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Effect of Multivitamin-Mineral *versus* Multivitamin Supplementation on Maternal, Newborns' Biochemical Indicators and Birth Size: A Double-Blind Randomized Clinical Trial

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Abstract

Objective: Micronutrient deficiency during pregnancy is associated with several complications. This study was designed to determine the effects of received multivitamin-mineral *vs.* multivitamin supplements on maternal, newborns' biochemical indicators, and birth size.

Methods: This double-blind randomized-controlled clinical trial was conducted among 48 Iranian pregnant women, primigravida, aged 18-35 years old in their second and third trimester from December 2011 to September 2012. Subjects were randomly assigned to receive either the multivitamin-mineral (n=24) or multivitamin supplements (n=24) for 20 weeks. Fasting blood samples were taken at baseline and after a 20-week intervention of pregnant women as well as umbilical cord blood of the babies immediately after delivery to measure serum calcium, vitamin D, iron, magnesium, zinc and biomarkers of oxidative stress including plasma total antioxidant capacity and total glutathione.

Results: Multivitamin-mineral compared to multivitamin supplementation resulted in a significant increase in maternal serum calcium (0.5 *vs.* -0.1 mg/dL, p=0.04) and magnesium levels (0.1 *vs.* -0.2 mg/dL, p<0.001). Furthermore, mean plasma total glutathione levels (1791 ± 566 *vs.* 1434 ± 622 µmol/l, p=0.04) of the newborns whose mothers received multivitamin-mineral were higher than those whose mothers received multivitamin supplements.

Conclusions: Overall, multivitamin-mineral compared to multivitamin supplementation for 20 weeks during pregnancy resulted in a significant increase in maternal serum calcium and magnesium levels as well as a significant elevation of newborn plasma total glutathione levels.

Keywords: Micronutrient; Supplementation; Pregnancy outcomes; Oxidative stress.

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Introduction

Owing to increased requirements for micronutrients during pregnancy, pregnant women are one of the most susceptible groups for nutritional insufficiency.[1-2] In Kashan, Iran, it has been reported that 96, 7 and 9% of pregnant women have low levels of vitamin D,[3] zinc and hemoglobin.[4] Furthermore, about 16% of all live births worldwide are low birth weight babies (LBW); 90% of whom are born in low-income countries.[5] This rate is considerably high in Asian countries.[6] Increased metabolic demands for micronutrients during pregnancy occur mainly due to changes in the women's physiology and the requirements of the growing fetus.[7] Micronutrient deficiencies during pregnancy may result in spontaneous abortion, fetal malformation,[8] placental abruption,[9] increased maternal morbidity,[10] pre-eclampsia, increased oxidative stress,[11] as well as LBW.[12]

Several studies have evaluated the effects of multiple micronutrients supplementation on pregnancy outcomes.[13-14] In a systematic review, it has been reported that multiple micronutrient supplementation as compared to the usual iron-folate supplements during pregnancy have beneficial effects in reducing LBW and small for gestational age (SGA) births.[15] However, there was no significant difference seen in the overall risk of preterm birth, stillbirth, and maternal or neonatal mortality following the intake of multiple micronutrients compared with iron-folate after the first trimester.[16] Furthermore, multiple micronutrient supplementation during pregnancy did not reduce early infant mortality;[17] however, it has resulted in improved folate status and reduced the prevalence of riboflavin, vitamin B6, vitamin B12, folate, and vitamin D deficiencies.[18] In another study, improved vitamin E and A status was also seen with consuming multiple micronutrient supplements (consisted of 15 vitamins and minerals) compared to controls from 20 to 32 weeks of gestation.[19] Most previous studies have been performed in communities with a high prevalence of maternal malnutrition and it remains unknown if these supplementations improved pregnancy outcomes in other populations. Evidence for the impact of multiple micronutrient supplementations on a number of outcomes is still inadequate and further research is required before a switch from iron-folate supplementation is implemented.[20] In addition, earlier studies have mostly compared micronutrient supplementation with the placebo or iron-folate intake. To date,

few studies have shown the impact of multiple micronutrient supplementations during pregnancy on biochemical indicators of pregnant women and especially their newborns. Furthermore, there are insufficient evidences whether different types of multiple micronutrient supplements may have had differential benefits for pregnant women. This study was therefore, conducted to investigate the effects of two types of multiple micronutrient (multivitamin-mineral *vs*. multivitamin) supplementations on maternal, newborn biochemical indicators, and birth size in pregnant Iranian women.

Methods

This randomized double-blind controlled clinical trial was conducted in Kashan, Iran during December 2011 to September 2012. A detailed description of multiple micronutrient supplementations, the intervention, data collection and primary results had been published previously worldwide.[21-23] The methods were reviewed briefly, with emphasis on those that are relevant to the assessment of micronutrients status. On the basis of that sample size formula suggested for randomized clinical trials,[24] the type I error of 5% (α=0.05) and type II error of 20% (β=0.20; Power=80%) and maternal serum iron as a key variable were considered and the sample size of 24 persons was reached for each group. The study was conducted at the Naghavi Maternity Clinic, Shaheed Beheshti Subspecialty Polyclinic and 20 antenatal centers affiliated with Kashan University of Medical Sciences. A total of 90 pregnant women were screened for this study wherein 54 met the inclusion criteria (25 women due to multiparous and 11 women because of not living in Kashan were excluded). Inclusion criteria were as follows: primigravidity, singleton pregnancy and age between 18-35 years. Women with hypertension, gestational diabetes mellitus (GDM), complete bed rest (CBR), intrauterine fetal death (IUFD), intrauterine growth retardation (IUGR), placental abruption, preterm delivery, hospitalization, signs of malabsorption and maldigestion, history or evidence of rheumatoid arthritis, thyroid, parathyroid or adrenal diseases, hepatic or renal failure and metabolic bone disease were excluded from the study. All pregnant women took 400 μg/d folic acid supplements from the beginning of pregnancy as well as 60 mg/d ferrous sulfate (before bedtime) from the second trimester to delivery time. The study was performed according to the guidelines expressed in the Declaration of Helsinki and approved by the Ethics Committee of Kashan University of Medical Sciences (P/29/5/1/1384, 21 May 2012). All participants provided informed written consent. The trial was registered in the Iranian website (www.irct.ir) for registration of clinical trials (IRCT code: IRCT201204065623N3).

Subjects were randomly assigned to receive either a multivitamin-mineral (n=24) or multivitamin supplements (n=24) from week 17 to 37 of gestation. All participants were asked to take one supplement a day (after lunch). Random assignment was done by the use of computer-generated random numbers. A trained midwife at the maternity clinic performed randomization. They were also asked not to alter their routine physical activity and usual diet throughout the study. Dietary intakes of participants were assessed by means of three-day dietary records completed at run-in period and throughout the study. Run-in period is a period before a clinical trial is commenced when no treatment is given. The dietary records were based on estimated values in household measurements. The multivitamin-mineral and multivitamin supplements were provided by Shahre Daru Co, Tehran, Iran. Supplements were provided to subjects monthly. The multivitamin-mineral supplement consisted of 13 micronutrients. The multivitamin supplement (the same substance without elements of iron, magnesium and calcium) was packed in identical tablets and coded by the producer to guarantee blinding. All supplements were kept under cool temperature before use. Compliance with the supplement consumption was monitored once per month through phone interviews. The compositions of the supplements are provided in Table 1. Data on anthropometric and biochemical measures were collected at the maternity clinic and Kashan reference laboratory affiliated to Kashan University of Medical Sciences, respectively. Gestational age was calculated from the date of last menstrual period and concurrent clinical assessment.[25]

Maternal anthropometric measurements were assessed at baseline and after 20 weeks of intervention. Maternal weight was assessed by trained midwives at maternity clinic in an overnight fasting status, without shoes and in minimal clothing using a digital scale (Seca, Hamburg, Germany) to the nearest 0.1 kg. Height was measured using a non-stretched tape measure (Seca, Hamburg, Germany) to the nearest 0.1 cm. BMI was calculated as weight in kg divided by height in meters squared. The pre-pregnancy weight and height were taken from the existing records of patients in the clinic.[26] Newborn height and weight were measured using standard methods (Seca 155 Scale, Hamburg, Germany) during the first 24 hours after birth and were recorded to the nearest 1 mm and 10 g, respectively.[4] Newborn head circumference was measured to the nearest 1 mm with a Seca girth measuring tape.[4]

For the biochemical assessment, maternal fasting blood samples (10 mL) were taken at baseline and after a 20-week intervention early in the morning at a Kashan reference laboratory after an overnight fast.[27] Furthermore, 5 mL cord blood was collected from the umbilical cord of the babies immediately after delivery by clamping and cutting the babies' end of the cord. Serum samples were analyzed for serum calcium, magnesium, zinc, iron and 25-hydroxy vitamin D levels. Serum calcium, iron and magnesium concentrations were assayed using mentioned kits (Pars Azmoon, Tehran, Iran) by automatic biochemistry analyzer (BT 3000, Monsano, Italy). A serum zinc concentration was assayed using zinc kit (Elitech, Puteaux, France) by automatic biochemistry analyzer (BT 3000, Monsano, Italy). Serum 25-hydroxy vitamin D was assayed by ELISA (Awareness Stat Fax 2100, Bohemia, USA) using available kits (IDS, Boldon, UK). Plasma samples were determined for total antioxidant capacity (TAC) and total glutathione (GSH) levels. TAC was assessed using the FRAP method developed by Benzie and Strain.[26] The plasma total GSH was measured using Beutler et al. method.[28] Plasma TAC and total GSH were determined using

spectrophotometry method (Cecil 2021, Cambridge, England).

To ensure normal distribution of variables, Kolmogrov-Smirnov test was applied for statistical analysis. The paired-samples *t*-test was used to identify within group differences (before and after intervention). Student's *t*-test was used to detect differences between the two groups (multivitamin-mineral and multivitamin supplements). Distribution of participants in terms of categorical variables was examined through the use of chi-square test. A *p*-value of <0.05 was considered as statistically significant. All statistical analyses were done using the Statistical Package for Social Science version 17 (SPSS Inc, Chicago, USA).

Results

The exclusions in the multivitamin-mineral group were three persons (hospitalization [n=1], GDM [n=1] and placenta abruption [n=1]) Among individuals in the multivitamin group, three women (CBR [n=1], IUGR [n=1] and severe pre-eclampsia [n=1]) were excluded. Finally, 48 participants (a multivitamin-mineral group [n=24] and a multivitamin [=24]) completed the trial. Mean age, pre-pregnancy weight and BMI were not statistically different between the two groups (Table 2). There were no significant differences as to the baseline weight and BMI as well as post-intervention means for these variables between the multivitamin-mineral and multivitamin groups. Gestational age and the rate of cesarean section were not significant between the two groups. Based on three-day dietary records, no significant difference between the two groups was found in terms of dietary intakes of energy, calcium, iron, magnesium, zinc and dietary fiber (data not shown).

A significant rise in maternal plasma total GSH (changes from baseline: +109 ± 420 *vs.* -163 ± 270 µmol/L, *p*=0.01) was observed following the consumption of multivitamin-mineral *vs.* multivitamin supplements. Multivitamin-mineral compared to multivitamin supplementation led to a significant increase in maternal serum calcium (0.5 *vs.* -0.1 mg/dL, *p*=0.04) and magnesium levels (0.1 *vs.* -0.2 mg/dL, *p*<0.001) (Table 3). No significant differences were seen comparing multivitamin-mineral and multivitamin in terms of their effects on maternal serum iron, zinc and vitamin D levels.

Although no significant difference was seen in newborn weight, height, head circumference, serum calcium, vitamin D, iron, magnesium, zinc and plasma TAC concentrations between the two groups, mean plasma total GSH levels (1791 ± 566 *vs.* 1434 ± 622 µmol/L, *p*=0.04) of the newborns whose mothers received multivitamin-mineral were higher than those whose mothers received multivitamin supplements. (Table 4)

Table 1: Composition of dietary supplements used in the study.

Variable	Multivitamin-mineral	Multivitamin	Unit
Vitamin A	5000	5000	IU
Vitamin E	15	15	IU
Vitamin D3	400	400	IU
Vitamin B1	1.5	1.5	mg
Vitamin B2	1.7	1.7	mg
Niacin	20	20	mg
Vitamin B6	2	2	mg
Folic acid	400	400	µg
Vitamin B12	6	6	µg
Vitamin C	60	60	mg
Calcium	125	-	mg
Iron	18	-	mg
Magnesium	100	-	mg

Values are for each tablet

Table 2: General characteristics of the study participants.

Characteristic	Multivitamin-mineral (n=24)	Multivitamin (n=24)	Range	*p-value*
Age (y)	24 ± 4	26 ±5	18-34	0.199
Height (cm)	158 ± 6	160 ± 5	143-169	0.322
Pre-pregnancy weight (kg)	61 ± 10	68 ± 12	44-92	0.069
Weight at study baseline (kg)	64 ± 10	70 ± 120	47-96	0.059
Weight at end-of-trial (kg)	73 ± 10	76 ± 12	55-109	0.312
Pre-pregnancy BMI (kg/m^2)	25 ± 4	26 ± 4	17-36	0.108
BMI at study baseline (kg/m^2)	26 ± 4	28 ± 4	18-37	0.093
BMI at end-of-trial (kg/m^2)	29 ± 3	30 ± 5	22-42	0.515
Gestational age (weeks)	39 ± 2	39 ± 1	37-41	0.789
Cesarean section (%)	10 (42)	11 (46)	-	0.771

Data are means± standard deviation, BMI: Body mass index

Table 3: Mean (±standard deviation) of maternal biochemical indicators at baseline and after the intervention.

Variable	Multivitamin-mineral (n=24)			Multivitamin (n=24)			%95CI
	Wk0	Wk20	Change	Wk0	Wk20	Change	
Calcium (mg/dl)	9 ± 1	9 ± 1	0.5 ± 0.9⋆	9 ± 0	9 ± 1	-0.1±0.8#	-1;-0.01
Vitamin D (ng/mL)	13 ± 6	14 ± 5	1 ± 4	9 ± 6	10 ± 4	1 ± 7	-4;3
Iron (mg/dL)	144 ±145	149 ± 139	5 ± 157	97 ± 79	97 ± 37	1 ± 82	-77;68
Magnesium (mg/dL)	2 ± 1	2 ± 1	0.1 ± 0.4	2 ± 0.3	2 ± 0.3	-0.2 ± 0.3⋆⋆##	-1;-0.17
Zinc (µg/dL)	88 ± 25	100 ± 40	12 ± 44	87 ± 16	109 ± 33	22 ± 37⋆⋆	-13;34

*CI: Confidence interval; * Significant difference in respect to baseline (by paired t-test): p<0.05; ** Significant difference in respect to baseline (by paired t-test): p<0.01; # Between group differences (by independent samples t test): p<0.05; # # Between group differences (by independent samples t test): p<0.01.*

Table 4: The effect of multivitamin-mineral *vs.* multivitamin supplementation on newborn biochemical indicators and birth size.

Variable	Multivitamin-mineral (n=24)	Multivitamin (n=24)
Calcium (mg/dL)	9 ± 1	9 ± 1
Vitamin D (ng/mL)	15 ± 5	16 ± 5
Iron (mg/dL)	106 ± 60	116 ± 102
Magnesium (mg/dL)	2 ± 0.3	2 ± 0.3
Zinc (µg/dL)	106 ± 28	107 ± 34
TAC (mmol/L)	1461 ± 322	1411 ± 410
GSH (µmol/L)	1791 ± 566	1434 ± 622⋆
Newborns' weight (kg)	3234 ± 480	3365 ± 374
Newborns' length (cm)	50 ±3	50 ± 1
Newborns' head circumference (cm)	35 ± 2	35 ± 1

Values are means ± standard deviation, ⋆Between group differences (by independent samples t test): p<0.05, TAC: Total antioxidant capacity, GSH: Total glutathione

Discussion

The present study showed that multivitamin-mineral *vs.* multivitamin supplementation for 20 weeks among pregnant women had beneficial effects on maternal serum calcium and magnesium as well as newborn plasma total GSH levels. No favorable effects were found with the patients who received multivitamin-mineral on maternal serum iron, zinc and vitamin D levels as well as on newborn serum calcium, vitamin D, iron, magnesium, zinc, plasma TAC levels and birth size compared to multivitamin supplements. Pregnant women are susceptible to nutritional micronutrients deficiency. It was reported that multiple micronutrients deficiency during pregnancy would result in several aberrations in maternal and fetal health.[9,11,29-30]

The current study demonstrated that multivitamin-mineral *vs.* multivitamin supplementation for 20 weeks during pregnancy increased maternal serum calcium and magnesium levels but could not affect maternal serum iron, zinc, vitamin D as well as newborn serum calcium, vitamin D, iron, magnesium and zinc levels. In line with this study, maternal increased levels of serum calcium has been reported with consumption of orange juice fortified with calcium in adolescent pregnant mothers but could not affect newborn serum calcium status.[31] Multiple micronutrient supplementations during pregnancy also decreased the prevalence of serum riboflavin, vitamin B6, vitamin B12, folate and vitamin D deficiencies compared to controls for 32 weeks.[18] Firouzabadi et al.[32] has also shown increased levels of serum calcium and vitamin D with 1000 mg/day calcium plus vitamin D 100000 IU/month supplementation for 6 months in infertile women with polycystic ovary syndrome (PCOS). Similar increase in maternal serum calcium status was also seen with consuming calcium during pregnancy.[33] Supplementation with multiple micronutrients has also resulted in improved folate, vitamin B12, B6 and riboflavin status between baseline and the third trimester compared to controls receiving vitamin C only.[18] However, supplementation with multiple micronutrients during pregnancy could not improve maternal or newborn serum zinc or vitamin A status compared to supplementation with iron only for 9 weeks.[21] Micronutrient malnutrition during pregnancy, particularly iron deficiency, continues to be an important public health problem among the poor in Iran. Although the prevalence of calcium, magnesium and iron deficiency was low and deficiency is rare, it is still of concern due to the important implications for pregnancy outcomes. The difference between the current findings and other studies might be explained by the different study designs, sample sizes, duration and dosage of supplementation as well as composition of nutrients used in the supplements. Furthermore, it is possible that the lack of impact observed in other studies is related to compliance with the supplementation. Compliance in this study was high (over 90% in both groups) and began at an average of 20 weeks of pregnancy, leaving ample time for impact.

There was no significant effect found with multivitamin-mineral *vs.* multivitamin supplementation after 20 weeks during pregnancy on newborns' birth size. In agreement with this study, Ramakrishnan et al.[23] has shown that multiple micronutrient supplementation from 13 weeks of gestation until delivery does not lead to greater newborn birth size when compared to iron-only supplementation. The administration of multimicronutrients to undernourished pregnant

women could not affect newborn birth size compared to the placebo for 2 months.[34] Similar findings were seen in a cluster-randomized controlled trial among pregnant women found receiving multiple micronutrients supplements for 5 days per weeks compared with iron-folic acid supplements.[35] However, prenatal supplementation with multiple micronutrients after 150 days had a greater positive impact on birth weight than supplementation with iron/folic acid.[36] Multiple micronutrient supplementations from weeks 12-16 of gestation to delivery also led to a significant increase in birth size compared with placebo but could not affect head circumference.[37] The inconsistency in the present findings with other studies may be due to the lack of a unique cutoff level for defining deficiency of micronutrient in pregnancy or because of considering deficiency of micronutrient regardless of the overall nutritional status of the pregnant women. Small sample size might also provide further reasons for multiple micronutrients supplementation's effects on birth size.

The present study showed that consuming multivitamin-mineral *vs*. multivitamin supplements for 20 weeks during pregnancy led to a significant increase in newborn plasma total GSH levels, but could not affect TAC levels. In a study by Adams et al.[38] vitamin/mineral supplementation in children and adults with autism resulted in significant improvements of metabolic status including total sulfate, reduced glutathione and ratio of oxidized glutathione to reduced glutathione (GSSG: GSH). A significant increase of GSH and uric acid levels with moderate multivitamin-mineral supplementation was also seen in athletes after three weeks.[39] The same findings have been documented with administration of multiple micronutrients in Chinese children after 3 weeks.[40] In addition, calcium supplementation (0.9%) in the nutrition of high-fat diet (HFD) mice after 9 weeks showed increased duodenal glutathione and oxidized glutathione (GSH/GSSG) ratios but could not affect TAC levels.[41] Magnesium supplementation (40 mg/kg) has also shown a significant increase in total GSH and TAC levels in male Wistar rats after four weeks.[42] Several mechanisms may explain the favorable effects of multivitamin-mineral supplementation on newborn biomarkers of oxidative stress. The calcium elements of multivitamin-mineral supplements may act as direct antioxidants and DNA damage reducing agents resulting in maternal free radical scavenging,[43] and then might lead to decreased transfer of free radicals from mother to fetus and thus increase the status of newborn plasma total GSH. Increased maternal plasma GSH levels following the consumption of multivitamin-mineral compared with multivitamin supplements may elevate its transfer to the fetus and then lead to increased newborn plasma GSH levels. In a study by Kuster et al.[44] a strong correlation was observed between maternal and fetal GSH and cysteine (precursor of GSH biosynthesis). Nonetheless, little evidence from trials exists to evaluate the effect of micronutrients supplementation during pregnancy on biomarkers of oxidative stress in pregnant women and their newborns. In addition, increased levels of maternal serum magnesium from multivitamin-minerals supplementation might result in elevated total GSH levels in newborns by restoring the activity of anti-oxidative enzymes and scavenging oxygen radicals.[45,46]

Several limitations must be considered in the interpretation of the findings of this study. Due to budget limitations, maternal systemic inflammatory factors, insulin resistance and other biomarkers of oxidative stress were not assessed. In addition, the beneficial effects of multivitamin-mineral and multivitamin supplementation on the other biochemical indicators of newborns could not be assessed. Small sample size could potentially account for lack of detecting significant difference on birth size despite the significant increase in maternal serum calcium and magnesium levels. Furthermore, the effect of water retention on biochemical markers was not assessed due to lack of resources and technical difficulties.

Conclusion

Multivitamin-mineral compared to multivitamin supplementation after 20 weeks during pregnancy resulted in improved biochemical indicators of pregnant women and their newborns including maternal serum calcium and magnesium levels as well as newborn plasma total GSH, but had no effect on maternal serum iron, zinc and vitamin D levels as well as newborns' serum calcium, vitamin D, iron, magnesium, zinc, plasma TAC levels and birth size. Further studies are recommended to assess the effects of multivitamin-mineral and multivitamin supplementation on lipid profiles, insulin resistance and inflammatory factors in pregnant women and their newborns as well as other pregnancy outcomes including neonatal hyperbilirubinemia and respiratory distress syndrome.

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