Selenium Supplementation and Gestational Diabetes: A Randomised Controlled Trial

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ABSTRACT

Objective: To assess the effects of selenium supplementation on blood glucose levels in women with gestational diabetes mellitus (GDM).

Study Design: Randomised controlled trial.

Place and Duration of the Study: Department of Internal Medicine, Istanbul Medipol University, Faculty of Medicine, Istanbul, Turkiye, from February to July 2023.

Methodology: In the first phase of this study, the selenium levels of the pregnant women who routinely had an oral glucose tolerance test were measured, and in the second phase of the study, the pregnant women diagnosed with GDM were randomly divided into two groups that received 4-week interventions: Diet alone and diet plus selenium supplementation (200 µg/day).

Results: Selenium level in pregnant women with GDM was significantly lower than in healthy pregnant women, and a selenium level less than 80 ng/ml predicted GDM diagnosis with a sensitivity of 58.59% and a specificity of 67.11%. Pregnant women with low selenium (<80 ng/ml) had a 2.709-fold higher risk for GDM compared to those with higher values. Fasting blood glucose levels decreased significantly in both groups after the respective interventions, but the decrease was greater in selenium recipients. Furthermore, fasting, 1st and 2nd hour blood glucose levels were lower in selenium recipients compared to those who only received diet.

Conclusion: Selenium level in pregnant women with GDM was low compared to healthy pregnant women. Selenium supplementation had a beneficial impact (compared to diet only) on blood glucose levels in pregnant women with GDM.

Key Words: *Pregnancy, Pregnancy outcome, Diabetes, Gestational, Dietary supplements, Selenium.*

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INTRODUCTION

Gestational diabetes mellitus (GDM) is characterised by the development of glucose intolerance during pregnancy in women who were previously healthy.[1] Maintaining safe blood glucose levels in GDM reduces morbidity for both the mother and infant. First-line treatment of GDM is diet and exercise. If glycaemic targets cannot be achieved with these measures, insulin therapy is started.[2] The hyperglycaemic state that occurs in GDM increases the production of reactive oxygen species (ROS) through various mechanisms, such as protein glycation, polyol pathway, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase pathway and glucose autoxidation.[3] Oxidative stress decreases the sensitivity of the liver, fat, and muscle tissues to insulin, leading to an increase in glucose intolerance.[3] As such, there appears to exist a vicious cycle between oxidative stress and GDM.[2]

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Selenium is an essential trace mineral. It functions as an integral component of many enzymes, including formate dehydrogenase, glutathione peroxidase, selenoprotein P and W, and deiodinases.[4] Glutathione peroxidase, which holds about 60% of selenium in the body, is an antioxidant enzyme that protects the cell against oxidative degradation and ROS.[5] It is assumed that selenium exerts antioxidant effects by increasing the activity of selenium-dependent enzymes such as glutathione peroxidase and glutathione reductase, exerts hypoglycaemic effects by significantly reducing fasting blood glucose levels and may have an anti-diabetic function.[3,6] Various studies have shown an inverse relationship between serum selenium levels and diabetes.[7] Selenium levels decrease during pregnancy due to various effects, including haemodilution phenomenon, increased foetal requirements, accumulation in the placenta, and activity of antioxidants such as glutathione peroxidase.[6] Excessive decreases in selenium levels could lead to a disruption in antioxidant capacity, thereby favouring oxidant states and potentially worsening GDM.

In this context, this study aimed to evaluate the effects of selenium supplementation on blood glucose levels in pregnant women with GDM.

METHODOLOGY

This randomised controlled trial was carried out at the Departments of Internal Medicine and Gynaecology and Obstetrics, Istanbul Medipol University, Faculty of Medicine, from February to July 2023. The Ethics Committee approval, in line with the Helsinki Declaration and Good Clinical Practice guidelines, was obtained from the local ethics committee (Decision date: 26.01.2023, Decision no: 72).

For inclusion in the study, pregnant women were assessed between the 24th and 28th gestational week in which oral glucose tolerance test (OGTT) was scheduled to detect GDM presence. Among these pregnant women, those under 18 years of age and over 45 years of age, those with any chronic disease before pregnancy, subjects who needed substitution treatments including hormones, patients who had received any oral hypoglycaemic agent or insulin treatment, those with conditions such as hypothyroidism, hyperthyroidism, liver dysfunction, renal dysfunction, hypertension, malignancy, and those who did not agree to participate in the study were excluded. After giving detailed information about the purpose and scope of the study, written consent was obtained from those who agreed to participate.

This study was carried out in two stages, the first stage in which selenium levels were measured in addition to the OGTT test and the second stage in which the effects of selenium supplementation were observed in pregnant women with GDM. Clinicodemographic data and the obstetric information of the pregnant women were recorded. Anthropometric parameters were measured. Weight measurement was performed using a standardised scale with subjects in light clothing. Height was measured using a standardised tape measure. Body mass index (BMI) (kg/m^2) was calculated by dividing the body weight (kilograms) by the square of the height (meters).

Blood samples were obtained to measure selenium, urea, creatinine, liver function, tests and thyroid stimulating hormone (TSH) levels and to determine fasting blood glucose (FBG) levels in pregnant women scheduled for OGTT. A hydride generation atomic absorption spectrometer (AAS 932 - HG3000-AUS) operating at 4 mA current, 196 nm wavelength and 2 nm spectral bandwidth was used to measure selenium levels. Fasting venous blood samples were taken into heparinised tubes after approximately 10-12 hours of night fasting. During OGTT, the standardised solution containing 75 g of anhydrous glucose was consumed within 3-5 minutes. Then, 1st-hour and 2nd-hour blood glucose measurements were performed. The diagnosis and treatment management of GDM was made according to the criteria of the International Association of Diabetes and Pregnancy Groups (IADPSG). According to these criteria, pregnant women with FBG ≥92 mg/dL, 1st-hour blood glucose value ≥180 mg/dL or 2nd-hour blood glucose value ≥153 mg/dL in 75 g OGTT test were considered to have GDM.[8] Dietary regulation and follow-up of pregnant women with GDM was organised by the same dietitian as a standard procedure. The dietitian called the pregnant women for follow-up at 10-day intervals. In the blood glucose follow-ups of patients with GDM, target values were determined as <95 mg/dL at fasting, <140 mg/dL at the 1st-hour, and <120 mg/dL at the 2ndhour.

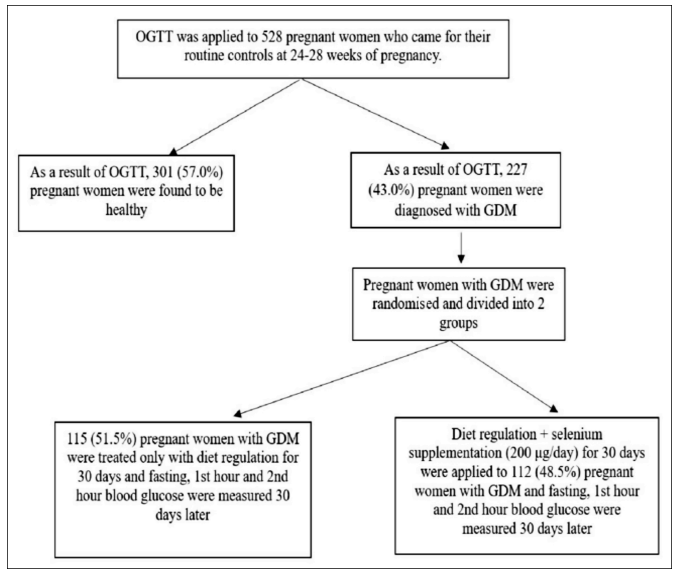

Figure 1: Flow diagram (OGTT: Oral glucose tolerance test, GDM: Gestational diabetes mellitus).

Pregnant women diagnosed with GDM according to the OGTT were divided into two groups in a randomised manner. While the first group received only diet intervention, the second group received diet plus selenium supplementation (Figure 1). Randomisation was carried out consecutively according to patient application. The first participant who met the inclusion criteria at the time of application and volunteered to participate in the study was randomised to the diet group, the second participant to the diet plus selenium supplementation group, the third participant to the diet group and so on. Thus, according to the order of participation, those with odd numbers were randomised to the diet group and those with even numbers were randomised to the diet plus selenium supplementation group. The selenium supplementation (200 µg/day, orzax ocean) was administered for one month, and the costs were covered by the researchers. The selenium dosage was in agreement with the guidelines of the National Academy of Sciences.[9] At the end of the one-month follow-up, the patients were instructed to monitor their fasting morning, 1st-hour and 2nd-hour fingerstick blood glucose for 3 days, while continuing to apply their current treatments. The average of 3-day measurements was taken and it was evaluated whether there was a difference in blood glucose monitoring between the diet-only group and the diet plus selenium supplement group.

An SPSS for Windows database was created (version 25.0, IBM Corp., Armonk, NY, USA) and was used to perform all statistical analyses. The normal distribution of continuous variables were assessed using histogram and Q-Q plots. Continuous variables were presented as mean ± standard deviation, while categorical variables were expressed as absolute and relative frequency (percentage). The Student's t-test was used for

between-group analysis of continuous variables due to normal distribution in variables, while the Chi-square test was used to assess categorical variable frequencies. The predictive ability of selenium was evaluated through receiver operating characteristic (ROC) curve analysis. Logistic regression analysis was employed to identify significant factors independently associated with GDM. Univariable regression was used for initial analysis of variables, and those demonstrating statistical significance were included in the multivariable model. Two-way repeated measures analysis of variances (ANOVA) was used to compare glucose levels after 30 days and oral glucose tolerance test results with respect to selenium supplement status. A two-tailed p-value less than 0.05 was considered statistically significant.

RESULTS

A total of 528 pregnant women had undergone OGTT to assess the potential for study inclusion (mean age: 28.79 ± 7.22, range: 18-45 years). Age ($p < 0.001$), weight ($p < 0.001$) and BMI ($p < 0.001$) were found to be higher in pregnant women with a diagnosis of GDM compared to healthy pregnant women. The frequencies of those with a gravidity of 1 ($p < 0.001$) and those with a parity of 0 ($p < 0.001$) were found to be higher in pregnant women with a diagnosis of GDM. Selenium levels in pregnant women with GDM were found to be significantly lower than in healthy pregnant women ($p < 0.001$, Figure 2). Alanine transaminase (ALT) ($p < 0.001$) and aspartate aminotransferase (AST) ($p < 0.001$) levels were found to be higher in pregnant women with GDM. Data for the initial patient group are summarised according to GDM diagnosis in Table I.

Table I: Summary of patients' characteristics and laboratory measurements with regards to gestational diabetes mellitus.

	Total (n = 528)	Gestational diabetes mellitus		p-value
		No (n = 301)	Yes (n = 227)	
Age	28.79 ± 7.22	26.82 ± 6.40	31.41 ± 7.43	<0.001
Weight, kg	70.40 ± 8.94	65.61 ± 6.77	76.75 ± 7.38	<0.001
Body mass index, kg/m^2	25.58 ± 3.23	24.13 ± 3.20	27.51 ± 2.05	<0.001
Gravidity	-	-	-	-
1	232 (43.94%)	170 (56.48%)	62 (27.31%)	<0.001
2	168 (31.82%)	88 (29.24%)	80 (35.24%)	
3	96 (18.18%)	34 (11.30%)	62 (27.31%)	
≥4	32 (6.06%)	9 (2.99%)	23 (10.13%)	
Parity	-	-	-	-
0	250 (47.35%)	185 (61.46%)	65 (28.63%)	<0.001
1	165 (31.25%)	82 (27.24%)	83 (36.56%)	
2	86 (16.29%)	27 (8.97%)	59 (25.99%)	
≥3	27 (5.11%)	7 (2.33%)	20 (8.81%)	
Selenium	87.49 ± 26.77	93.02 ± 25.63	80.15 ± 26.53	<0.001
Urea	26.92 ± 8.07	26.77 ± 8.04	27.12 ± 8.12	0.616
Creatinine	0.60 ± 0.15	0.61 ± 0.14	0.59 ± 0.15	0.216
ALT	26.54 ± 8.27	23.61 ± 6.80	30.43 ± 8.46	<0.001
AST	24.93 ± 7.43	22.86 ± 6.01	27.67 ± 8.22	<0.001
TSH	1.67 ± 0.75	1.67 ± 0.76	1.66 ± 0.73	0.988
OGTT	-	-	-	-
Fasting	83.51 ± 9.19	80.04 ± 6.99	88.11 ± 9.73	<0.001
1st hour	161.37 ± 18.66	149.99 ± 14.97	176.45 ± 10.66	<0.001
2nd hour	137.06 ± 15.47	127.93 ± 12.75	149.17 ± 9.18	<0.001

Data are given as mean ± standard deviation for continuous variables and as frequency (percentage) for categorical variables.
ALT: Alanine transaminase, AST: Aspartate aminotransferase, TSH: Thyroid stimulating hormone, OGTT: Oral glucose tolerance test.

Table II: Association between factors and gestational diabetes mellitus, logistic regression analysis results.

	Univariable		Multivariable	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.098 (1.069 - 1.127)	<0.001	1.010 (0.961 - 1.062)	0.690
Weight, kg	1.253 (1.205 - 1.303)	<0.001	1.312 (1.220 - 1.412)	<0.001
Body mass index, kg/m^2	1.594 (1.459 - 1.742)	<0.001	0.964 (0.815 - 1.139)	0.664
Gravidity	2.047 (1.670 - 2.510)	<0.001	1.679 (1.061 - 2.656)	0.027
Parity	2.308 (1.855 - 2.872)	<0.001	2.181 (1.364 - 3.485)	0.001
Selenium, <80	2.887 (2.020 - 4.126)	<0.001	2.709 (1.551 - 4.731)	<0.001
Urea	1.005 (0.984 - 1.027)	0.616	-	-
Creatinine	0.479 (0.149 - 1.536)	0.216	-	-
ALT	1.132 (1.100 - 1.164)	<0.001	1.160 (1.100 - 1.225)	<0.001
AST	1.103 (1.073 - 1.134)	<0.001	0.981 (0.930 - 1.035)	0.478
TSH	0.998 (0.792 - 1.258)	0.988	-	-
Nagelkerke R^2	-		0.698	

OR: Odds ratio, CI: Confidence interval, ALT: Alanine transaminase, AST: Aspartate aminotransferase, TSH: Thyroid stimulating hormone.

Table III: Summary of patients' characteristics and laboratory measurements with regards to selenium supplement.

	Selenium supplement		p-vaue
	No (n = 115)	Yes (n = 112)	
Age	30.72 ± 7.21	32.11 ± 7.61	0.160
Weight, kg	77.17 ± 7.46	76.31 ± 7.31	0.380
Body mass index, kg/m^2	27.54 ± 2.01	27.49 ± 2.10	0.863
Gravidity			
1	42 (36.52%)	20 (17.86%)	0.001
2	43 (37.39%)	37 (33.04%)	
3	22 (19.13%)	40 (35.71%)	
≥4	8 (6.96%)	15 (13.39%)	
Parity			
0	37 (32.17%)	28 (25.00%)	0.506
1	37 (32.17%)	46 (41.07%)	
2	31 (26.96%)	28 (25.00%)	
≥3	10 (8.70%)	10 (8.93%)	
Selenium	78.77 ± 25.81	81.58 ± 27.30	0.425
Urea	27.40 ± 7.79	26.84 ± 8.46	0.604
Creatinine	0.58 ± 0.16	0.59 ± 0.15	0.585
ALT	32.79 ± 7.36	28.01 ± 8.86	<0.001
AST	29.90 ± 6.87	25.38 ± 8.88	<0.001
TSH	1.61 ± 0.77	1.72 ± 0.69	0.266
Glucose, Fasting			
OGTT	88.23 ± 10.09	87.99 ± 9.39	0.856
After 30 days	86.14 ± 8.02	82.14 ± 6.23	<0.001
p (within groups)	0.001	<0.001	
Change (1)	-2.08 ± 3.01	-5.85 ± 8.53	<0.001
Glucose, 1st hour			
OGTT	177.12 ± 10.23	175.77 ± 11.08	0.340
After 30 days	150.07 ± 7.06	145.28 ± 6.46	<0.001
p (within groups)	<0.001	<0.001	
Change(1)	-27.06 ± 10.21	-30.49 ± 11.00	0.016
Glucose, 2nd hour			
OGTT	149.88 ± 9.41	148.44 ± 8.92	0.238
After 30 days	129.25 ± 6.75	124.51 ± 6.57	<0.001
p (within groups)	<0.001	<0.001	
Change (1)	-20.63 ± 9.17	-23.92 ± 9.43	0.008
Glucose after 30 days, Fasting			
<95	91 (79.13%)	110 (98.21%)	<0.001
≥95	24 (20.87%)	2 (1.79%)	
Glucose after 30 days, 1st hour			
<140	7 (6.09%)	29 (25.89%)	<0.001
≥140	108 (93.91%)	83 (74.11%)	
Glucose after 30 days, 2nd hour			
<120	7 (6.09%)	28 (25.00%)	<0.001
≥120	108 (93.91%)	84 (75.00%)	

Data are given as mean ± standard deviation for continuous variables and as frequency (percentage) for categorical variables. (1) Difference between glucose after 30 days and oral glucose tolerance test results. Negative values represent decrease in measurements.
ALT: Alanine transaminase, AST: Aspartate aminotransferase, TSH: Thyroid stimulating hormone, OGTT: Oral glucose tolerance test.

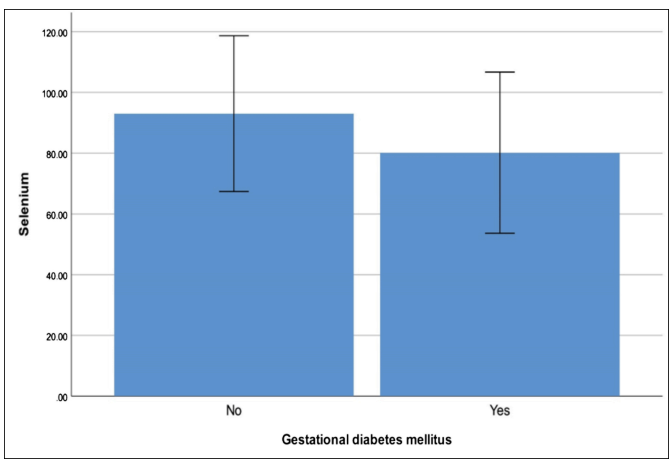

Figure 2: Selenium levels (mean ± standard deviation) with regards to gestational diabetes mellitus.

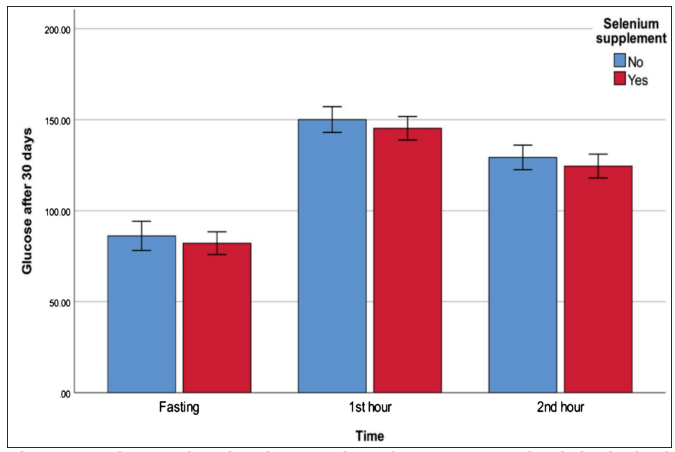

Figure 3: Glucose levels after 30 days (mean ± standard deviation) with regards to selenium supplementation.

A selenium level less than 80 ng/ml had a sensitivity of 58.59% and a specificity of 67.11% for the diagnosis of GDM (Area under ROC curve (AUC): 0.655, 95% Confidence intervals (CI): 0.607-0.702, accuracy: 63.45%, positive predictive value: 57.33%, negative predictive value: 68.24%). Selenium level was found to be significantly lower in pregnant women with GDM than in healthy pregnant women (p <0.001). Multivariable logistic regression revealed that pregnant women with low selenium (<80 ng/ml) had 2.709-fold higher risk for GDM than those with higher levels (OR: 2.709, 95% CI: 1.551 - 4.731, p <0.001). It was found that higher weight (p <0.001), gravidity (p = 0.027), parity (p = 0.001), and ALT (p <0.001) values were independently associated with GDM (Table II).

Among the initial group of 528 patients, 43.0% (n = 227) were diagnosed with GDM and were randomised into the intervention groups. There were no subjects who were lost to follow-up, and none of the patients developed an adverse effect due to OGTT, selenium, or GDM.

Pregnant women with and without selenium supplementation were similar in terms of age (p = 0.160), weight (p = 0.380), BMI (p = 0.863), parity (p = 0.506), selenium (p = 0.425), urea (p = 0.604), creatinine (p = 0.585), TSH (p = 0.266), and FBG values (p = 0.856). Both interventions resulted in significant decreases in FBG and 1st-hour and 2nd-hour glucose levels (p <0.001 for all). However, in recipients of selenium, FBG was lower (p <0.001) and the amount of decrease in FBG was greater compared to the diet only group (p <0.001). Selenium recipients also had significantly greater reductions in 1st-hour (p = 0.016) and 2nd-hour (p = 0.008) glucose values. When glucose values were categorised with respect to fasting, 1st-hour, and 2nd-hour thresholds (95, 140, and 120), a significantly higher percentage of selenium recipients were found to have values lower than the thresholds compared to the diet-only group (p <0.001 for all, Table III, Figure 3).

DISCUSSION

During pregnancy, the elevated demand for selenium due to foetal growth is met from maternal sources, potentially leading to a decrease in maternal selenium. These decreases are greater in pregnant women with GDM.[10] In this prospective study, the relationship between selenium levels and GDM in pregnant women and the effects of selenium supplementation on the regulation of blood glucose levels was evaluated.

A negative relationship between selenium level and glucose tolerance has been demonstrated in GDM.[6] The association between selenium and GDM risk has been supported by evidence from a nested case-control study, which reported that lower urinary selenium levels could increase risk for GDM.[11] Lower selenium levels have also been demonstrated in other sample types obtained during delivery from women with GDM, such as the umbilical artery and vein.[12] Various studies have shared similar results describing the relationship between selenium levels, GDM, and glucose levels.[6,13,14]

In a meta-analysis evaluating the data of 940 GDM cases, it was reported that selenium levels were found to be significantly lower in women with GDM when compared to the control group.[1] In the meta-analysis of Xu *et al*., it was reported that the selenium level in 1588 pregnant women with GDM was significantly lower than those without GDM.[15] In the current study, selenium level was significantly lower in pregnant women with GDM compared to healthy pregnant women, which supports the literature.[16,17] The risk of GDM in pregnant women with a selenium level of <80 ng/ml was 2.709 times higher compared to those with higher levels. Despite this, there are also various studies in which no relationship was found. Liu *et al*. reported no relationship between selenium deficiency and the risk of GDM in Chinese women.[18] In a meta-analysis evaluating the results of twelve studies, it was reported that selenium levels in women with GDM were lower compared to those without GDM; however, the significance was found to have disappeared after correcting for reporting bias.[1] The differences in factors such as age, ethnic group, nutritional behaviours, pregnancy-related history, level of access to supplements and differences between the measurement and evaluation techniques of selenium among the research groups may have caused the variations in studies.

Moshfeghy *et al*. reported a very strong predictive capability for selenium levels in identifying patients with GDM (sensitivity: 83.3%, specificity: 94%).[6] In the present study, the selenium level was found to be successful in distinguishing pregnant women with GDM from healthy women, with a cut-off value of 80 ng/ml (sensitivity: 58.59%, specificity: 67.11%). Despite the low predictive results, selenium levels could be used as a supportive parameter to assess GDM likelihood among pregnant women. Of note, this research performed measurements after the second trimester, and further studies are needed to assess whether earlier quantification of selenium levels can be useful.

To date, selenium supplementation has been evaluated in various animal and human studies Zeng *et al*. found that oral selenium-polysaccharide supplementation to pregnant GDM rats caused a decrease in FBG and fasting blood insulin levels.[19] In a randomised, double-blind, placebo-controlled study, significant improvements in FBG, insulin level and insulin resistance were detected in pregnant women with GDM who had received 200 µg/day selenium supplementation for 6 weeks.[20] In a randomised, double-blind, placebo-controlled study, it was reported that a 6-week selenium + probiotic supplement (200 µg/day) improved FBG, insulin levels and insulin resistance.[21] Although the duration of selenium supplementation was 6 weeks in other studies and 4 weeks in the current study, still selenium supplementation protocol significantly improved blood glucose values in pregnant women with GDM. However, in a randomised placebo-controlled trial, blood glucose parameters, insulin levels and resistance did not change significantly after 100 µg/day selenium supplementation for 12 weeks.[10] This suggests that selenium dosage should be higher when providing supplements to pregnant women. Currently, the evidence concerning the optimal dosage and duration of selenium supplementation is unclear.

The antioxidant properties of selenium may improve insulin resistance by reducing cellular stress and positively affect glucose metabolism. Evaluating the potential effects of selenium supplementation in GDM management and identifying areas for future research could play an important role in clinical practice. This trial can help improve maternal and infant health by providing better guidelines on how selenium can be used in the treatment and prevention of GDM. The findings of the current study may be an important additional step in the early diagnosis of GDM and the development of effective treatment methods. However, further research needs to be conducted and these findings need to be confirmed based on the results of clinical trials. Future research directions should focus on better understanding the effects of selenium on GDM. In particular, it is important to determine how selenium functions in reducing the risk of GDM and its mechanisms of action. It also needs to be clarified at what dose and in what forms selenium should be used in the treatment of GDM in terms of its efficacy and safety. In addition, the long-term effects of selenium supplementation and post-pregnancy outcomes should also be investigated.

One of the limitations of the study is that it was conducted at a single-centre and that it only assessed blood glucose levels of pregnant women at a single time point after 30 days of

selenium supplementation in a population-based sample. A longer-term follow-up would be beneficial to determine the trend of change in selenium and blood glucose levels in the later stages of pregnancy and after birth. It did not evaluate other parameters associated with glucose homeostasis, such as HbA1C, HOMAIR, and serum insulin, despite showing positive results for blood glucose levels. The absence of a placebo group may have made it difficult to determine the exact effect of selenium supplementation and may have created a risk of bias. However, it would be unethical to include a non-treatment group since patients with GDM should routinely receive dietary therapy.

CONCLUSION

Pregnant women with GDM have significantly lower selenium levels compared to healthy pregnant women indicating promising predictive value. Women with GDM who received a 4-week selenium supplementation of 200 µg/day in addition to diet demonstrated significant improvements in blood glucose levels compared to those who received only a diet.

ETHICAL APPROVAL:
The Ethics Committee approval, in line with the Helsinki Declaration and Good Clinical Practice guidelines, was obtained from Istanbul Medipol University Ethics Committee (Decision date: 26.01.2023, decision no: 72).

PATIENTS' CONSENT:
All patients were informed that the results of the study would be published and their written consent was obtained.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
EY: Study design, statistical assistance, drafting, revision, and editing.
IS: Literature search, study design, and conduction of the study.
Both authors approved the final version of the manuscript to be published.

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