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Original Article

Relation of multimineral-vitamin D supplementation and the risk of preeclampsia

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Abstract

Background

The objective of this study was to determine the favorable effects of multimineral-vitamin D supplementation on pregnancy outcomes among women at risk for preeclampsia.

Patients and methods

This randomized double-blind controlled clinical trial was conducted among 46 women at risk for preeclampsia at 27 weeks of gestation, with positive roll-over test. Pregnant women were randomly assigned to receive either the multimineral-vitamin D supplements (n = 23) or the placebo (n = 23) for 9 weeks. Multimineral-vitamin D supplements were containing 800 mg calcium, 200 mg magnesium, 8 mg zinc, and 400 IU vitamin D3. Fasting blood samples were taken at baseline and after 9-week intervention to measure related factors. Newborns' outcomes were determined.

Results

Although no significant difference was seen in newborns' weight and head circumference between the two groups, mean newborns' length (51.3 ± 1.7 vs. 50.3 ± 1.2 cm, P = 0.03) was significantly higher in multimineral-vitamin D group than that in the placebo group. Compared to the placebo, consumption of multimineral-vitamin D supplements resulted in increased levels of serum calcium (+0.19 vs. −0.08 mg/dl, P = 0.03), magnesium (+0.15 vs. −0.08 mg/dl, P = 0.03), zinc (+8.25 vs. −21.38 mg/dl, P = 0.001), and vitamin D (+3.79 vs. −1.37 ng/ml, P = 0.01). In addition, taking multimineral-vitamin D supplements favorably influenced systolic blood pressure (−1.08 vs. 6.08 mmHg, P = 0.001) and diastolic blood pressure (DBP) (−0.44 vs. 3.05 mmHg, P = 0.02).

Conclusions

Multimineral-vitamin D supplementation for 9 weeks in pregnant women at risk for preeclampsia resulted in increased newborns' length; increased circulating levels of maternal serum calcium, magnesium, zinc, and vitamin D; and led to decreased maternal systolic blood pressure and diastolic blood pressure.

Keywords: Multimineral-vitamin D supplementation, preeclampsia, pregnancy outcomes

Introduction

Hypertensive disorders complicate 5–10% of all pregnancies, and they form one member of the deadly triad, along with hemorrhage and infection, that contribute greatly to maternal morbidity and mortality rates. There has been a significant reduction in the rates of eclampsia, maternal mortality, and maternal morbidity in the developed countries in contrast with the rates in the developing countries. These differences are mainly owing to universal access to prenatal care, access to timely care, and proper management of patients with preeclampsia and eclampsia in the developed countries [1].

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Preeclampsia manifests after 20 weeks of gestation and constitutes a life-threatening condition for both fetuses and pregnant women. The prevalence of Growth Hormone (GH) increases with age and is higher in overweight and obese women [2].

Vitamin D plays important role in bone and mineral metabolism. During pregnancy, vitamin D plays important role in implantation and placental function owing to angiogenic, immunomodulatory, and anti-inflammatory effects. Although still incompletely understood, the pathophysiology of hypertensive disorders in pregnancy involves abnormal placentation and angiogenesis. Several studies have demonstrated an association between higher 25-hydroxyvitamin D [25(OH)D] levels and reduced risk of hypertensive disorders in pregnancy, especially in preeclampsia [3].

Vitamin D may have a role in the etiology of preeclampsia by regulating the transcription and function of genes associated with placental function, including placental invasion, normal implantation, and angiogenesis. Vitamin D also modulates immune function and inflammatory response. Maternal vitamin D concentration may be influenced by several factors, including diet, supplementation, sun exposure, skin pigmentation, and genetics; therefore, vitamin D deficiency is a potentially modifiable risk factor for preeclampsia [4].

Low vitamin D status, among other risk factors, is linked to the development of preeclampsia. Systematic reviews and meta-analyses have concluded that decreased serum vitamin D levels (25(OH) D) in pregnancy are associated with a higher risk of preeclampsia and suggest a preventive role of vitamin D supplementation [5].

There is growing evidence that the maternal vitamin D (25(OH)D) deficiency in early pregnancy is a strong independent risk factor for occurrence of preeclampsia. Vitamin D has direct and indirect influence (immune dysfunction, excess inflammation, hypertension, abnormal angiogenesis, and placental implantation) on the biological processes occurring in the pathophysiology of preeclampsia [6].

Aim

The aim of this study was to find out if multimineral-vitamin D supplementation during pregnancy decreases the risk of preeclampsia and improves the fetal outcome.

Patients and methods

Methods

Participants

This randomized double-blind placebo-controlled clinical trial was performed at Benha and El Galla Teaching Hospitals from January 2017 to January 2020. For estimating sample size, we used a randomized clinical study sample size formula where type one (α) and type two errors (β) were 0.05 and 0.20 (power = 80%), respectively, and considering newborns' weight at birth as a key variable, we considered 0.4 as standard deviation and 0.3 kg as the difference in the mean (d). According to this, we needed 22 participants in each group, to have 80% study power. Pregnant women at risk for preeclampsia with positive roll-over test, primigravida, aged 18–40 years old who were carrying singleton pregnancy at their third trimester were recruited in this study. Gestational age was assessed from the date of last menstrual period and concurrent clinical assessment. Individuals with the aforementioned inclusion criteria were called for participation in the study from among those that attended maternity clinics at Benha and El Galla Teaching Hospitals. A total of 70 women were screened for risk of preeclampsia, of whom 52 met the inclusion criteria. We did not include those with maternal severe preeclampsia, intrauterine fetal death, premature preterm rupture of membrane, completed bed rest, placenta abruption, preterm delivery, and gestational diabetes mellitus. A total of 52 pregnant women were recruited in the study and were randomly assigned to receive either the placebo ($n = 26$) or multimineral-vitamin D supplements ($n = 26$) for 9 weeks.

Study design

The study included participants considered as high risk for preeclampsia when they had positive roll-over test at the study baseline (25 weeks of gestation). Patients were randomly assigned to receive either the placebo or multimineral-vitamin D supplements for 9 weeks. Random assignment was done by the use of computer-generated random numbers. Participants were asked not to alter their routine physical activity or usual diets and not to consume any supplements other than the one provided to them by the investigators. The multimineral-vitamin D supplements contained 800 mg calcium, 200 mg magnesium, 8 mg zinc, and 400 IU vitamin D3. All participants also consumed 400 μg/d folic acid from the beginning of pregnancy and 50 mg ferrous sulfate from the second trimester. We kept all supplements in a cool temperature before using. Compliance with the consumption of supplements was monitored once a week.

Assessment of variables

Anthropometric measurements of pregnant women were done at baseline (25 weeks of gestation) and after 9 weeks of intervention (34 weeks of gestation). Body weight was measured using a digital scale to the nearest 0.1 kg. Height was measured using a nonstretched tape, measuring to the nearest 0.1 cm. BMI was calculated as weight in kg divided by height in meters squared. Newborn's length and weight were measured using standard methods during the first 24 h after birth and were recorded to the nearest 1 mm and 10 g, respectively. Newborn's head circumference was measured to the nearest 1 mm. Fasting blood samples (10 ml) from pregnant women were taken at baseline and after 9-week intervention in an early morning after an overnight fast. Serum samples were analyzed for serum calcium, magnesium, zinc, iron, and 25(OH)D levels. Serum calcium, magnesium, and iron concentrations were assayed. Serum zinc concentrations were examined. Serum 25(OH)D levels were quantified by enzyme-linked immunosorbent assay (ELISA). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were

determined via a sphygmomanometer. Blood pressure values were reported in millimeters of mercury.

Ethical considerations

The study was approved by the institutional Ethics Committee of Benha Teaching Hospital no. BNH-00010.

Statistical analysis

To ensure the normal distribution of variables, histogram, and Kolmogorov–Smirnov test were applied. We used paired samples *t* test to identify within-group differences. Independent samples Student's *t* test was used to detect differences between groups. Pearson χ^2 test was used to detect an association between categorical variables. *P* value less than 0.05 was considered as statistically significant. All statistical analyses were done using the Statistical Package for Social Science, version 17 (SPSS Inc., Chicago, Illinois, USA).

Results

Among individuals in the placebo group, three women [premature preterm rupture of membrane (n = 1), gestational diabetes mellitus (n = 1), and severe preeclampsia (n = 1)] were excluded. The exclusions in the multimineral-vitamin D group were three persons [completed bed rest (n = 1), severe preeclampsia (n = 1), and placenta abruption (n = 1)]. Finally, 46 participants [placebo (n = 23) and multimineral-vitamin D supplements (n = 23)] completed the trial. The mean age of the study participants was not statistically different between multimineral-vitamin D and placebo groups. Baseline prepregnancy weight and BMI, as well as their means before and after intervention, were not significantly different between the two groups (Table 1). Although no significant difference was seen in newborn's weight and head circumference between the two groups, mean newborns' length (51.3 ± 1.7 vs. 50.3 ± 1.2 cm, P = 0.03) was significantly higher in multimineral-vitamin D group than that in the placebo group (Table 2). The supplementation did not significantly influence mode of delivery. As compared with the placebo, consumption of multimineral-Vitamin D supplements resulted in increased levels of serum calcium (+0.19 vs. −0.08 mg/dl, P = 0.03), magnesium (+0.15 vs. −0.08 mg/dl, P = 0.03), zinc (+8.25 vs. −21.38 mg/dl, P = 0.001), and vitamin D (+3.79 vs. −1.37 ng/ml, P = 0.01) (Table 3). Additionally, taking multimineral-vitamin D supplements favorably influenced SBP (−1.08 vs. 6.08 mmHg, P = 0.001) and DBP (−0.44 vs. 3.05 mmHg, P = 0.02).

We did not find a significant difference in mean changes of maternal serum iron levels comparing the two groups. Within-group comparisons in the multimineral-vitamin D group revealed a significant increase in serum calcium (+0.19 mg/dl, P = 0.03), magnesium (+0.15 mg/dl, P = 0.01), zinc (+8.25 mg/dl, P = 0.003), and vitamin D levels (+3.79 ng/ml, P = 0.04). In addition, within-group comparisons in placebo group revealed a significant reduction in serum zinc (−21.38 mg/dl, P = 0.01) and vitamin D levels (−1.37 ng/ml, P = 0.02) and a significant increase in SBP and DBP (+6.08 mmHg, P = 0.001, and +3.05 mmHg, P = 0.007, respectively).

Discussion

Preeclampsia is a major contributor to maternal mortality worldwide and remains a leading cause of perinatal mortality and morbidity, complicating 2–8% of pregnancies [7].

Table 1: General characteristics of the study participants

	Multimineral-vitamin D group (n=23)	Placebo group (n=23)	*P*
Maternal age (year)	25.0±4.2	24.4±3.6	0.57
Height (cm)	161.8±4.5	161.0±7.7	0.71
Prepregnancy weight (kg)	66.6±10.9	66.3±10.7	0.92
Weight at study baseline (kg)	71.0±11.5	71.5±11.6	0.89
Weight at end-of-trial (kg)	74.4±11.3	75.3±11.8	0.82
Prepregnancy BMI (kg/m^2)	25.4±3.7	25.5±3.7	0.91
BMI at study baseline (kg/m^2)	27.0±3.8	27.5±4.2	0.69
BMI at end-of-trial (kg/m^2)	28.4±3.7	28.9±4.0	0.63

Data are presented as means±SD, obtained from independent *t* test.

Table 2: The effect of multimineral-vitamin D supplementation on pregnancy outcomes

	Multimineral-vitamin D group (n=23)	Placebo group (n=23)	*P*
Cesarean section	11 (47.8)	13 (56.5)	0.55†
Gestational age (weeks)	39.5±1	39.1±1.2	0.21
Newborn's weight (kg)	3315.7±460.4	3300.0±411.5	0.90
Newborn's length (cm)	51.3±1.7	50.3±1.2	0.03
Newborn's head circumference (cm)	35.5±1.2	35.2±1.5	0.41
Severe preeclampsia rate	1 (3.8)	1 (3.8)	1.00†
GDM rate	0	1 (3.8)	0.31†

Values are presented as means±SD and *n* (%), obtained from independent *t* test, obtained from Pearson χ^2 test. GDM, gestational diabetes.

Table 3: Means±SD of serum minerals, vitamin D levels, and blood pressure at baseline and after the intervention

	Multimineral-vitamin D group ($n=23$)				Placebo group ($n=23$)				
	Week 0	Week 9	Change	P^a	Week 0	Week 9	Change	P^b	P
Calcium (mg/dl)	8.66±0.49	8.85±0.63	0.19±0.39	0.03	9.16±0.35	9.08±0.37	−0.08±0.42	0.35	0.03
Magnesium (mg/dl)	1.80±0.21	1.95±0.22	0.15±0.28	0.01	2.12±0.32	2.04±0.30	−0.08±0.42	0.37	0.03
Zinc (mg/dl)	57.08±8.13	65.33±12.55	8.25±11.79	0.003	88.09±36.7	66.71±13.14	−21.38±36.47	0.01	0.001
Iron (mg/dl)	94.04±56.88	75.52±25.62	−18.52±50.73	0.09	97.47±84.44	103.34±68.26	5.87±69.54	0.69	0.18
Vitamin D (ng/ml)	18.25±6.74	22.04±9.26	3.79±8.17	0.04	15.58±6.53	14.21±6.21	−1.37±2.23	0.02	0.01
SBP (mmHg)	113.47±4.86	112.39±6.88	−1.08±5.42	0.34	110.00±6.03	116.08±5.83	6.08±7.82	0.001	0.001
DBP (mmHg)	66.30±6.43	65.86±7.17	−0.44±5.41	0.70	66.95±5.38	70.00±5.83	3.05±4.94	0.007	0.02

DBP, diastolic blood pressure; SBP, systolic blood pressure. [a]Within-group differences (paired samples *t* test), [b]Between group differences (independent samples *t* test).

Recent epidemiological studies have emphasized the role of vitamin D deficiency in the occurrence of preeclampsia. Recent in-vitro studies have demonstrated the improvement of angiogenesis and inhibition of release of adhesion molecules from endothelial cells by vitamin D. The role of vitamin D deficiency in immunomodulation and placental development has been emphasized in various studies, and thus, they put the emphasis on vitamin D deficiency, regarding its possible role in the pathophysiology of preeclampsia [8].

Two studies had confirmed the current findings, as those performed by Wetta *et al.* [9] and Burris *et al.* [10], but at different gestational ages, as Wetta *et al.* [9] performed a nested case–control study at 15–21 weeks of gestation and found that mean 25(OH) D levels did not differ in preeclamptic cases (68 nmol/l) and controls (71 nmol/l) and Burris *et al.* [10] also studied associations of 25(OH) D levels obtained at 16.4–36.9 weeks of gestation (mean, 27.9 weeks) with preeclampsia and found no association between plasma 25(OH) D concentration and preeclampsia.

Most prior studies, as done by Xu *et al.* [11] and Bodnar *et al.* [11], have evaluated mostly women of white race and found a significant association between vitamin D deficiency and preeclampsia. No previous studies evaluated women of African–American race, who because of melanin inhibition of UVB-mediated synthesis of vitamin D are at increased risk for insufficiency or deficiency. This may give possible explanation for different findings among studies.

In contrary with the current findings, Baker *et al.* [12] conducted a nested case–control study in United States to assess relationship between midgestation vitamin D deficiency and severe preeclampsia between 43 cases and 198 controls and found that maternal midgestation vitamin D deficiency was associated with increased risk of severe preeclampsia, and Xu *et al.* [13] conducted a large cohort study on 100 preeclamptic and 100 normotensive pregnant women. Both were screened for Vitamin D and interleukin-6 concentrations. They found that the mean concentration of 25(OH) D was 49.4 ± 22.6 nmol/l in normotensives and 42.3 ± 17.3 nmol/l in preeclamptic women ($P = 0.01$). So, it was hypothesized that the plasma concentrations of maternal 25(OH) D measured at an average of 35-week gestational age were statistically significantly lower in women with preeclampsia compared with nonpreeclamptic controls.

Using several different assays to measure vitamin D may lead to the discrepant findings, as Wang *et al.* [14] used chemiluminescence immunoassay in assessment of maternal serum 25(OH)D concentrations at 12–18 and 24–26 weeks of gestation and found a strong positive correlation regarding maternal 25(OH)D concentrations between the two gestational ages. Mean maternal 25(OH)D concentrations at 24–26 weeks of gestation were significantly lower in women who subsequently developed preeclampsia compared with those who did not (mean ± SD: 48.9 ± 16.8 vs. 57.0 ± 19.1 nmol/l, $P = 0.03$), though the association was not statistically significant for maternal 25(OH)D level at 12–18 weeks of gestation.

However, Wetta *et al.* [9] used liquid chromatography-tandem mass spectrometry and found no association between vitamin D deficiency and preeclampsia.

Halhali *et al.* [15] found a significant association between vitamin D deficiency and preeclampsia using radioimmunoassay in vitamin D assay. Using radioimmunoassay is difficult because such technique works best in aqueous environment, and vitamin D is poorly soluble in water.

Singla *et al.* [16] used ELISA technique in comparing serum vitamin D concentration between two groups (74 nulliparous preeclamptic women with singleton pregnancy and without any known medical disorder and 100 healthy nulliparous controls of same age). They found mean serum 25(OH)D was significantly lower among cases as compared with controls, so hypothesized that women with preeclampsia had significantly lower vitamin D level as compared with normal women.

The current study used ELISA for testing, as it was available, sensitive, rapid, and more accurate than other assays, which may need radioisotope or costly radiation counter (radiation-counting apparatus).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients

understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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