Original Article

Effects of Magnesium-Vitamin E Co-supplementation on Glucose Metabolism, Oxidative Stress, and Pregnancy Outcomes Among Women with Gestational Diabetes: A Double-blind Clinical Trial Study

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Abstract

Background & Objective: Dietary antioxidants may play a protective role in the pathophysiology of gestational diabetes mellitus (GDM). The present study aimed to evaluate the effect of magnesium-vitamin E co-supplementation on glycemic control and pregnancy outcomes in women with GDM.

Materials & Methods: This randomized clinical trial was conducted among GDM pregnant women at 24-28 weeks of gestation. The study did not include mothers who needed medication to control their blood glucose levels or had a history of DM. The subjects were randomly divided into two 30-member groups, one of which received magnesium (250 mg), and vitamin E (400 mg) daily, while the other was given a placebo. Blood samples were taken at the study baseline and six weeks after the intervention to quantify oxidative stress biomarkers, fasting plasma glucose (FPG), and fasting plasma insulin (FPI). Additionally, the effect of supplementation was assessed on neonatal outcomes. Data analysis was performed using SPSS 20 (SPSS, Chicago, IL).

Results: A significant decrease was observed in the FPG and FPI of the supplementation group ($p<0.05$). However, FPI elevated by progressing pregnancy in the placebo group ($p=1.99\times10^{-4}$). The homeostasis model assessment (HOMA) revealed that supplementation was associated with improved insulin sensitivity ($p=3.38\times10^{-13}$). In addition, total antioxidant capacity increased to 5.66 ± 0.86% in the treatment group. Finally, no significant difference was found between the groups regarding neonatal outcomes.

Conclusion: The results represented that magnesium-vitamin E co-supplementation significantly reduced oxidative biomarkers and improved glycemic control in GDM.

Keywords: Magnesium, Vitamin E, Pregnancy, Diabetes Mellitus, Oxidative stress

Introduction

Gestational diabetes mellitus (GDM) is the most common metabolic disorder during pregnancy, accompanied by various complications for mother and fetus. GDM is first detected during pregnancy and increases the risk of maternal diabetes after delivery (1). According to the international diabetes federation, 223 million women were living with diabetes by 2019, and were expected to grow more than 1.5 times by 2045 (2). In Iran, gestational diabetes has been considered in the national diabetes plan (3, 4). The physiological changes occurring during a normal

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pregnancy can lead to GDM in susceptible individuals. The second and third trimesters of pregnancy are associated with elevated insulin resistance, which results in more insulin secretion (5). In addition, human placental growth hormone (hPGH) is mainly secreted from placental syncytiotrophoblast and mediates insulin resistance by regulating insulin-like growth factor 1 (IGF-1) (6). The hPGH responds inversely to maternal insulin levels and facilitates glucose delivery to the fetus (7, 8). Impaired insulin response increases plasma ketones, leading to adverse outcomes for both mother and developing fetus.

Several biochemical studies have reported the relationship between hyperglycemia with oxidative stress. The overproduction of free radicals and impairment of radical scavenger mechanisms can be observed in patients with poor glycemic control. An increase in reactive oxygen species (ROS) is related to DNA methylation patterns, affecting fetal programming (9, 10).

GDM is accompanied by an elevated risk of advanced fetal macrosomia, premature birth, fetal death, respiratory distress syndrome in newborns, and maternal mortality (11, 12). Non-enzymatic antioxidants such as glutathione, natural flavonoids, and vitamins (A, C, and E) can improve defense against the adverse action of ROS (13-15). In addition, numerous reports revealed that the plasma level of vitamin E is significantly lower in GDM women than in healthy ones (16, 17). Also, the lower plasma magnesium concentration in pregnant women with GDM is related to impaired insulin secretion, and recent studies showed that oral magnesium supplementation improves glycemic control (18-20). In a previous study, our research team investigated the effect of magnesium and vitamin E oral supplementation on glucose homeostasis and lipid profile in women with GDM (21). The primary goal of the recent clinical trial was to assess the effect of magnesium-vitamin E co-supplementation on oxidative stress and metabolic status in women with GDM and to evaluate the correlation between supplementation and maternal and neonatal outcomes.

Materials & Methods

Trial design

A double-blind, randomized clinical trial was performed among pregnant women with GDM at Akbarabadi Hospital in Tehran, Iran, from January 2019 to January 2020.

Participants

All the pregnant women (at 24-28 weeks of gestation) attending the obstetrics outpatient unit of the hospital were screened for GDM according to the American Diabetes Association criteria (21, 22). Computer-generated random numbers were utilized for the randomization. All low-risk individuals were assessed using a one-step 75 g oral glucose tolerance test (OGTT). Fasting plasma glucose (FPG) level > 92 mg/dL, ≥180 mg/dL after 1 hour, and >153 mg/dL after 2 hours meet the threshold for diagnosing diabetes. The inclusion criteria of this study were 18-40-year women with GDM who had no history of diabetes mellitus (DM) before pregnancy. Also, participants in the study were not taking oral hypoglycemic agents. On the other hand, those taking the supplements containing magnesium and vitamin E in the last three months, smoking, and forgetting to consume supplements for three consecutive or five non-consecutive days were excluded from the study. The insulin therapy required during the study, pre-eclampsia, eclampsia, preterm delivery, and hypo or hyperthyroidism were among the other exclusion criteria.

Study Design

At the onset of the study, all participants were matched based on baseline body mass index and age. The individuals were then randomly assigned to supplementation and placebo groups (n=30). Six patients in each group were excluded from the study during follow-up due to unwillingness to continue cooperation (loss of follow-up). Thus, 24 individuals remained in each group who were analyzed (Figure 1). A standard scale (Seca, Hamburg, Germany) was used to measure the subjects' weight and height at baseline and six weeks after intervention. Body mass index (BMI) was calculated using equation 1.

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Eqn 1. $BMI = \frac{\text{weight (kg)}}{(\text{height})^2}$

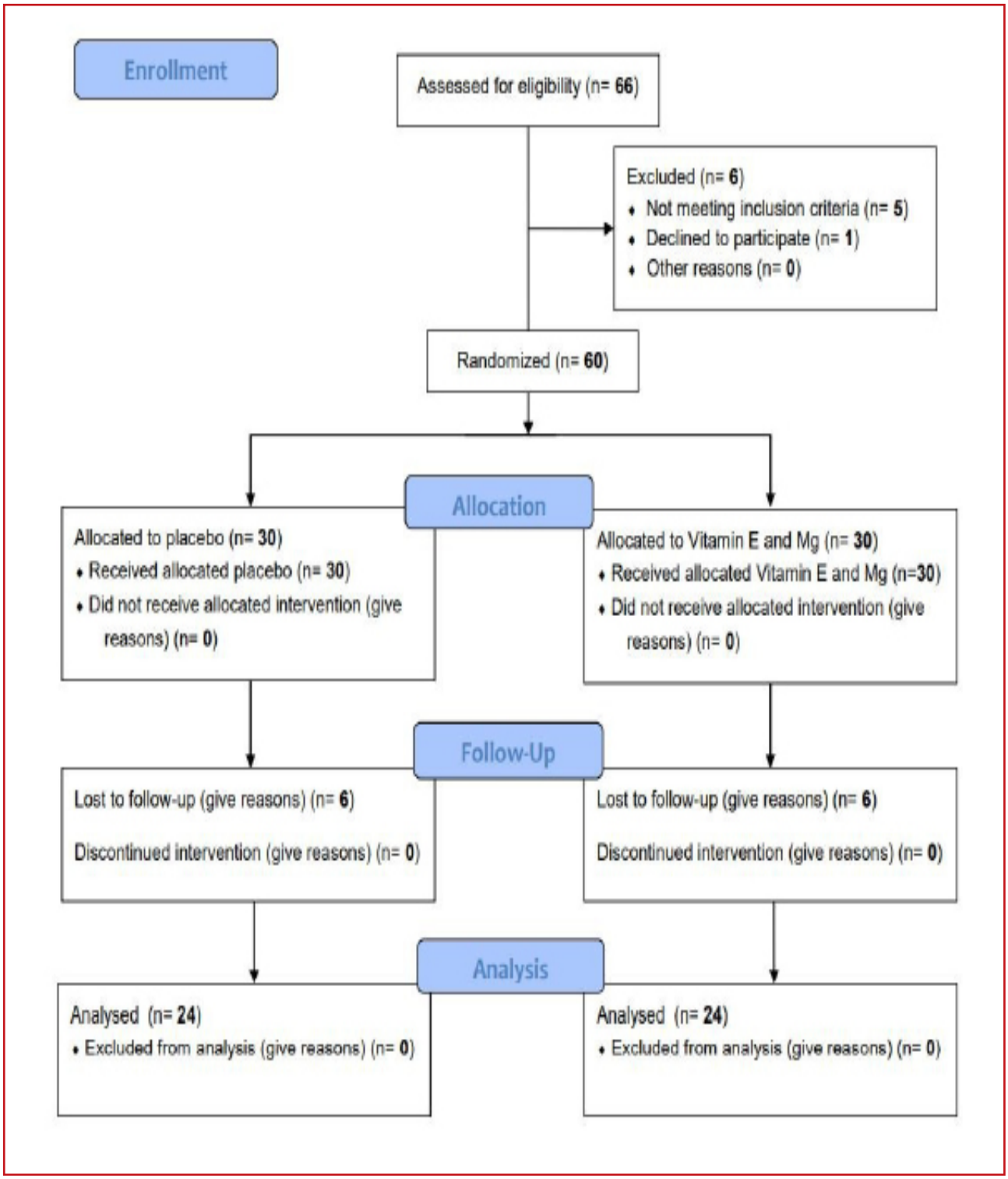

Figure 1. CONSORT diagram of recruitment, randomization, and withdrawal

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The blood glucose level of the subjects was assessed every two weeks to identify and exclude the cases meeting diabetes criteria (FPG of 126 mg/dL or 2-h glucose of 200 mg/dL) (23).

Intervention

The supplementation group was treated with a combination of 250 mg of magnesium oxide (Tablet, 21st Century Pharmaceutical Company, AZ, USA) and 400 mg of vitamin E (Soft gel capsule, Zahravi Pharmaceutical Company, Tabriz, Iran). Tablets and soft gel capsules without the active ingredients were provided by Barij Essence Company (Kashan, Iran) and used as a placebo. The supplements were given once a day for six weeks, and the recommended intake time was two hours after breakfast. The dose of vitamin E and magnesium was selected based on the study previously conducted by the research team on the effect of oral supplementation on glucose homeostasis and lipid profile in women with GDM (21). The gestational age of the subjects was determined according to the first day of the last menstrual period. Ultrasound measurement of the fetus in the first trimester was set up as a reliable method to determine the gestational age. Pregnant women included in the study were asked not to change their physical activity and called via telephone once a week to check the supplement consumption. All the individuals were recommended to use a standard GDM diet containing 40-50% carbohydrates, 20-30% protein, and 25-35% total fat. The range of main nutrients was obtained based on the new diet studies during pregnancy (24, 25). The study method and its objectives were clearly explained to patients at the beginning of the trial, and all cases signed a consent form.

Biochemical Assessment

A trained nutritionist monitored the subjects' conditions during treatment and recorded the changes in weight and BMI. In addition, 10-mL blood samples were taken for biochemical evaluations at weeks 0 and 6 of the intervention. A high Sensitive ELISA Kit (Monobind, California, USA) was utilized to determine serum C-reactive protein (CRP). Plasma nitric oxide (NO) levels were specified with a Natrix™ Kit (Navand Salamat, Urmia, Iran). In this regard, NO concentration was calculated by employing the Griess reaction method (26). Further, plasma total antioxidant capacity (TAC) was obtained using the Naxifer™ Kit (Navand Salamat, Urmia, Iran). In this technique, iron reducibility ($Fe^{3+} \rightleftharpoons Fe^{2+}$) was measured using the FRAP method. Glutathione (GSH) is a low-molecular-weight peptide in mammalian cells, protecting the organism from oxidative damage. The present study determined plasma GSH concentration by NarGul™ Kit (Navand Salamat, Urmia, Iran). Furthermore, MDA is considered an end product of lipid peroxidation in tissue, frequently utilized as an oxidative damage indicator (27). A Nalondi™ Kit (Navand Salamat, Urmia, Iran) was used to examine plasma MDA levels based on the thiobarbituric acid test. FPI was assayed by an ELISA kit (Merck KGaA, Germany), while Enzymatic Kits (Pars Azmoun, Tehran, Iran) were applied for measuring plasma magnesium and glucose concentration. The homeostatic model assessment (HOMA) is performed to estimate insulin resistance (IR) and β-cell function using FPG and FPI (28). The model was developed for IR and β-cell as follows.

$$\text{Eqn 2. HOMA-IR} = \frac{\text{FPG (mg/dL)} \times \text{FPI}(\mu\text{U/mL})}{405}$$

$$\text{Eqn 3. HOMA-}\beta = \frac{360 \times \text{FPI } (\mu\text{U/mL})}{\text{FPG (mg/dL)-63}} \times 100$$

Statistical Analysis

The data are expressed as the numbers, n (%), or mean ± standard deviation (SD). The normality of the data was assessed using Shapiro–Wilk tests. The student's paired t-test was performed to assess differences within groups over time (pre–post-intervention). Comparisons between groups were performed using the student's unpaired t-test for continuous data and chi-square tests for categorical data. A probability value of less than 0.05 ($p<0.05$) was accounted for statistically significant in all tests. Data management was

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performed using SPSS 20 (SPSS, Chicago, IL).

Results

In the present study, the treatment group received the supplements, while the other consumed the placebo. The two groups were compared in terms of mean age, BMI, and weight gain during the intervention, but no significant difference was observed (Table 1).

Table 1. General characteristics of all pregnant women with GDM included per groups

Variables	Supplement	Placebo	p-value
Age (Year)	25.20 ± 2.30	25.80 ± 2.20	0.412
Height (cm)	163.17 ± 2.67	161.83 ± 4.08	0.093
Weight at study baseline (kg)	71.60 ± 5.15	70.54 ± 4.65	0.233
Weight at end of trial (kg)	73.38 ± 5.13	72.42 ± 4.55	0.253
Weight gain during the intervention (kg)	1.77 ± 0.02	1.88 ± 0.09	0.434
BMI at study baseline (kg/m^2)	26.78 ± 1.87	27.01 ± 2.26	0.689
BMI at end-of-trial (kg/m^2)	27.73 ± 2.27	27.45 ± 1.85	0.648
BMI change (kg/m^2)	0.66 ± 0.02	0.72 ± 0.19	0.133

Also, the plasma levels of supplements and metabolic biomarkers were compared between the groups at baseline and 6 weeks after the intervention (Table 2).

Table 2. The metabolic profiles, Plasma levels of magnesium, vitamin E, and metabolic biomarkers at the study baseline and after 6-week intervention in women with GDM who received either the supplements or placebo

Variables	Placebo (means±SE; n = 24)			Supplement (means±SD; n = 24)		
	Baseline	Week 6 (p-value[a])	Changes %	Baseline	Week 6 (p-value[a])	Changes % (p-value[b])
Magnesium (mg/dL)	2.11±0.03	2.13±0.03 (0.62)	1.35±1.86	2.1±0.02	2.26±0.03 (4.62×10^{-4})	8.09±1.99 (1.76×10^{-2})
Vit. E (mg/dL)	6.180±0.035	6.097±0.034 (2.91×10^{-3})	-1.32±0.4	6.112±0.036	6.31±0.04 (6.86×10^{-7})	3.26±0.48 (3.29×10^{-9})
FPG (mg/dL)	92.15±0.38	92.72±0.35 (0.26)	0.65±0.53	92.49±0.32	85.35±0.81 (9.84×10^{-8})	-7.69±0.94 (1.26×10^{-9})
Insulin (µIU/L)	13.363±0.0.5	13.8±0.07 (1.99×10^{-4})	3.29±0.74	13.38±0.07	12.61±0.08 (4.19×10^{-7})	-5.72±0.81 (1.44×10^{-10})
HOMA-IR	3.04±0.02	3.16±0.02 (1.71×10^{-4})	3.98±1.02	3.06±0.02	2.66±0.03 (6.35×10^{-9})	-12.93±1.37 (3.82×10^{-13})
HOMA-β	165.65±2.12	167.64±2.09 (0.96)	1.54±1.74	163.79±1.9	208.3±6.69 (2.12×10^{-6})	27.37±4.04 (1.48×10^{-6})
hs-CRP (µg/dL)	3.70±0.17	4.03±0.19 (7.93×10^{-6})	8.81±1.52	4.18±0.18	3.57±0.15 (2.5×10^{-8})	-14.36±1.69 (2.29×10^{-13})
NO (µmol/L)	47.88±0.75	48.02±0.52 (0.84)	0.68±1.47	47.28±0.8	50.55±0.89 (2.86×10^{-5})	7.09±1.35 (2.4×10^{-3})
TAC (mmol/L)	756.21±19.16	748.33±21.48 (0.22)	-1.16±0.85	747.21±10.92	788.92±11.58 (1.09×10^{-6})	5.66±0.86 (1.01×10^{-6})
GSH (µmol/L)	487.54±8.46	463.75±6.92 (3.35×10^{-4})	-4.64±1.09	472.75±7.98	505.88±8.08 (3.9×10^{-5})	7.26±1.47 (5.41×10^{-8})
MDA (µmol/L)	3.28±0.11	3.46±0.12 (3.08×10^{-3})	5.82±1.78	3.89±0.11	3.62±0.1 (1.92×10^{-4})	-6.71±1.64 (4.72×10^{-6})

a Different from the baseline study by the student's paired t-test
b different from the corresponding placebo by the unpaired t-test

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Mg magnesium; FPG fasting plasma glucose; HOMA-β homeostatic model assessment–β cell function; HOMA-IR homeostasis model of assessment–insulin resistance; hs-CRP high-sensitivity C-reactive protein; NO nitric oxide; TAC total antioxidant capacity; GSH total glutathione; MDA malondialdehyde.

The plasma levels of magnesium elevated by 8.09 ± 1.99% in the supplementation group, significantly higher than in the control group (p=0.017). Also, vitamin E was enhanced in the treatment group (3.26 ± 0.48%), considerably higher than in the control group ($p=3.29\times10^{-9}$). Furthermore, FPG and FPI diminished in the treatment group with a p-value of 9.84×10^{-8} and 4.15×10^{-7}, respectively. On the other hand, an elevation was obtained in the FPI of the placebo group ($p=1.99\times10^{-4}$). HOMA-IR and HOMA-β were calculated based on the FPG and FPI data. The calculations revealed that the supplements improved insulin sensitivity ($p=3.38\times10^{-13}$) and β-cell activity ($p=1.49\times10^{-6}$). In the supplementation group, the plasma levels of inflammatory markers decreased (hs-CRP: -14.36 ± 1.69% and MDA: -6.71 ± 1.64), while antioxidant parameters elevated (TAC: +5.66 ± 0.86% and GSH: +7.26 ± 1.47%). In contrast, the control group represented an increase in MDA ($p=3.08\times10^{-3}$) but a reduction in GSH ($p=3.35\times10^{-4}$).

In this study, the effect of the therapeutic intervention was evaluated on pregnancy outcomes (Table 3).

Table 3. Comparison of the pregnancy outcomes and complications in all pregnant women with GDM included per group between baseline and six weeks after intervention

Variables	Placebo (n=24)	Supplement (n=24)	P-value
Maternal Outcomes			
Cesarean (No, %)	9 (37.5 %)	7 (29.17 %)	0.54
Pre-eclampsia (No, %)	3 (12.5%)	2 (8.33%)	0.636
Polyhydramnios (No, %)	2 (8.33%)	0 (0%)	0.148
Hyperbilirubinemia (No, %)	6 (25%)	4 (16.67%)	0.477
Hypoglycemia (No, %)	2 (8.33%)	2 (8.33%)	1
Preterm Delivery (No, %)	0 (0%)	0 (0%)	-
Neonatal Outcomes			
Weight (g)	3443.333 ± 75.488	3344.583 ± 65.111	0.327†
Height (cm)	50.708 ± 0.348	50.438 ± 0.355	0.589†

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Head circumference (cm)	35.354 ± 0.230	34.929 ± 0.185	0.157†
1- min Apgar score	8.958 ± 0.042	8.875 ± 0.069	0.306†
5- min Apgar score	9.833 ± 0.098	9.875 ± 0.069	0.73†

Results are reported as means±SE for continuous variables and number (%) for dichotomous variables.
†Obtained from the Pearson Chi-square test

The results showed that the two groups were not significantly different in cesarean delivery and polyhydramnios. Supplementation failed to make any significant difference in neonatal outcomes (Table 3).

Discussion

The latest research has highlighted the effect of supplements on improving DM. Minerals, probiotics, and fat-soluble vitamins are among the most frequently-studied compounds (29, 30). The clinical trial focused on the relationship between magnesium-vitamin E co-supplementation and oxidative stress in GDM.

The first trimester of a normal pregnancy is defined as the maternal anabolic phase, in which high insulin sensitivity augments energy storage. Glucose catabolism increases in the second and third trimesters to provide the energy needed for fetal growth (6). A high level of plasma glucose concentration stimulates insulin secretion, and β-cell dysfunction may occur in GDM patients (31). The present study results revealed an elevation in the insulin secretion and resistance related to the placebo group after six weeks. However, FPG concentration and β-cell activity did not change significantly. The results of a study on the effects of magnesium and vitamin E oral administration on glucose homeostasis in GDM women indicated an improved glycemic control and a significant enhancement in lipid profiles (triglycerides, VLDL, and LDL reduced) (21). Castellanos et al. assessed the effect ofdietary magnesium intake on the BMI and serum glucose of healthy Mexican adults (both genders) between 2011 and 2012. They found that magnesium intake is significantly associated with lower BMI and serum glucose (32).

Furthermore, the increased plasma glucose concentration induces excess ROS production. GDM is accompanied by high oxidative stress, which defects the antioxidant defenses (9, 14). Hekmat et al. designed a case-control trial in which pregnant women with GDM and healthy ones were recruited. They aimed to study the relationship between fat-soluble antioxidants (retinol and vitamin E) with GDM. The vitamin E concentration in the GDM women was 6.21 mg/dL, while 6.92 mg/dL in the control group (33).

Interestingly, in the current study, the concentration of vitamin E in the supplementation group was significantly elevated (6.31±0.04 mg/dL at week 0, 6.11±0.03 mg/dLweek 6). In addition, the plasma levels of the vitamin in the treatment group were higher than in the control group ($p=3.29\times10^{-9}$). Alpha-tocopherol molecules exhibit antioxidant activities due to their ability to donate phenolic hydrogens to lipid radicals (34). Numerous studies have confirmed a correlation between magnesium deficiency and oxidative stress (35-37). Veronese et al. investigated the effect of oral magnesium supplementation on insulin sensitivity parameters in participants with DM. They analyzed studies up to 2016 using systematic review and meta-analysis techniques. They concluded that magnesium supplementation improves FPG levels in diabetic patients, although its mechanism of action has not been identified precisely (38). In the resent trial, plasma levels of magnesium in

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supplementation group was found significantly higher than in the control group (p=0.017). Moreover, FPG and FPI were effectively reduced in the treatment group compared to the other group. Although we did not administer magnesium separately to the cases, the recent findings, along with evidence from previous research, suggest that the factor is potentially effective in controlling plasma glucose.

Comparing the plasma concentrations of hs-CRP and MDA between weeks 0 and 6 demonstrated a significant elevation in oxidation level and a diminution in GSH concentration in the placebo group. However, the level of all oxidation factors declined, and GSH was enhanced in the treatment group. Therefore, supplementation was associated with decreased oxidation and increased antioxidant stores in GDM women. Researchers have examined the relationship between infant metabolic abnormalities and GDM. According to Pedersen's hypothesis, impaired maternal glycemic control leads to fetal hyperglycemia and potentially stimulates fat and glycogen storage (12, 39). Oxidative stress down-regulates GLUT1 (major glucose transporter) and reduces glucose transfer through the placenta (40). Additionally, the placenta contains antioxidant stores which can significantly resist oxidative stress (14, 41).

Oxidative stress, glycemic status, and pregnancy outcomes are complexly related and balanced. A drastic change in maternal glycemic or antioxidant state may have significant consequences for the metabolic status and anatomy of the fetus. In the present study, significantly higher oxidative stress markers were observed in the placebo group compared to the supplementation one. However, the changes were not correlated with the pregnancy outcomes. Furthermore, the subjects had no history of DM and did not require insulin therapy.

Asemi et al. studied the effect of magnesium supplementation on metabolic status and pregnancy outcomes. The trial was conducted among 70 women with GDM in Kashan, Iran, from February 2014 to July 2014. They observed that magnesium supplements resulted in significant decries in insulin and malondialdehyde plasma levels. However, they found no significant relationships between supplementation and pregnancy outcomes (preterm delivery, Apgar scores, and newborns' weight, height, head circumference) in line with the present study observations (18). Wang et al. assessed the relationship between the level of maternal and cord vitamins (A, E, and C) with birth outcomes. Their study reflected the insignificant effect of vitamin E levels during pregnancy on birth outcomes (42). Other researchers outlined that the maternal plasma α:γ-tocopherol levels are correlated with cesarean delivery by examining the relationship between vitamin E levels and pregnancy outcomes in Nigerian and a United States population. They suggested that pro-inflammatory properties of vitamin E can be accompanied by a reduction in the ability to have a natural delivery. However, little is currently known about the δ isoform (43). In the recent trial, supplementation was not significantly related to neonatal outcomes (Table 3). However, recent studies demonstrate that establishing a strong relationship between oral supplementation and neonatal outcomes requires more clinical research among large populations of different races.

Conclusion

The present study revealed that magnesium and vitamin E co-supplementation was associated with enhanced antioxidant stores in GDM women. Also, a remarkable decrease was observed in the FPG and FPI of the supplementation group. However, the study had a few limitations, such as a small population size. So, further studies are needed in larger populations to confirm the findings and expand them. Also, prescribing each supplement in a separated group is beneficial in comparing their efficacy. It should be noted that research on mothers who receive medication to control plasma glucose levels may lead to new results.

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Conflict of interest

The authors declare that they have no conflict of interest.

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