label[30]	Since 24th–28th week, for 8 wk	MYO: 24 Control: 45 Jadad: 2	Pregnant women affected by GDM diagnosed at 24th–28th week	Not described	Fasting glucose, insulin, and Homeostasis Model Assessment of Insulin Resistance, decreased in both groups (50% in the study group vs 29% in the control group). The decline in the study group was significantly greater (P = 0.0001)
Double-blind[31]	From the 1st trimester to 12 mo after delivery	Diet/probiotic: 73 Diet/placebo: 69 Control/placebo: 66 Jadad: 5	Pregnant women, <17-wk gestation	Metabolic/chronic disorders (ie, diabetes)	Lowest glucose and insulin concentrations in diet/probiotics group. Better Homeostasis Model Assessment and highest quantitative insulin sensitivity check index in diet/probiotic group
Single-blind[32]	Since 3rd trimester, for 9 wk	Probiotic: 37 Yogurt: 33 Jadad: 2	Singleton pregnancy and nulliparity	Multiparity, maternal hypertension, liver/renal diseases, GDM	Significant changes from baseline on insulin levels, and in Homeostasis Model Assessment of Insulin Resistance score

free MYO; inositol uptake is inhibited by glucose.[47] In particular, MYO had 10 times more affinity for the transporter compared with DCI.[48] D chiro-inositol is synthesized by an epimerase that converts MYO into DCI, with each tissue having its own particular conversion rate, likely because of the specific needs for the 2 different molecules.[49,50]

The binding between insulin and its receptor mediates the production of low-molecular-weight IPGs that act as secondary messengers of insulin action. Hence, both MYO and DCI lead to a decrease in blood glucose levels.

Myo-inositol

In our review, we found 3 RCTs on the efficacy of prevention of GDM with MYO supplementation.

The MYO supplementation was performed at the same dose and with the same compound in all studies (MYO 2 g + folic acid 200 μg, twice daily). Placebo was used in none of them. In all studies, the control arm was represented by treatment with 400 g/d of folic acid.

D'Anna et al[28] evaluated whether MYO supplementation during pregnancy was able to reduce the GDM diagnosis in women at high risk because of a positive family history of type 2 diabetes mellitus.

The main outcome was the rate of GDM, which occurred significantly more in women assigned to the control group (15.3% vs 6.1%, P = 0.04; OR, 0.35 [CI, 0.13 to 0.96]). Moreover, the mean birth weight and the number of babies with birth weight of greater than 4000 g were significantly higher in the control group, whereas preterm delivery and gestational hypertension were similar.

Adverse events were not analyzed.

In the study by Matarelli et al,[29] the authors evaluated the effects of MYO supplementation in women with elevated fasting glucose since the first/early second trimester.

The group of those allocated to receive MYO had a lower incidence of GDM (6% vs 71%, P = 0.001; OR, 0.13; 95% CI, 0.03 to 0.50). The fetal abdominal circumference measured at oral glucose tolerance test time (MYO, 41.7 [17.9], vs controls, 65.6 [22.1]; P = 0.001) and the birth weight (MYO, 42.8 [20.4], vs controls, 56.6 [25.9]; P = 0.001), both expressed as percentiles, were lower in the MYO group. None of the babies born in the MYO group experienced neonatal hypoglycemia, whereas this occurred in 10 of the control group (P = 0.038).

Assumption of MYO was not associated with any serious AE.

Corrado et al[30] conducted an RCT involving women affected by newly discovered GDM. They were randomized (1:2). After 8 weeks, fasting insulin (MYO, from 31.2 [7.1] to 19.0 [5.8] μIU/mL; controls, from 33.9 [5.3] to 26.0 [6.8] μIU/mL; $P < 0.05$) and glucose (MYO, from 5.5 [0.3] to 4.6 [0.3] mmol/L; controls, from 5.4 [0.2] to 5.1 [0.3] mmol/L; $P < 0.05$) levels decreased in both groups.

Adverse events were not analyzed.

PROBIOTICS

The World Health Organization defines *probiotics* as "microorganisms … able to confer defined health benefits on the host."[51]

Most probiotic products are either in food items or supplied as dietary supplements. These products vary considerably in their microbial composition and number of viable bacteria.

The endogenous intestinal microflora of the human being is an "organ" necessary to provide nourishment, regulate the epithelial development, and instruct innate immunity. In fact, the gut microbiome ("intestinal flora"), composed of trillions of nonpathogenic microorganisms usually commensal, serves as a filter for the largest environmental exposure to which we are exposed, that is, what we eat.[52]

Several biological studies demonstrate that probiotics can constantly modulate the gastrointestinal immune system and thus the systemic low-grade inflammation state because of the changes that the probiotic determines on the inflammatory response.[53–56]

Obesity[57] and type 2 diabetes[55] are associated with divergent changes in the gut microbiome.

Several trials conducted in humans with type 2 diabetes showed a preservation of insulin sensitivity as well as improvements in glycemia and lipids.[56,58,59]

Women with GDM are known to be at high risk for developing type 2 diabetes and have a similar abnormal insulin resistance and alteration in lipid metabolism.[4]

In our review, we found 2 RCTs on the efficacy of prevention of GDM with probiotics supplementation.

In the prospective RCT by Laitinen et al,[31] women at the first trimester of pregnancy were randomized to receive nutrition counseling to modify dietary intake or as controls; the dietary intervention group was further randomized to receive probiotics (diet/probiotics) or placebo (diet/placebo) in a double-blind manner, and the control group received placebo (control/placebo).

Blood glucose concentrations were lowest in the diet/probiotics group during pregnancy (baseline-adjusted means: 4.45, 4.60, and 4.56 mmol/L in the diet/probiotics, diet/placebo, and control/placebo, respectively; $P = 0.025$). Better glucose tolerance in the diet/probiotics group was confirmed by a reduced risk for elevated glucose concentration compared with the control/placebo group (OR, 0.31 [95% CI, 0.12 to 0.78]; $P = 0.013$) as well as by the lowest insulin concentration (adjusted means, 7.55, 9.32, and 9.27 mU/L; $P = 0.032$) and homeostatic model assessment (adjusted means, 1.49, 1.90, and 1.88; $P = 0.028$) and the highest quantitative insulin sensitivity check index (adjusted means, 0.37, 0.35, and 0.35; $P = 0.028$) during the last trimester of pregnancy. The effects observed extended during the 12-month postpartum period.

On initiation of capsule consumption, 7% of the women in the diet/probiotics group versus 8% in the diet/placebo group and 3% in the control/placebo group reported gut-associated AE; subsequently, the prevalence of reported symptoms was reduced to 2% and 0.5% at subsequent study visits.

In the RCT conducted by Ansemi et al,[32] primigravida pregnant women with singleton pregnancy at their third trimester were randomized to receive 200 g/d of conventional yogurt or the probiotic yogurt. It was a commercially available product prepared with the starter cultures of *Streptococcus thermophilus* and *Lactobacillus bulgaricus*, enriched with probiotic culture of 2 strains of lactobacilli and bifidobacteria.

Significant differences were found comparing changes in these variables between probiotic and conventional yogurts (changes from baseline in serum insulin levels: +1.2 [1.2] vs +5.0 [1.1] mIU/mL, respectively; $P = 0.02$; and homeostatic model assessment score, 0.2 [0.3] vs 0.7 [0.2], respectively; $P = 0.01$). Consumption of probiotic yogurt did not influence fasting plasma glucose compared with conventional yogurt.

Consumption of probiotic yogurts was not associated with any serious AE.

DISCUSSION

Although there were a relatively high number of reports addressing the efficacy of the various approaches to prevent GDM before or during pregnancy, few of the studies analyzed reached a high-quality score.

As far as preconceptional intervention, every international guideline advises weight loss before both ART and non-ART conception, in obese women.[60,61]

Data from observational and small intervention studies suggested that reduction in weight increases the chances of conception, decreases pregnancy complications, and improves perinatal outcome.[39,62] The only available trial actually provided the first preliminary

evidence to support the efficacy of lifestyle treatment in reducing total and central adiposity. Unfortunately, no data on GDM or any other pregnancy complication have been reported.

Exercise started early in pregnancy seems to lower the risk for developing GDM in previous prospective cohort, retrospective case-control, or cross-sectional studies.[63–66] Results from RCTs, however, indicated no significant difference in GDM incidence between women receiving an additional exercise and those receiving routine care.[19–23] Such discrepant findings could be related to design and size of the studies. The only RCT reporting an improvement in maternal glucose tolerance was performed with a reduced glucose load (50 g), suggesting that physical intervention alone has limited possibility to improve metabolism.[19] Anyway, on the basis of the limited data, current evidence cannot guide practice.

Several trials have been aimed at reducing both GDM and GWG through dietary interventions (restrictions), and data have recently been reported in systematic reviews and/or meta-analyses.[9,10,63,64] Interventions were so diverse and inclusion criteria were so heterogeneous that no definite conclusions could be drawn. To prevent maternal and neonatal complications, the Institute of Medicine recommends a GWG between 5 and 9 kg (11 to 20 lbs) for obese women. However, only approximately one third of subjects and even less among obese women reached a weight gain in line with Institute of Medicine recommendations.[67] The additional RCTs we evaluated are not of high quality, still reported controversial results, and did not shed light on the effectiveness of dietary restriction as the single intervention to prevent GDM.

It has been proposed that this lack of effectiveness may be related also to the fact that psychological factors were not sufficiently considered.[68] Pregnant women with elevated levels of stress and anxiety consume more fats, oils, sweets, and snacks as well as have decreased intakes of vitamins,[69] and some researches demonstrated a positive correlation between prepregnancy BMI, GWG, anxiety, and depressive symptoms, suggesting an association between weight status and psychosocial vulnerability.[70–72]

On the other hand, a multitargeted approach was analyzed in several RCTs in which a lifestyle intervention program in obese pregnant women included diet counseling, PA, and sometimes psychological assistance. In every study, the authors observed a reduced GWG in obese women receiving intervention, compared with standard care. Noteworthy, a reduction in GDM was observed in 9 of the 13 trials we analyzed. In addition, lifestyle intervention was associated with a reduction in gestational hypertension and preterm delivery rates, whereas considerable heterogeneity was found in terms of birth weight and fetal macrosomia occurrence.

Considering dietary supplements, data seem to indicate that the use of MYO could be beneficial on the glucose/insulin homeostasis in pregnancy, and it is associated with a reduction in GDM onset. This finding has been confirmed in a preliminary report of another trial that included women with a BMI of greater than 27.[73] Thus, these few evidences seem to suggest a role for MYO supply in the prevention of GDM, in different categories of women at risk. Moreover, 2 of the studies also reported that MYO-treated women gave birth to babies of reduced weight compared with controls.

On the other hand, probiotic supplementation, either alone or in combination with pharmacological and nonpharmacological interventions, is a further area of research in the prevention of GDM. The results from the available RCTs suggest that probiotics may reduce the risk for GDM, a conclusion in line with the recent Cochrane Review.[74] As reported for MYO, there was a reduction in birth weight in the women taking probiotics.

CONCLUSIONS

Implementing prevention requires the knowledge of the mechanisms allowing the target disorders. This condition is not fully reached in the case of GDM although we all are aware of the risk factors. Indeed, studies were directed toward the correction of energy balance through both appropriate qualitative/quantitative intake and stimulating energy expenditure.

Trials in which only intake or expenditure has been targeted mostly reported negative results. On the contrary, combined lifestyle programs including diet control (orienting food intake, restricting energy intake) associated with moderate but continuous PA exhibit better efficacy in reducing GDM prevalence.

The results from dietary supplements with MYO or probiotics are promising. The actual evidences provide enough arguments for implementing large-scale, high-quality RCTs looking at the possible benefits of these new approaches for preventing GDM.

Generally speaking, one issue is represented by the heterogeneous prescriptions that have been applied in the different reports and that cannot be easily standardized. Another issue is represented by women's compliance.

Indeed, changing habits even for a limited period is not an easy task. In this respect, health providers need

to produce similar efforts and investments as already done for smoking cessation. Obstetricians should be aware and therefore disseminate the concept that the gestational period is so crucial for the health of the next generation.

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