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REVIEW

Progress of Clinical Trials for the Treatment of Gestational Diabetes Mellitus

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Abstract: Gestational diabetes mellitus (GDM) is one of the most common and severe complications of pregnancy, which is not only associated with perinatal complications but also has a long-term adverse effect on maternal and their offsprings. At present, the treatment of GDM focuses on the control of maternal blood glucose. Although lifestyle changes, hypoglycemic drugs, blood glucose monitoring, and other medicines that can improve maternal blood glucose to a certain extent, there are still some patients affected and have adverse pregnancy outcomes. The prevention of GDM and the treatment of improving pregnancy outcomes are urgently needed. This review summarized recently published clinical trials related with the treatment of GDM, aiming to provide additional options for the treatment of GDM.

Keywords: gestational diabetes mellitus, clinical trials, review

Introduction

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance onset identified during pregnancy,[1] has a wide range of prevalence worldwide, with higher rates in the Middle East and North Africa, Southeast Asia and the Western Pacific, and lowest rates in Europe.[2] A systematic review and meta-analysis results showed that the incidence of GDM in mainland China was 14.8%, suggesting that China may be the country with the most GDM patients in the world.[3]

GDM can lead to a variety of severe perinatal complications, including macrosomia, fetal demise, shoulder dystocia, birth traumas, congenital anomalies, neonatal hypoglycemia, hyperbilirubinemia. The offspring of GDM also have an increased risk of diabetes mellitus,[4] which is in accordance with the high prevalence of type 2 diabetes mellitus (T2DM)/pre-diabetes in adult offspring of women with GDM or type 1 diabetes mellitus (T1DM).[5] Furthermore, GDM is correlated with an increased incidence of diabetes in offspring during childhood and adolescence.[6] In addition, mothers with GDM are associated with an increased risk of T2DM and cardiovascular disease later in life.[7] It is a recognized fact that GDM affects the health of the fetus and mother. Therefore, the prevention and treatment of GDM is extremely urgent.

At present, the treatment of GDM mainly includes medical nutrition therapy, hypoglycemic drugs, blood glucose monitoring, among which the use of insulin is still the main treatment. Although the use of insulin for women suffered from GDM has already been demonstrated effective, the subcutaneous injection of insulin has some inevitable disadvantages. Besides, the choice of oral hypoglycemic drugs is

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limited. Clinical trials have found that probiotics, fish oil, Epigallocatechin 3-gallate (EGCG), minerals, and vitamins may bring additional benefits to patients with GDM.

Use "gestational diabetes mellitus" or "diabetes in pregnancy " AND "clinical trials" as the search query to search the PubMed database systematically, and at the same time apply the literature retrospective method to search for appropriate articles. The inclusion criteria are the literature of all clinical trials related to the treatment of GDM in the PubMed database. Articles published between 2015 and 2020 are given priority. The exclusion criteria are non-clinical randomized controlled trials. In this review, the recent clinical trials related to the treatment of GDM are summarized and compared in order to intervene in time for GDM patients or high-risk women of GDM and ultimately improve pregnancy outcomes.

Lifestyle Intervention

Diet management and moderate exercise are included in lifestyle interventions. Lifestyle interventions are safe interventions that are beneficial for a wide range of diseases, and physical exercise as one of these lifestyle interventions is important for reducing the risk of cardiovascular disease and T2DM.[8,9]

In a small-scale study (n=38), on the basis of standard prenatal care, women with GDM were instructed to engage in personalized, structured aerobic and resistance exercise for 50–55 minutes twice a week until delivery (at least six weeks).[10] The study found that in the intervention group, the average postprandial blood glucose levels were lower at the end of pregnancy and absence of pregnancy complications. However, there was no significant improvement in weight gain in pregnancy and neonatal body mass index (BMI). It suggested that structured aerobic and resistance exercise is safe and effective in improving postprandial blood glucose in patients with GDM.

Regarding whether lifestyle has a preventive effect on women at high risk of GDM, in 2017, a prospective randomized trial in China divided early pregnant women who were overweight or obese (BMI≥ 24 kg/m^2) into exercise group (n=150) and control group (n=150) until 37 weeks of gestation, the results showed that the incidence of GDM in the experimental group who received cycling at least 30 minutes three times a week was significantly lower than that in the control group.[11] The Finnish Gestational Diabetes Prevention study (RADIEL) found that pregnant women with a high risk of GDM who were prior to 20 weeks of gestation (with a previous history of GDM, BMI ≥ 30 kg/m^2 or both) received personalized lifestyle interventions (n=144), including appropriate exercise and diet interventions, the incidence of GDM was 13.9%, while the incidence of GDM in the control group (received standard prenatal care, n=125) was 21.6%.[12] Besides, weight gain in pregnancy in the intervention group was less. It indicated that appropriate lifestyle intervention for patients with a high risk of GDM is beneficial to reduce the incidence of GDM and reduce weight gain in pregnancy.

Although the specific schemes of the intervention group were different in these studies, personalized lifestyle interventions benefited both the improvement of blood glucose in patients with GDM and the prevention of patients at high risk of GDM. However, the GeliS study showed that recommendations for lifestyle changes did not significantly improve pregnancy weight gain and the risk of GDM in pregnant women with pre-pregnancy BMI between 18.5 and 40 kg/m^2.[13] It is worth mentioning that these studies do not clarify whether lifestyle intervention has a beneficial effect on the long term.

In Table 1, we summarize basic characteristics and advantages/disadvantages of clinical trials related to lifestyle intervention.

Hypoglycemic Agents

Insulin and Insulin Analogs

Insulin and insulin analogs are often recommended as a first-line treatment when blood glucose fails to reach the target blood glucose levels after controlled diet and physical activity. The benefit of insulin and insulin analogs is that they cannot cross the placental barrier. Insulin reduces blood glucose levels by regulating glucose metabolism. There are a variety of commonly used insulin preparations, including rapid insulin, short-acting insulin, intermediate-acting insulin, long-acting insulin. It is easier to use short-acting insulin or rapid-acting insulin before each meal in combination with basal insulin at night for blood glucose control. However, it is not clear which of certain types of insulin has the best efficacy and safety.

A small clinical study compared the efficacy and safety of insulin aspart 5 minutes before each meal or regular human insulin injection 30 minutes before each meal on women with GDM (n=27) who used insulin neutral protamine Hagedorn (NPH) two daily doses as basal insulin, and the results indicated that mean blood glucose level 30 minutes after the meal in insulin aspart group was lower than that in regular human insulin group (4.7±0.19 mmol/l

Table 1 Basic Characteristics and Advantages/Disadvantages of Clinical Trials Related to Lifestyle Intervention

Clinical Trials	Participants	Group Assignment	Outcome Assessments	Advantages/Disadvantages of Clinical Trials
Sklempe Kokic, I. et al[10] (2018)	GDM patients	Exercise: n=18 Control: n=20	GC and other health-related outcomes	Combination of a structured aerobic and resistance exercise/Small sample size
Wang, C. et al[11] (2017)	Overweight/obese pregnant women	Exercise: n=150 Control: n=150	The prevalence of GDM	Regular cycling exercise/Lack of dietary intervention
Koivusalo, S. B. et al[12] (2016)	Pregnant women with high-risk of GDM	Lifestyle: n=144 Control: n=125	The prevalence of GDM	Individualized counseling on lifestyle
Kunath, J. et al[13] (2019)	Pregnant women	Lifestyle: n=1152 Control: n=1134	The prevalence of GDM	Face-to-face counselling sessions

Abbreviations: GDM, gestational diabetes mellitus; GC, glycaemic control.

vs 5.1±0.23 mmol/l), mean peak blood glucose concentration and change from baseline for C-peptide in the insulin aspart group was lower. Overall efficacy and safety were similar between the two groups.[14]

Another clinical trial compared the effects of insulin aspart, regular human insulin and no exogenous insulin on the treatment of GDM (n=15), the results showed that insulin aspart decreased the peak postprandial blood glucose more significantly than that of regular human insulin as well as no exogenous insulin.[15]

As mentioned above, insulin aspart may have an advantage in reducing postprandial blood glucose and keeping postprandial blood glucose stable. Since the increase in postprandial blood glucose concentration is associated with an increased risk of macrosomia,[16] the use of insulin aspart may have a potentially more beneficial effect on the reduction of newborn birth weight, although Pettitt DJ et al found that neonatal weight was comparable in both groups.[14] Nevertheless, the sample size of the above two studies is small, and large-scale studies are needed to confirm this hypothesis.

Insulin detemir and NPH are used as basal insulin in patients with GDM. In 2015, a prospective randomized controlled non-inferiority trial found that pregnant women with GDM and T2DM (n=87) were randomly treated with insulin detemir or NPH on the basis of adding insulin aspart as needed, the study reported that the overall mean blood glucose, fasting plasma glucose and postprandial blood glucose were similar in the two groups, and the results were similar after removing T2DM.[17] There was no difference in perinatal outcomes and maternal weight gain between the two groups. Still, the proportion of hypoglycemia was higher in the NPH group (36% vs 26%), and half of the hypoglycemia events were nocturnal, although there was no statistical difference.

However, in another randomized controlled trial, treatment of pregnant women with T1DM with insulin aspart plus insulin detemir (n=152) or NPH (n=158), the results showed that fasting plasma glucose levels were lower in the insulin detemir group than in the NPH group at 24 weeks of gestation (96.8 vs 113.8 mg/dL) and 36 weeks of gestation (85.7 vs 97.4 mg/dL), and there was no increased risk of occurrence of hypoglycemic events. The estimated A1c at 36 weeks of gestation was slightly lower (6.27% vs 6.33%) in insulin detemir group.[18]

In regards to the effectiveness of the treatment regimen of basal insulin in combination with bolus insulin, a randomized controlled study in 2019 compared the effects of regular human insulin and NPH with Novo-rapid and Levemir insulin on blood glucose control in patients with GDM (n=100), the study found that the two groups were similar in controlling blood sugar, but the latter had more advantages in terms of patient satisfaction and hospital stays.[19]

Table 2 Basic Characteristics and Advantages/Disadvantages of Clinical Trials Related to Insulin Intervention

Clinical Trials	Participants	Group Assignment	Outcome Assessments	Advantages/Disadvantages of Clinical Trials
Pettitt, D. J. et al[14] (2007)	GDM patients	IAsp: n=14 HI: n=13	GC	Contains an analysis of the safety and immunogenicity
Pettitt, D. J. et al[15] (2003)	GDM patients	3 meal tests with no exogenous insulin, HI, or IAsp (n=15)	GC	Short-term efficacy and small sample size
Herrera, K. M. et al[17] (2015)	GDM patients and T2DM in pregnancy	NPH: n=45 IDet: n=42	Overall mean BG	Open-label and lack of cost analysis of interventions
Mathiesen, E. R. et al[18] (2012)	Pregnant women with T1DM	NPH: n=158 IDet: n=152	GC, maternal hypoglycemia, and maternal safety	Open-label
Amini, F. G. et al[19] (2019)	GDM patients	HI + NPH: n=50 IAsp + IDet: n=50	GC	Contains comparison of patients' satisfaction

Abbreviations: GDM, gestational diabetes mellitus; GC, glycaemic control; BG, blood glucose; IAsp, insulin aspart; HI, regular human insulin; IDet, insulin detemir; NPH, neutral protamine Hagedorn.

In Table 2, we summarize basic characteristics and advantages/disadvantages of clinical trials related to insulin intervention.

Oral Anti-Diabetic Agents

Metformin

Metformin is a biguanide oral hypoglycemic drug, which can reduce gluconeogenesis and increase insulin sensitivity.[20] It is widely used in T2DM.

With regards to the effects of metformin on mothers during pregnancy, a study compared the efficacy of metformin (initial dose of 500mg at noon, maximum dose of 1500mg in three doses) and insulin (insulin detemir at night and insulin aspart before meals) in the treatment of GDM (n=286).[20] The results showed that metformin and insulin were equally effective in controlling maternal blood glucose. A recently published prospective, multicenter, international, randomized controlled clinical trial (MiTy) included a total of 502 women with T2DM in pregnancy who were given placebo (n=249) or metformin (n=253) 1000 mg twice a day on the basis of insulin treatment, the study found that compared with the placebo group, women in the metformin group had better glycaemic control and less weight gain.[21] Besides, in 2016, a meta-analysis included 1712 patients with GDM from eight randomized controlled trials, and the study found that most patients in the metformin group had their blood glucose well controlled, and their total weight gain reduced.[22] The incidence of preeclampsia and cesarean section was similar in the metformin group compared with the insulin group.

With regards to the effects of metformin on postpartum or long-term outcomes in patients with GDM, a follow-up study compared the effects on maternal weight and postpartum glucose tolerance in women diagnosed GDM who needed medication treatment to achieve the target value of blood glucose including metformin group (n=110) and insulin group (n=107) with patients who needed only diet (n=128).[23] The results showed that there was no significant difference in weight gain, oral glucose tolerance test (OGTT) glucose values, and glycosylated hemoglobin A1c (HbA1c) between metformin group and insulin group and diet-only group in 6–8 weeks or one year postpartum. However, the risk of impaired glucose tolerance or diabetes in the diet-only group was lower than that in the metformin group and insulin group. Another randomized controlled study confirmed that women with a history of GDM had a higher risk of developing diabetes than women without a history of GDM.[24] Moreover, metformin has been found to be effective in slowing down the progression of diabetes.

Metformin can penetrate the placenta, so it is worried about whether it will affect the fetus or newborn. B. Zhu et al found that metformin treatment of GDM reduced neonatal hypoglycemia and neonatal at intensive care unit (NICU) admissions, did not increase the risk of preterm delivery, and no other severe adverse reactions were

observed.[22] A clinical trial found that adverse neonatal outcomes including neonatal hypoglycemia, NICU, gestational age <37 weeks at birth, birth trauma, term birth, Apgar score at 5 min <7, birth weight were not significantly improved in women with GDM treated with metformin compared with insulin treatment.[20] However, the MiTy study found that the metformin group was beneficial to neonatal adiposity compared with the placebo group, but it increased the proportion of infants who were small-for-gestational-age infants.[21]

Metformin was similar to insulin in controlling blood glucose, and no obvious adverse pregnancy outcomes were observed. However, the associated potential and the long-term effects caused by metformin on generations need to be further evaluated.

Glyburide

Glyburide is a sulfonylurea oral anti-diabetic agent. The American College of Obstetricians and Gynecologists considers glyburide as the first-line drug for blood glucose control.[1]

In 2015, a randomized placebo-controlled trial divided women with mild GDM who received dietary therapy (at least two abnormal values in a 3-hour 100g OGTT and fasting plasma glucose less than 105 mg/dl between 24 and 30 weeks of pregnancy) into two groups: glyburide group (n = 189) and placebo group (n = 186).[25] The results revealed that on the basis of dietary therapy, the addition of glyburide significantly improved maternal blood glucose control, but no benefits were found to improve birth weight and pregnancy outcomes compared with the placebo group.

In addition, a French multicenter non-inferiority study compared glyburide (initial dose 2.5 mg/d, maximum dose 20 mg/d) and insulin (rapid-acting analogs 1 to 3 times before meals and basal insulin at bedtime as needed) on perinatal complications in patients with GDM (n=809).[26] The study found that the proportion of well-controlled fasting plasma glucose in the glyburide group (71.7%) was higher than that in the insulin group (63.2%); however, a composite criterion includes macrosomia, neonatal hypoglycemia, and hyperbilirubinemia in glyburide group is 4.2% higher than that in insulin group, suggesting that glyburide is beneficial to blood glucose control, but may have adverse effects on newborns. Post hoc analysis showed that the proportion of neonatal hypoglycemia in the glyburide group was higher than that in the insulin group. Ancillary analysis of the above study showed that 41.1% of women with GDM treated with glyburide had at least one episode hypoglycemia, compared with 9.1% in the insulin group. It is worth mentioning that the proportion of severe maternal hypoglycemia in the glyburide group decreased during the course of the trial.[27] Therefore, pregnant women receiving glyburide should closely monitor glucose of pregnant women and newborns to reduce the occurrence of hypoglycemic events, whether it is maternal hypoglycemia or neonatal hypoglycemia. To sum up, glyburide is beneficial to maternal blood glucose control, but it is not considered the first choice because of the increased risk of perinatal complications.

There are relatively many studies on metformin and glyburide in GDM compared with other oral antidiabetic agents; metformin and glyburide have the advantages of easy management, low cost, and high patients' compliance.[28] Few studies have compared metformin with glyburide in the treatment of GDM. A prospective randomized controlled study used glyburide (n=53) and metformin (n=51) as first-line treatment in GDM women between 13 and 33 weeks of gestation.[29] Treatment failures included poor blood glucose control or adverse reactions, adding or replacing another drug as second-line treatment, and insulin as third-line treatment. The study found that the success rate of metformin group was higher than that of glyburide group after second-line treatment (87% vs 50%); the glyburide group was more likely to end up receiving insulin treatment than the metformin group (17% vs 4%); mean daily blood glucose and obstetric and neonatal outcomes were similar in both groups. It is worth mentioning that the proportion of adverse reactions caused by glyburide (hypoglycemic) is slightly higher than that of metformin (gastrointestinal discomfort), although there was no statistical significance. It is suggested that metformin may have more advantages than glyburide in the treatment of GDM. Nevertheless, the sample size of above clinical trial is small, and large-scale studies are needed to confirm the results.

Based on the above studies, clinical trials have found that regardless of whether metformin or glyburide is used to treat GDM, there will eventually be different proportions of pregnant women who need insulin treatment in order to achieve the target blood glucose values.[20,23,25,26,29] The treatment of mild GDM with glyburide on the basis of dietary therapy did not reduce the use of insulin.[25] However, another prospective randomized controlled trial, using insulin as a third-line treatment, found that the combination of glyburide and metformin significantly reduced

insulin use.[29] Since oral anti-diabetic agents seem to be more acceptable than insulin, which can be reflected in the results of Brian M. Casey et al[25] insulin can be used as second-or third-line therapy for GDM who prefer oral hypoglycemic drugs. Although no FDA approval for oral hypoglycemic agents, more and more studies on oral hypoglycemic agents used in patients with GDM have shown that metformin or glyburide can provide good glycaemic control. However, they also have different safety issues. Therefore, when using oral hypoglycemic agents to treat pregnant women, they should be informed of the possible risks due to oral hypoglycemic agents that can penetrate the placenta. The long-term effect of oral hypoglycemic agents used in pregnant women on the offspring still needs numerous studies to verify.

In Table 3, we summarize basic characteristics and advantages/disadvantages of clinical trials related to oral anti-diabetic agents' intervention.

Other Treatments

Anti-Inflammatory and Antioxidant Stress

Probiotics and Fish Oil

GDM is associated with insulin resistance, which is also associated with inflammation and oxidation. Probiotics and fish oil have been shown to have anti-inflammatory and antioxidant effects. Probiotics and fish oil may improve insulin resistance through this mechanism and have a beneficial effect on GDM.

A small randomized controlled trial compared the effects of probiotic supplements (including 1000 million colony-forming units (CFU) of Lactobacillus acidophilus and 1000 million CFU of Bifidobacterium bifidum, n=28) and placebo (n=29) for four weeks on insulin resistance in GDM who needed only dietary therapy at 24–28 weeks of gestation.[30] The results showed that probiotic supplements greatly reduced fasting plasma glucose (0.68±5.88 vs 4.620±7.78 mg/dL), fasting plasma insulin (1.11±1.71 vs

Table 3 Basic Characteristics and Advantages/Disadvantages of Clinical Trials Related to Oral Anti-Diabetic Agents Intervention

Clinical Trials	Participants	Group Assignment	Outcome Assessments	Advantages/Disadvantages of Clinical Trials
Ghomian, N. et al[20] (2019)	GDM patients	Metformin: n=143 Insulin: n=143	GC and fetal outcomes	Lack of prolonged follow-up of the infants
Feig, D. S. et al[21] (2020)	Pregnant women with T2DM	Metformin + insulin: n=253 Placebo + insulin: n=249	GC, neonatal morbidity and mortality	A prospective, multicentre, international, double-masked trial/The results might not apply to women on metformin alone
Pellonpera, O. et al[23] (2016)	GDM patients	Metformin: n=110 Insulin: n=107 Diet: n=128	Weight gain and glucose tolerance postpartum	A prospective clinical trial (6–8 weeks and 1 year postpartum)
Aroda, V. R. et al[24] (2015)	Women with and without a history of GDM	History of GDM (Placebo/Metformin/Lifestyle): n=122/111/117 No history of GDM (Placebo/Metformin/Lifestyle): n=487/464/465	Fasting plasma glucose and OGTT	A 10-year follow-up period
Casey, B. M. et al[25] (2015)	Mild GDM patients	Glyburide + diet: n=189 Placebo + diet: n=186	Pregnancy outcomes	The study was performed at a single institution
Senat, M. V. et al[26] (2018)	GDM patients	Glyburide: n=367 Insulin: n=442	Neonatal perinatal complications	A multicenter study/Some criteria were not prespecified in the initial protocol
Nachum, Z. et al[29] (2017)	GDM patients	Glyburide: n=53 Metformin: n=51	The rate of treatment failure and GC	A prospective trial and the use of multiple aspects for evaluating treatment results/No blind allocation of treatment

Abbreviations: GDM, gestational diabetes mellitus; GC, glycaemic control; OGTT, oral glucose tolerance tests.

3.77±1.70 mIU/L), and homeostasis model assessment-insulin resistance (HOMA-IR) in GDM who only needed dietary therapy in the late second- and early third trimester of pregnancy, but had no effect on maternal weight gain.

Another clinical trial found that daily administration of probiotics including Lactobacillus acidophilus ($2*10^9$ CFU/g), L.casei ($2*10^9$ CFU/g) and Bifidobacterium bifidum ($2*10^9$ CFU/g) for six weeks improved fasting plasma glucose, serum insulin levels, HOMA-IR, HOMA for β-cell function (HOMA-B) and increased insulin sensitivity check index in women with GDM compared with the placebo group.[31] In addition, probiotics were found to be effective in decreased triglycerides and very low-density lipoprotein (VLDL).

However, a meta-analysis in 2017 included four high-quality clinical trials involving 288 patients with GDM, and the results showed that probiotics supplement for 6 to 8 weeks significantly reduced insulin resistance, but had no effect on fasting plasma glucose, gestational weight gain, low-density lipoprotein (LDL), delivery method and neonatal outcomes.[32] Thus, whether probiotic supplements are beneficial to improving fasting plasma glucose levels and maternal weight change is still controversial, and further clinical trials are needed.

Probiotic supplements have been shown to improve insulin resistance in pregnant women with GDM, which can be used as adjuvant drugs for patients with GDM, but the time of taking probiotics is short and contains different probiotic components and dosages. The most beneficial probiotic composition, dosages, and intervention times are worth further exploration. Besides, it is worth mentioning that the above studies lack data of probiotics on fetuses or newborns, and attention should be paid to whether it will affect the offspring of GDM.

Given the benefits of probiotics for insulin resistance in patients with GDM, it is not surprising to consider whether probiotics can prevent GDM. The Study of Probiotics In Gestation (SPRING) divided overweight and obese pregnant women (n=411) who were prior to 20 weeks of gestation into probiotics group (Lactobacillus rhamnosus and Bifidobacterium animalis subspecies lactis) and placebo group, and the results showed that the incidence of GDM was 18.4% in the probiotics group diagnosed by OGTT at 28 weeks of gestation, and 12.3% in the placebo group, with no statistically significant difference.[33] It was also found that in the OGTT, the probiotic group had higher mean fasting plasma glucose than the placebo group, and the incidence of excessive weight was lower. This study failed to conclude that taking probiotics in the second trimester of overweight and obese pregnant women can prevent GDM.

In another randomized controlled trial, pregnant women with a history of atopic diseases in a person or partner randomly taken the probiotic Lactobacillus rhamnosus HN001 (6*109 CFU, n=212) or placebo (n=211) for the pregnancy, the results showed that the incidence of GDM was assessed using the International Association of Diabetes and Pregnancy Study Groups (IADPSG) guideline at 24 to 30 weeks of gestation in the HN001 group had lower tendency than the control group, using New Zealand guideline, significantly lower incidence of GDM in the HN001 group than the placebo group (2.1% vs 6.5%).[34] Also, a higher 5-min Aspar score was observed in the HN001 group, and no detrimental effect was found on birth outcome. In the clinical trials described above, differences between the guidelines used to assess the prevalence of GDM and in the included population may have an impact on the results, and future studies need to take these factors into account.

Fish oil contains omega-3fatty acid. A clinical study observed the effects of 1000 mg omega-3fatty acid (containing 360 mg eicosapentaenoic acid (EPA) and 240 mg docosahexaenoic acid (DHA)) twice a day and/or 50000 IU vitamin D every 2 weeks for six weeks on glucose metabolism in patients with GDM (n=140).[35] The results showed that omega-3 fatty acid combined with vitamin D had positive effects on fasting plasma glucose and improved insulin resistance, and found a reduction in serum triglyceride and very low-density lipoprotein. This result is similar to that of probiotics in patients with GDM.[31]

A meta-analysis in 2020 included four clinical randomized controlled trials of patients with GDM and concluded that the combination of vitamin and omega-3fatty acid was beneficial to the metabolism of patients with GDM.[36] Due to the small sample size of the included studies, large-scale studies were needed to evaluate the effect of their combination.

However, a double-blind, randomized controlled trial found that patients with GDM (n=20) who took 1000 mg fish oil capsule containing 180 eicosapentaenoic acid and 120 mg docosahexaenoic acid twice daily for six weeks had lower fasting plasma glucose and serum triglyceride levels and increased levels of low-density lipoprotein and high-density lipoprotein than those in the placebo group.[37] In general, fish oil/omega-3 fatty acid can improve the glucose and lipid metabolism of GDM. A randomized controlled trial compared the prevalence of GDM in overweight and obese women (BMI≥ 25 kg/m^2, n=439) who took fish oil + placebo, fish oil + probiotics, probiotics + placebo and placebo + placebo, and the results showed that there was no significant difference in the prevalence of

GDM among groups, suggesting that fish oil and/or probiotics did not reduce the risk of GDM in overweight or obese women.[38]

In Table 4, we summarize basic characteristics and advantages/disadvantages of clinical trials related to probiotics and fish oil intervention.

Table 4 Basic Characteristics and Advantages/Disadvantages of Clinical Trials Related to Probiotics and Fish Oil Intervention

Clinical Trials	Participants	Group Assignment	Outcome Assessments	Advantages/Disadvantages of Clinical Trials
Kijmanawat, A. et al[30] (2019)	Diet-controlled GDM patients	Probiotic: n=28 Placebo: n=29	Insulin resistance	A double-blind study/Lack of data on the gut microbiota composition at baseline or after the intervention
Karamali, M. et al[31] (2016)	GDM patients	Probiotic: n=30 Placebo: n=30	GC and lipid profiles	Double-blind design and its consideration of confounding variables/small sample size
Callaway, L. K. et al[33] (2019)	Overweight and obese pregnant women.	Probiotic: n=207 Placebo: n=204	The prevalence of GDM	A double-blind RCT
Wickens, K. L. et al[34] (2017)	Women in early pregnancy	HN001: n=212 Placebo: n=211	The prevalence of GDM	Good follow-up rates and good generalisability/Lack of maternal anthropometric measures
Jamilian, M. et al[35] (2017)	GDM patients	Vitamin D: n=35 Omega-3: n=35 Vitamin D + omega-3: n=35 Placebo: n=35	GC and lipid concentrations	A single-center study and lack of measurements of fatty acids fractions at the baseline and end of the trial
Jamilian, M. et al[37] (2018)	GDM patients	Omega-3: n=20 Placebo: n=20	Gene expression related to insulin action, blood lipids, and inflammation	Lack of evaluation of fatty acids profiles levels and plasma adiponectin levels at the baseline and end of the trial
Pellonpera, O. et al[38] (2019)	Overweight and obese pregnant women.	Fish oil + placebo: n=109 Probiotics + placebo: n=110 Fish oil + probiotics: n=109 Placebo + placebo: n=110	Glucose metabolism and prevalence of GDM	Combine fish oil with probiotics

Abbreviations: GDM, gestational diabetes mellitus; GC, glycaemic control; RCT, randomized controlled trial.

EGCG

GDM is associated with oxidative stress and inflammation. EGCG has the effects of anti-inflammation, antioxidation and promoting insulin secretion, and is currently used as an anti-tumor agent. A clinical trial observed the effects of EGCG (n=176) on maternal and neonatal outcomes in pregnant women diagnosed with GDM in the third trimester of pregnancy and found that 500 mg EGCG daily was effective in eliminating diabetic symptoms and improving maternal and neonatal outcomes in patients with GDM.[39]

Minerals and Vitamins

Existing relevant clinical trials demonstrated that some minerals and vitamins, including magnesium,[40] zinc,[41] calcium, and vitamin D,[42] could reduce inflammation and oxidative stress. Pregnant women with GDM have significantly lower serum levels of magnesium, calcium, zinc, and vitamin D than healthy pregnant women,[43,44] leading to an interest in treating GDM with minerals and/or vitamins.

In a clinical trial, 70 patients with GDM who were given either 250 mg of magnesium oxide or placebo for six weeks, magnesium oxide supplementation was shown to be beneficial in reducing fasting plasma glucose, plasma insulin concentration, HOMA-IR, HOMA-B, high sensitivity C-reactive protein and plasma malondialdehyde concentrations, besides, magnesium supplement group the prevalence of neonatal hyperbilirubinemia was 5.9%, while in the control group was 26.5%.[40] It is suggested that magnesium supplementation may improve glucose metabolism and reduce certain adverse pregnancy outcomes in patients with GDM. In another clinical study, improvements in blood glucose control and blood lipids (except for HDL levels) were found in women with GDM who received supplements of 250 mg magnesium oxide plus 400 IU/day vitamin E (n=30) or placebo (n=30) orally for six weeks.[45] However, the sample size of the above research is small, which needs to be confirmed by large-scale studies in the future.

Magnesium, zinc, calcium, and vitamin D are related to anti-inflammation, antioxidant, and lipid metabolism, and in theory their combination may be more effective than a single drug. A randomized controlled trial observed the effects of oral magnesium-zinc-calcium-vitamin D co-supplementation (100 mg magnesium, 4 mg zinc, 400 mg calcium, 200 IU vitamin D) or placebo on biomarkers associated with inflammation and oxidative stress in GDM patients (n=60) without taking oral hypoglycemic drugs for six weeks.[46] The results showed that magnesium-zinc-calcium-vitamin D co-supplementation could reduce the concentration of serum high-sensitivity C-reactive protein and plasma malondialdehyde and increase the total antioxidant capacity. Also, neonatal weight and the incidence of macrosomia in the intervention group tended to decrease.

Another study observed the effects of oral magnesium-zinc-calcium-vitamin D co-supplementation (100 mg magnesium, 4 mg zinc, 400 mg calcium, 200 IU vitamin D) or placebo on glycemic control and cardio-metabolic risk biomarkers in GDM patients (n=60) for six weeks.[47] The study found that magnesium-zinc-calcium-vitamin D co-supplementation treatment for six weeks significantly improved glycemic control and significantly reduced serum triglycerides and VLDL concentrations. However, the study did not compare and analyze single minerals or vitamins with combined use.

In general, taking some mineral and vitamin supplements, either alone or in combination, is beneficial for patients with GDM, and no obvious adverse effects have been found. Therefore, it is hoped that they will be widely used as adjunct drugs for patients with GDM. However, the above studies are small in scale and are given six weeks of intervention, and although some trials evaluate pregnancy outcomes, they do not cover all pregnancy outcomes. Therefore, large-scale studies are needed to evaluate the effects of minerals and/or vitamins.

In Table 5, we summarize basic characteristics and advantages/disadvantages of clinical trials related to EGCG, mineral and vitamin intervention.

Blood Glucose Monitoring

Blood glucose monitoring is essential throughout pregnancy in patients with GDM, whether for the health of the pregnant woman or the fetus. The frequency of blood glucose monitoring should be paid attention to. A randomized controlled trial found that for well-controlled GDM patients, blood glucose monitoring every other day (n=144) compared with daily blood glucose monitoring (n=149) found no increase in pregnancy complications and adverse neonatal outcomes, and higher compliance.[48] It is suggested that blood glucose monitoring every other day is more acceptable to GDM patients with good glycemic control than daily blood glucose monitoring and does not come at the expense of increasing the adverse pregnancy outcomes.

Continuous glucose monitoring (CGM) has high sensitivity and can dynamically reflect the changes in blood

Table 5 Basic Characteristics and Advantages/Disadvantages of Clinical Trials Related to EGCG, Minerals and Vitamins Intervention

Clinical Trials	Participants	Group Assignment	Outcome Assessments	Advantages/Disadvantages of Clinical Trials
Zhang, H. et al[39] (2017)	GDM patients	EGCG: n=176 Placebo: n=150	Maternal and neonatal outcomes	Report the potential therapeutic value of EGCG in GDM
Asemi, Z. et al[40] (2015)	GDM patients	Magnesium: n=35 Placebo: n=35	Metabolic status and pregnancy outcomes	A double-blind RCT/Lack of other biomarkers of systemic inflammation or oxidative stress
Maktabi, M. et al[45] (2018)	GDM patients	Magnesium and vitamin E: n=30 Placebo: n=30	Metabolic status	Lack of assessment of the effects of each supplement on GC and lipid profiles
Jamilian, M. et al[46] (2019)	GDM patients	Magnesium-zinc-calcium-vitamin D: n=30 Placebo: n=30	Parameters of inflammation and oxidative stress, and pregnancy outcomes	Small sample size and short duration of intervention
Karamali, M. et al[47] (2018)	GDM patients	Magnesium-zinc-calcium-vitamin D: n=30 Placebo: n=30	GC and cardio-metabolic risk markers	Lack of assessment of single supplementation comparison with co-supplementation the beneficial effects

Abbreviations: GDM, gestational diabetes mellitus; EGCG, epigallocatechin 3-gallate; GC, glycaemic control; RCT, randomized controlled trial.

glucose. A randomized controlled trial in Malaysia found that glycosylated hemoglobin (HbA1c) increased by 1mmol/L from 28 to 37 weeks gestation in patients with GDM (n=50) who needed insulin therapy using retrospective CGM (6-day sensor) at 28, 32, and 36 weeks gestation, compared with an increase of 3 mmol/L in the control group.[49] Mean HbA1c in the retrospective CGM group remained stable with the progression of pregnancy, while that in the control group increased, and retrospective CGM did not increase the incidence of hypoglycemia events.

However, in another multicenter Glucose Monitoring with Sensor (GlucoMOMS) trial, intermittent retrospective CGM (n=147) or standard treatment (n=153) was performed in pregnant women (n=300) who were diagnosed with T1DM or T2DM or GDM who needed insulin therapy, the results showed that the incidence

Table 6 Basic Characteristics and Advantages/Disadvantages of Clinical Trials Related to CGM Intervention

Clinical Trials	Participants	Group Assignment	Outcome Assessments	Advantages/Disadvantages of Clinical Trials
Mendez-Figueroa, H. et al[48] (2017)	Well-controlled GDM patients	Testing BG daily: n=149 Testing BG every other day: n=144	Birth weights	The primary endpoint, birth weight, may lack clinical meaningfulness
Paramasivam, S. S. et al[49] (2018)	Insulin-treated GDM patients	CGM: n=25 Control: n=25	HbA1c	Small sample size and single centre
Voormolen, D. N. et al[50] (2018)	Diabetic pregnancies	CGM: n=147 Control: n=153	Macrosomia, GC, maternal and neonatal complications	Inclusion of all types of diabetes/The high number of patients that refused continued use of the CGM after the first or second time

Abbreviations: GDM, gestational diabetes mellitus; BG, blood glucose; CGM, continuous glucose monitoring; HbA1c, glycosylated hemoglobin A1c; GC, glycaemic control.

of macrosomia was 31.0% in the CGM group and 28.4% in the control group,[50] suggesting that intermittent retrospective CGM had no improvement in reducing the risk of macrosomia.

In Table 6, we summarize basic characteristics and advantages/disadvantages of clinical trials related to CGM intervention.

CGM is a blood glucose monitoring method that should not been ignored, which is beneficial to the blood glucose control and the avoidance of hypoglycemia, but there are few studied on the effect of CGM on pregnancy outcomes in patients with GDM, which may require further attention.

Conclusions

Most patients with diabetes in pregnancy can be controlled with basic treatment such as insulin and lifestyle interventions, and the development of CGM also provides convenience. However, for some patients, especially those with pregestational diabetes mellitus, glycemic control is difficult, so the application of oral agents and other adjuvant therapy is possible, and its safety and effectiveness need to be supported by large sample clinical trials.

Disclosure

The authors report no conflicts of interest for this work.

References

1. Committee on Practice, B.-O. Practice Bulletin No. 137: gestational diabetes mellitus. *Obstet Gynecol*. 2013;122(2, PART 1):406–416. doi:10.1097/01.AOG.0000433006.09219.f1.
2. Zhu Y, Zhang C. Prevalence of gestational diabetes and risk of progression to type 2 diabetes: a global perspective. *Curr Diab Rep*. 2016;16(1):7. doi:10.1007/s11892-015-0699-x
3. Gao C, Sun X, Lu L, Liu F, Yuan J. Prevalence of gestational diabetes mellitus in mainland China: a systematic review and meta-analysis. *J Diabetes Investig*. 2019;10(1):154–162. doi:10.1111/jdi.12854
4. Dabelea D, Hanson RL, Lindsay RS, et al. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. *Diabetes*. 2000;49(12):2208–2211. doi:10.2337/diabetes.49.12.2208
5. Clausen TD, Mathiesen ER, Hansen T, et al. High prevalence of type 2 diabetes and pre-diabetes in adult offspring of women with gestational diabetes mellitus or type 1 diabetes: the role of intrauterine hyperglycemia. *Diabetes Care*. 2008;31(2):340–346. doi:10.2337/dc07-1596
6. Blotsky AL, Rahme E, Dahhou M, Nakhla M, Dasgupta K. Gestational diabetes associated with incident diabetes in childhood and youth: a retrospective cohort study. *Canadian Medical Association Journal*. 2019;191(15):E410–e417. doi:10.1503/cmaj.181001
7. Brewster S, Zinman B, Retnakaran R, Floras JS. Cardiometabolic consequences of gestational dysglycemia. *J Am Coll Cardiol*. 2013;62(8):677–684. doi:10.1016/j.jacc.2013.01.080
8. Barengo NC, Antikainen R, Borodulin K, Harald K, Jousilahti P. Leisure-time physical activity reduces total and cardiovascular mortality and cardiovascular disease incidence in older adults. *J Am Geriatr Soc*. 2017;65(3):504–510. doi:10.1111/jgs.14694
9. La Vecchia C, Gallus S, Garattini S. Effects of physical inactivity on non-communicable diseases. *Lancet*. 2012;380(9853):1553. doi:10.1016/S0140-6736(12)61872-8
10. Sklempe Kokic I, Ivanisevic M, Biolo G, et al. Combination of a structured aerobic and resistance exercise improves glycaemic control in pregnant women diagnosed with gestational diabetes mellitus. A randomised controlled trial. *Women and Birth*. 2018;31(4):e232–e238. doi:10.1016/j.wombi.2017.10.004
11. Wang C, Wei Y, Zhang X, et al. A randomized clinical trial of exercise during pregnancy to prevent gestational diabetes mellitus and improve pregnancy outcome in overweight and obese pregnant women. *Am J Obstet Gynecol*. 2017;216(4):340–351. doi:10.1016/j.ajog.2017.01.037
12. Koivusalo SB, Rönö K, Klemetti MM, et al. Gestational diabetes mellitus can be prevented by lifestyle intervention: the Finnish Gestational Diabetes Prevention Study (RADIEL): a randomized controlled trial. *Diabetes Care*. 2016;39(1):24–30. doi:10.2337/dc15-0511
13. Kunath J, Günther J, Rauh K, et al. Effects of a lifestyle intervention during pregnancy to prevent excessive gestational weight gain in routine care – the cluster-randomised GeliS trial. *BMC Med*. 2019;17(1):5. doi:10.1186/s12916-018-1235-z
14. Pettitt DJ, Ospina P, Howard C, Zisser H, Jovanovic L. Efficacy, safety and lack of immunogenicity of insulin aspart compared with regular human insulin for women with gestational diabetes mellitus. *Diabetic Medicine*. 2007;24(10):1129–1135. doi:10.1111/j.1464-5491.2007.02247.x
15. Pettitt DJ, Ospina P, Kolaczynski JW, Jovanovic L. Comparison of an insulin analog, insulin aspart, and regular human insulin with no insulin in gestational diabetes mellitus. *Diabetes Care*. 2003;26(1):183–186. doi:10.2337/diacare.26.1.183
16. Combs CA, Gunderson E, Kitzmiller JL, Gavin LA, Main EK. Relationship of fetal macrosomia to maternal postprandial glucose control during pregnancy. *Diabetes Care*. 1992;15(10):1251–1257. doi:10.2337/diacare.15.10.1251
17. Herrera KM, Rosenn BM, Foroutan J, et al. Randomized controlled trial of insulin detemir versus NPH for the treatment of pregnant women with diabetes. *Am J Obstet Gynecol*. 2015;213(3):426–427. doi:10.1016/j.ajog.2015.06.010
18. Mathiesen ER, Hod M, Ivanisevic M, et al. Maternal efficacy and safety outcomes in a randomized, controlled trial comparing insulin detemir with NPH insulin in 310 pregnant women with type 1 diabetes. *Diabetes Care*. 2012;35(10):2012–2017. doi:10.2337/dc11-2264
19. Amini FG, Nia AF, Sharbafi MH, Khandari A, Gargari SS. Comparison between the effect of regular human insulin and NPH with novo-rapid and levemir insulin in glycemic control in gestational diabetes. *Hum Antibodies*. 2019;27(4):285–289. doi:10.3233/HAB-190385
20. Ghomian N, Vahed SHM, Firouz S, et al. The efficacy of metformin compared with insulin in regulating blood glucose levels during gestational diabetes mellitus: a randomized clinical trial. *J Cell Physiol*. 2019;234(4):4695–4701. doi:10.1002/jcp.27238
21. Feig DS, Donovan LE, Zinman B, et al. Metformin in women with type 2 diabetes in pregnancy (MiTy): a multicentre, international, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol*. 2020;8(10):834–844. doi:10.1016/s2213-8587(20)30310-7
22. Zhu B, Zhang L, Fan YY, et al. Metformin versus insulin in gestational diabetes mellitus: a meta-analysis of randomized clinical trials. *Irish J Med Sci*. 2016;185(2):371–381. doi:10.1007/s11845-016-1414-x

23. Pellonpera O, Ronnemaa T, Ekblad U, Vahlberg T, Tertti K. The effects of metformin treatment of gestational diabetes on maternal weight and glucose tolerance postpartum - a prospective follow-up study. *Acta Obstet Gynecol Scand*. 2016;95(1):79–87. doi:10.1111/aogs.12788
24. Aroda VR, Christophi CA, Edelstein SL, et al. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without gestational diabetes: the Diabetes Prevention Program outcomes study 10-year follow-up. *J Clin Endocrinol Metab*. 2015;100(4):1646–1653. doi:10.1210/jc.2014-3761
25. Casey BM, Duryea EL, Abbassi-Ghanavati M, et al. Glyburide in women with mild gestational diabetes: a randomized controlled trial. *Obstet Gynecol*. 2015;126(2):303–309. doi:10.1097/AOG.0000000000000967
26. Senat M-V, Affres H, Letourneau A, et al. Effect of glyburide vs subcutaneous insulin on perinatal complications among women with gestational diabetes: a randomized clinical trial. *JAMA*. 2018;319(17):1773–1780. doi:10.1001/jama.2018.4072
27. Affres H, Senat M-V, Letourneau A, et al. Glyburide therapy for gestational diabetes: glycaemic control, maternal hypoglycaemia, and treatment failure. *Diabetes Metab*. 2020:101210. doi:10.1016/j.diabet.2020.11.002.
28. Balsells M, Garcia-Patterson A, Sola I, et al. Glibenclamide, metformin, and insulin for the treatment of gestational diabetes: a systematic review and meta-analysis. *BMJ*. 2015;350(jan21 14):(h102. doi:10.1136/bmj.h102
29. Nachum Z, Zafran N, Salim R, et al. Glyburide versus metformin and their combination for the treatment of gestational diabetes mellitus: a randomized controlled study. *Diabetes Care*. 2017;40(3):332–337. doi:10.2337/dc16-2307
30. Kijmanawat A, Panburana P, Reutrakul S, Tangshewinsirikul C. Effects of probiotic supplements on insulin resistance in gestational diabetes mellitus: a double-blind randomized controlled trial. *J Diabetes Investig*. 2019;10(1):163–170. doi:10.1111/jdi.12863
31. Karamali M, et al. Effects of probiotic supplementation on glycaemic control and lipid profiles in gestational diabetes: a randomized, double-blind, placebo-controlled trial. *Diabetes Metab*. 2019;10(1):234–241. doi:10.1111/jdi.12854
32. Taylor BL, et al. Effect of probiotics on metabolic outcomes in pregnant women with gestational diabetes: a systematic review and meta-analysis of randomized controlled trials. *Nutrients*. 2017;9:5. doi:10.3390/nu9050461
33. Callaway LK, et al. Probiotics for the prevention of gestational diabetes mellitus in overweight and obese women: findings from the SPRING double-blind randomized controlled trial. *Diabetes Care*. 2019;42(3):364–371. doi:10.2337/dc18-2248
34. Wickens KL, et al. Early pregnancy probiotic supplementation with Lactobacillus rhamnosus HN001 may reduce the prevalence of gestational diabetes mellitus: a randomised controlled trial. *Br J Nutr*. 2017;117(6):804–813. doi:10.1017/S0007114517000289
35. Jamilian M, et al. The effects of vitamin D and omega-3 fatty acid co-supplementation on glycemic control and lipid concentrations in patients with gestational diabetes. *J Clin Lipidol*. 2017;11(2):459–468. doi:10.1016/j.jacl.2017.01.011
36. Li F, Pei L, Huang G, Ye H. Influence of omega-3 fatty acid and vitamin co-supplementation on metabolic status in gestational diabetes: a meta-analysis of randomized controlled studies. *Eur J Obstet Gynecol Reprod Biol*. 2020;247:191–197. doi:10.1016/j.ejogrb.2020.02.024
37. Jamilian M, et al. A randomized double-blinded, placebo-controlled trial investigating the effect of fish oil supplementation on gene expression related to insulin action, blood lipids, and inflammation in gestational diabetes mellitus-fish oil supplementation and gestational diabetes. *Nutrients*. 2018;10:2. doi:10.3390/nu10020163
38. Pellonpera O, et al. Efficacy of fish oil and/or probiotic intervention on the incidence of gestational diabetes mellitus in an at-risk group of overweight and obese women: a randomized, placebo-controlled, double-blind clinical trial. *Diabetes Care*. 2019;42(6):1009–1017. doi:10.2337/dc18-2591
39. Zhang H, Su S, Yu X, Li Y. Dietary epigallocatechin 3-gallate supplement improves maternal and neonatal treatment outcome of gestational diabetes mellitus: a double-blind randomised controlled trial. *J Hum Nutr Diet*. 2017;30(6):753–758. doi:10.1111/jhn.12470
40. Asemi Z, et al. Magnesium supplementation affects metabolic status and pregnancy outcomes in gestational diabetes: a randomized, double-blind, placebo-controlled trial. *Am J Clin Nutr*. 2015;102(1):222–229. doi:10.3945/ajcn.114.098616
41. Karamali M, et al. Zinc supplementation and the effects on pregnancy outcomes in gestational diabetes: a randomized, double-blind, placebo-controlled trial. *Exp Clin Endocrinol Diabetes*. 2016;124(1):28–33. doi:10.1055/s-0035-1564146
42. Karamali M, Asemi Z, Ahmadi-Dastjerdi M, Esmaillzadeh A. Calcium plus vitamin D supplementation affects pregnancy outcomes in gestational diabetes: randomized, double-blind, placebo-controlled trial. *Public Health Nutr*. 2016;19(1):156–163. doi:10.1017/S1368980015000609
43. Barbosa KB, et al. Low energy and carbohydrate intake associated with higher total antioxidant capacity in apparently healthy adults. *Nutrition*. 2014;30(11–12):1349–1354. doi:10.1016/j.nut.2014.03.031
44. Asemi Z, et al. Assessment of the relationship of vitamin D with serum antioxidant vitamins E and A and their deficiencies in Iranian pregnant women. *Saudi Med J*. 2010;31(10):1119–1123.
45. Maktabi M, Jamilian M, Amirani E, Chamani M, Asemi Z. The effects of magnesium and vitamin E co-supplementation on parameters of glucose homeostasis and lipid profiles in patients with gestational diabetes. *Lipids Health Dis*. 2018;17(1):163. doi:10.1186/s12944-018-0814-5
46. Jamilian M, et al. The effects of magnesium-zinc-calcium-vitamin D co-supplementation on biomarkers of inflammation, oxidative stress and pregnancy outcomes in gestational diabetes. *BMC Pregnancy Childbirth*. 2019;19(1):107. doi:10.1186/s12884-019-2258-y
47. Karamali M, Bahramimoghadam S, Sharifzadeh F, Magnesium-zinc-calcium-vitamin AZ. D co-supplementation improves glycemic control and markers of cardiometabolic risk in gestational diabetes: a randomized, double-blind, placebo-controlled trial. *Appl Physiol Nutr Metab*. 2018;43(6):565–570. doi:10.1139/apnm-2017-0521
48. Mendez-Figueroa H. Gestational diabetes mellitus and frequency of blood glucose monitoring: a randomized controlled trial. *Obstet Gynecol*. 2017;130(1):163–170. doi:10.1097/AOG.0000000000002101
49. Paramasivam SS. Continuous glucose monitoring results in lower HbA1c in Malaysian women with insulin-treated gestational diabetes: a randomized controlled trial. *Diabetic Medicine*. 2018;35(8):1118–1129. doi:10.1111/dme.13649
50. Voormolen DN. Continuous glucose monitoring during diabetic pregnancy (GlucoMOMS): a multicentre randomized controlled trial. *Diabetes Obes Metab*. 2018;20(8):1894–1902. doi:10.1111/dom.13310