

Multivitamin Versus Multivitamin-mineral Supplementation and Pregnancy Outcomes: A Single-blind Randomized Clinical Trial

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ABSTRACT

Background: Increased requirement and decreased dietary intakes of micronutrients during pregnancy might affect maternal health and pregnancy outcomes. This study was aimed to examine the effects of two types of multiple micronutrient supplementations on pregnancy outcomes in Kashan, Iran.

Methods: In a randomized single-blind controlled clinical trial, 104 primigravid singleton pregnant women aged 18-30 years were randomly assigned to receive either a multivitamin ($n = 51$) or a multivitamin-mineral ($n = 53$) supplements for 20 weeks. Participants consumed supplements once a day at week 16 of gestation. Maternal anthropometric data as well as newborn's weight, height, head circumference and 5-min Apgar score were also determined. Independent samples *t*-test was used for comparing between-group means. Multivariate linear regression analysis was used to identify determinants of newborn's weight, height and head circumference.

Results: Women taking multivitamin-mineral supplements gained marginally less weight until week 28 than those taking multivitamin supplements (weight at week 28 of gestation: 67.5 ± 11.4 vs. 71.6 ± 10.3 kg, $P = 0.06$). Mean body mass index at week 28 (25.8 ± 4.0 vs. 28.4 ± 3.7 kg/m², $P = 0.001$) as well as at delivery (28.0 ± 3.9 vs. 30.1 ± 3.8 kg/m², $P = 0.006$) was lower among women taking multivitamin-mineral supplements than those taking multivitamin supplements. Although no significant difference was seen in newborns' height and Apgar score between the two groups, mean birth weight (3.3 ± 0.4 vs. 3.1 ± 0.4 kg, $P = 0.04$) and head circumference (35 ± 1.4 vs. 34 ± 1.3 cm, $P < 0.0001$) of the infants whose mothers receiving multivitamin-mineral supplements were higher than those whose mothers received multivitamins. Multivitamin-mineral use by pregnant women was a significant predictor of infants' weight ($\beta = 0.191$, $P = 0.03$) and head circumference ($\beta = 0.907$, $P = 0.005$).

Conclusions: In conclusion, we found that birth weight and head circumference was increased in infants whose mothers received multivitamin-mineral supplements for 5 months during pregnancy compared with infants whose mothers received multivitamin supplements.

Keywords: Birth head circumference, birth weight, multivitamin, multivitamin-mineral, pregnancy outcome

INTRODUCTION

Appropriate nutrition during the pregnancy plays an important role in the growth and development of the fetus.^[1-3] Pregnant women are one of the most susceptible groups for nutritional insufficiency due to increased requirements of micronutrients during the period of pregnancy. Several studies have reported insufficient dietary micronutrients intake in pregnant women.^[1,2] Increased metabolic demands for micronutrients during pregnancy occur mainly due to changes in the women's physiology and the requirements of the growing fetus.^[4,5] Micronutrient deficiencies during pregnancy might lead to spontaneous abortion, fetal malformation,^[6] placental abruption,^[7] increased maternal morbidity^[8] as well as low birth weight (LBW) babies.^[9] Approximately, 16% of all live births worldwide are LBW; 90% of which are born in low-income countries.^[10] This rate is considerably high in Asian countries.^[11] It is, therefore, expected that providing multiple micronutrients, rather than iron and folic acid (IFA) alone, as currently recommended, might beneficially affect both maternal health and fetal growth.

Several investigators have evaluated the effect of multiple micronutrients supplementation on pregnancy outcome.^[12-16] Micronutrient supplementation during pregnancy has been reported to improve fetal growth compared with the placebo; however, no significant difference was found compared to iron or IFA supplementation.^[17] In a study in Nepal, multiple micronutrient supplementations during pregnancy did not reduce early infant mortality,^[18] however, it led to improved folate status and reduced the prevalence of riboflavin, vitamin B6, vitamin B12, folate and vitamin D deficiencies.^[19] Evidence for the impact of micronutrient supplementation on pregnancy outcomes is still inadequate and further research is required before a switch from iron-folate supplementation is implemented.^[17] Furthermore, most of the previous studies have been conducted in communities with a high prevalence of maternal malnutrition and it remains unknown if these supplementations would improve pregnancy outcomes in other populations. In addition, earlier studies have mostly compared micronutrient supplementation with the placebo intake. Although few studies have assessed maternal multiple micronutrient supplementation with IFA, to

the best of our knowledge no report is available examining the efficacy of multivitamin supplements compared with multivitamin-mineral supplements on pregnancy outcomes. This study was therefore performed to investigate the effects of two types of maternal multiple micronutrient (multivitamin vs. multivitamin-mineral) supplementation on maternal health and pregnancy outcomes in Iranian pregnant women.

METHODS

Participants

This randomized single-blind controlled clinical trial was carried out in Kashan, Iran during March 2010 to May 2011. On the basis of sample size formula suggested for randomized clinical trials,^[11] we considered the type I error of 5% ($\alpha = 0.05$) and type II error of 20% ($\beta = 0.2$; Power = 80%) and birth weight as a key variable, we reached the sample size of 51 persons for each group. The present study was carried out in the Naghavi Maternity Clinic, Shaheed Beheshti Subspecialty Polyclinic and twenty four antenatal centers, affiliated to Kashan University of Medical Sciences. A total of 104 primigravida pregnant women aged range from 18 to 30 years who were carrying a singleton pregnancy participated in the current study. Multiparous women as well as those with hypertension, mild and severe pre-eclampsia, intrauterine growth retardation (IUGR), intra-uterine fetal death, gestational diabetes mellitus (GDM), completed bed rest (CBR), history or evidence of rheumatoid arthritis, thyroid, parathyroid or adrenal diseases, hepatic or renal failure and metabolic bone disease were not included in the current study. All pregnant women were taking 400 $\mu\text{g}/\text{d}$ folic acid supplements from the beginning of pregnancy as well as 30 mg/d ferrous sulfate from the second trimester. 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, Kashan, Iran. All participants provided informed written consent.

Study design

Subjects were randomly assigned to receive either a multivitamin ($n = 51$) or multivitamin-mineral supplements ($n = 53$) from week 16 of gestation

through to delivery. All participants were asked to take one supplement a day orally. They were also asked not to alter their routine physical activity and usual diet throughout the study. The multivitamin and multivitamin-mineral supplements were provided by Shahre Daru Co., Tehran, Iran and NatureMade Co., USA, respectively. Supplements were provided to subjects monthly. We kept all supplements in a cool temperature before using. Compliance with the supplements consumption was monitored once per month through phone interviews. The composition of the supplements is provided in Table 1.

Data collection

Detailed information about health and reproductive status, supplement use and life-style were collected through the use of a questionnaire by face-to-face interview. Gestational age was calculated from the date of last menstrual period and concurrent clinical assessment.^[20] Data on pre-pregnancy weight and height (measured values) were taken from the records of pregnant women existed in the clinic. Maternal weight at week 16 and 28 of gestation and on delivery was measured (Digital Floor Scale; Seca, Hamburg, Germany) without shoes and with minimum clothing to the nearest 0.1 kg. Height was measured using a non-stretchable tape measure and recorded to the nearest 0.1 cm (Seca, Hamburg, Germany). Body mass index (BMI) was calculated as weight in kilogram divided by height in meters squared. Newborn's height and weight were measured using

standard methods (Seca 155 Scale, Hamburg, Germany) 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 with a Seca girth measuring tape. We also determined newborn's 5-min Apgar score as another measure of pregnancy outcome.

Statistical analysis

To ensure normal distribution of variables, Kolmogorov-Smirnov test was applied. We used independent samples *t*-test to compare means between the two groups. To assess if the magnitude of the changes depended on pre-pregnancy and baseline BMI values, we conditioned all analyses on pre-pregnancy and baseline BMI values to avoid the potential bias that might have resulted. These adjustments were done using analysis of covariance. Multivariate linear regression analysis was used to identify determinants of pregnancy outcomes in this population. In these analyses, supplement use was treated as dichotomous variable (multivitamin use = 0 and multi-vitamin-mineral consumption = 1). All other possible determinants of pregnancy outcomes including maternal age, height, pre-pregnancy weight, maternal weight at week 16 and 28, maternal weight at delivery as well as gestational age were simultaneously considered in these regression models. Before entering the variables in the linear regression model, we examined the correlation between the variables. The stability of the models was considered to be disturbed by the multi-collinearity if tolerance was <0.1. As we did not find any evidence of multi-collinearity, therefore all variables were entered simultaneously to the model. $P < 0.05$ was considered to be statistically significant. All analyses were performed by the use of statistical package for social sciences (SPSS, version 17; SPSS Inc., Chicago, Illinois, USA).

RESULTS

Among individuals in a multivitamin group, 4 women (pre-eclampsia [$n = 2$], GDM [$n = 1$] and CBR [$n = 1$]) were excluded. The exclusions in a multivitamin-mineral group was 2 persons (pre-eclampsia [$n = 1$] and CBR [$n = 1$]). Finally, 104 participants a multivitamin group ($n = 51$) and a multivitamin-mineral ($n = 53$) completed the trial [Figure 1].

Table 1: Composition of dietary supplements used in the study^a

	Multi-vitamin	Multi-vitamin-mineral	Unit
Vitamin A	5000	4000	IU
Vitamin E	15	11	IU
Vitamin D3	400	400	IU
Vitamin B1	1.5	1.5	mg
Vitamin B2	1.7	1.8	mg
Niacin	20	18	mg
Vitamin B6	2	2.8	mg
Folic acid	400	800	µg
Vitamin B12	6	4	µg
Vitamin C	60	100	mg
Calcium	-	250	mg
Iron	-	27	mg
Zinc	-	25	mg

^aValues are for each tablet

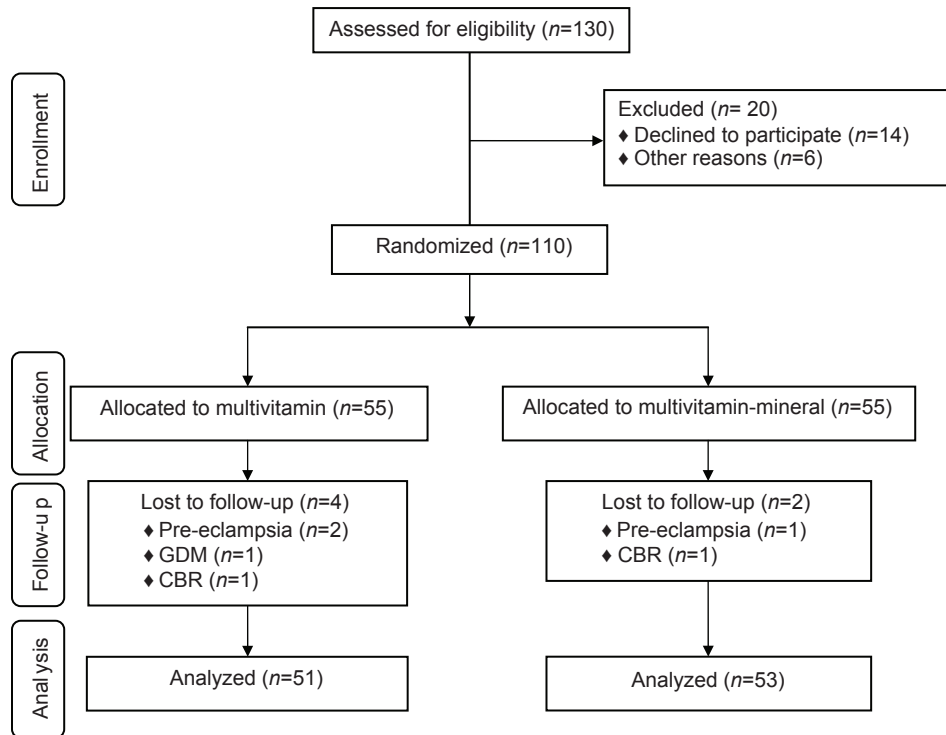


Figure 1: Summary of patient flow. GDM=Gestational diabetes mellitus, CBR=Completed bed rest

Characteristics of the study population are provided in Table 2. Mean age of the studied population was 24.4 years with no significant difference between the two groups. Women in the multi-vitamin-mineral group were significantly taller than those in the multivitamin group (161.6 ± 4.8 vs. 158.6 ± 4.7 cm, $P = 0.002$). Although we did not find a significant difference in pre-pregnancy weight between the two groups, pre-pregnancy BMI was significantly higher among women taking multi-vitamin compared with those taking multivitamin-mineral (25.6 ± 3.9 vs. 23.9 ± 3.7 kg/m², $P = 0.03$). This was also the case for BMI at week 16 of gestation (26.5 ± 3.9 vs. 24.5 ± 3.8 kg/m², $P = 0.01$). No significant difference in weight at week 16 was found between the two groups.

Women taking multivitamin-mineral supplements gained marginally less weight until week 28 than those taking multivitamin supplements (weight at week 28 of gestation: 67.5 ± 11.4 vs. 71.6 ± 10.3 kg, $P = 0.06$). Mean BMI at week 28 (25.8 ± 4.0 vs. 28.4 ± 3.7 kg/m², $P = 0.001$) as well as at delivery (28.0 ± 3.9 vs. 30.1 ± 3.8 kg/m², $P = 0.006$) was lower among women taking multivitamin-mineral supplements than those taking multivitamin supplements. Although no significant difference was seen in newborns' height

Table 2: Baseline characteristics of the study participants

	Multi-vitamin (n=51)	Multi-vitamin-mineral (n=53)	P ^a
Age (year)	24.5±3.1	24.3±3.5	0.81
Height (cm)	158.6±4.7	161.6±4.8	0.002
Pre-pregnancy weight (kg)	64.4±10.8	62.6±10.4	0.37
Weight at baseline (kg)	66.7±10.6	64.3±10.8	0.26
Pre-pregnancy BMI (kg/m ²)	25.6±3.9	23.9±3.7	0.03
BMI at baseline (kg/m ²)	26.5±3.9	24.5±3.8	0.01
Gestational age (weeks)	39.3±1.2	39.3±1.0	0.88

^aObtained from independent *t*-test. BMI=Body mass index

and Apgar score between the two groups, mean birth weight (3.3 ± 0.4 vs. 3.1 ± 0.4 kg, $P = 0.04$) and head circumference (35 ± 1.4 vs. 34 ± 1.3 cm, $P < 0.0001$) of the infants whose mothers receiving multivitamin-mineral supplements were higher than those whose mothers received multivitamins [Table 3]. After adjustment for pre-pregnancy and baseline BMI values, the above-mentioned findings remained significant, except for weight at delivery ($P = 0.02$) and BMI at delivery ($P = 0.22$).

Regression coefficients for identification of factors influencing infants' weight, length and

Table 3: The effect of dietary supplements on maternal weight gain and pregnancy outcomes^a

	Multi-vitamin (n=51)	Multi-vitamin-mineral (n=53)	P ^b
Maternal anthropometric measures			
Weight at week 28 (kg)			
Crude	71.6±10.3	67.5±11.4	0.06
Model 1c	69.2±6.4	71.1±5.8	0.13
Weight at delivery (kg)			
Crude	76.0±10.3	73.4±11.1	0.23
Model 1	74.0±6.4	76.8±5.8	0.02
BMI at week 28 (kg/m ²)			
Crude	28.4±3.7	25.8±4.0	0.001
Model 1	27.6±1.4	27.0±1.5	0.01
BMI at delivery (kg/m ²)			
Crude	30.1±3.8	28.0±3.9	0.006
Model 1	29.5±1.4	29.2±1.5	0.22
Pregnancy outcomes			
Newborn's weight (kg)			
Crude	3.1±0.4	3.3±0.4	0.04
Model 1	3.2±0.5	3.4±0.5	0.01
Newborn's length (cm)			
Crude	50.2±2.3	50.9±2.2	0.11
Model 1	50.2±2.8	51.1±2.9	0.13
Newborn's head circumference (cm)			
Crude	34.0±1.3	35.0±1.4	<0.001
Model 1	34.1±1.4	35.4±1.5	<0.001
Apgar score			
Crude	9.9±0.2	9.9±0.1	0.61
Model 1	9.9±0.2	9.9±0.2	0.52

^aValues are means±SD, ^bObtained from independent *t* test,

^cObtained from ANCOVA (adjusted for pre-pregnancy and baseline BMI values). BMI=Body mass index, SD=Standard deviation, ANCOVA=Analysis of covariance

head circumference are indicated in Table 4. Multivitamin-mineral use by pregnant women was a significant predictor of infants' weight ($\beta = 0.191$, $P = 0.03$) and head circumference ($\beta = 0.907$, $P = 0.005$). Gestational age has been found as a significant contributor to infants' birth weight ($\beta = 0.145$, $P < 0.0001$) and length ($\beta = 0.578$, $P = 0.006$). We also found that infants' length is affected by maternal height as well ($\beta = 0.102$, $P = 0.04$). No significant associations were found between mothers' weight and their infants' birth sizes.

DISCUSSION

In the present study, we found that multivitamin-mineral supplementations along with other routine supplements used in pregnancy would significantly affect infants' birth weight and head circumference compared with multivitamin supplements.

Earlier studies have assessed the effect of multiple micronutrients supplementation during pregnancy on birth size.^[21-28] Most of the previous studies have compared multivitamin-mineral supplements with placebo or IFA supplement. To the best of our knowledge, this is the first study in which the use of multivitamin-mineral supplements in pregnant women has been compared with multivitamin supplements. Furthermore, this study has assessed this comparison along with the other routine supplements administered during pregnancy.

Replacing IFA supplements with multiple micronutrient supplements during pregnancy has been reported to improve both birth weight and child growth. Furthermore, meaningful improvements have been shown in height and cognitive development of children by 2 years of age.^[16] Multiple micronutrient supplements from week 12 to 16 of gestation to delivery resulted in a significant increase in birth size compared with placebo, but did not affect head circumference.^[29] Unlike these studies, Sunawang *et al.* in a cluster-randomized controlled trial among pregnant women found no significant difference in birth weight of infants whose mothers receiving multiple micronutrients supplements for 5 days/week compared with those whose mothers taking IFA supplements.^[21] Such finding has also been reached when the pregnant women receiving multiple micronutrients supplement for 6 days/week from week 13 of gestation through delivery was compared with those receiving iron supplements.^[25] In a double-blind randomized controlled trial in rural Burkina Faso, multiple micronutrient supplementations was associated with increased birth weight and height compared with standard IFA, but the differences were not statistically significant.^[11] Multiple micronutrients supplementation has also been reported to have no additional benefits over folic acid-iron supplements on birth length and infants' head circumference and on lowering incidence of preterm birth; however, it has led to increased birth weight by 7 g.^[30] Different

Table 4: Regression coefficients to identify determinants of pregnancy outcomes

	Newborn's weight			Newborn's length			Newborn's head circumference		
	β	SE	P^a	β	SE	P^a	β	SE	P^a
Supplement use	0.191	0.087	0.03	0.499	0.507	0.32	0.907	0.313	0.005
Maternal age	0.015	0.012	0.20	0.028	0.068	0.68	-0.037	0.042	0.37
Maternal height	0.006	0.009	0.52	0.102	0.051	0.04	0.059	0.031	0.06
Maternal pre-pregnancy weight	-0.009	0.015	0.56	0.115	0.089	0.19	-0.028	0.055	0.61
Maternal weight at week 16	0.020	0.024	0.42	-0.221	0.141	0.12	0.075	0.087	0.39
Maternal weight at week 28	0.000	0.018	0.98	0.071	0.106	0.50	-0.013	0.065	0.84
Maternal weight at delivery	0.000	0.015	0.99	0.036	0.089	0.68	-0.031	0.055	0.58
Gestational age	0.145	0.035	<0.001	0.578	0.204	0.006	0.198	0.126	0.11

^aSupplement use was treated as dichotomous variable (multi-vitamin use=0 and multi-vitamin-mineral consumption $n=1$). SE=Standard error

findings might be explained by the different study designs, sample sizes, duration and dosage of supplementation as well as composition of nutrients used in supplements. Most of previous studies have used usual multi-micronutrient supplements available in the market, but we used supplements that were prepared for pregnancy period. For instance, the supplements used in previous studies did not contain some potentially important micronutrients, like calcium, but the high amount of calcium (250 mg) and zinc (27 mg) in multi-prenatal supplements we used might affect birth weight and head circumference. In a study in India, when 14 other micronutrients were added to UNICEF/WHO/UNU-designed supplements for pregnant women; impressive results on birth size were observed.^[31] Furthermore, several studies have indicated that deficiencies of zinc,^[5,13] iron^[32,33] and calcium^[34] during pregnancy could affect birth size. In the current study, the folic acid content of the multivitamin-mineral supplement was 2 times higher than the multivitamin supplement alone. It seems that folic acid has a positive effect on infants' size. In a study by Rao *et al.*^[35] has been reported that maternal erythrocyte folate at 28 week gestation was positively associated with birth weight. Some randomized trials have also been shown that prenatal use of vitamins, including folic acid, is associated with infant birth size.^[36,37] The improvement in the birth size due to high content of folic acid in the multivitamin-mineral supplement group may be resulted from its effect in the increase of placental size, cell number^[38] and rescue the gene expressions negatively induced by IUGR.^[39] Despite the non-significant effect

of received supplements by pregnant women in this study, we found a significant predictor of between the two groups in terms of their effects on infants' weight and length. In consistent our study, several researchers have also been shown that birth size is associated with gestational age.^[40,41] Emerging evidence indicates that the use of micronutrient-containing prenatal vitamins during pregnancy is associated with reduced risk of congenital defects, preterm delivery, LBW and pre-eclampsia.^[42] It must be kept in mind that the current study has been performed in a developing country setting. The dietary reference intakes of micronutrients for pregnant women is based on requirements of women residing in the United States or Canada. Such levels might be insufficient to meet the requirements of pregnant women living in communities with mild to moderate deficiencies of micronutrients. In Guinea-Bissau, providing supplements containing twice the RDA of micronutrients resulted in a lower incidence of LBW infants by 69%.^[43] In Tanzania, when micronutrient supplements providing amounts twice the recommended dietary allowance (RDA) for vitamin E and 6-10 times for vitamin C and several B vitamins were administered, mean birth weight increased by 67 g.^[36] Finally, the provision of multivitamin and multivitamin-mineral supplements from two different pharmaceutical companies might be influenced infants' size.

Our findings must be interpreted in the context of some limitations. As the current study included both underweight (BMI < 20) and obese (BMI \geq 30 kg/m²) participants, therefore the findings must be interpreted cautiously because

both underweight and overweight has been shown to influence pregnancy outcomes. In addition, we could not assess the effects of micronutrients supplementation on biochemical indicators of newborns.

CONCLUSIONS

We found that compared with those who had multivitamin supplements, pregnant women that received multivitamin-mineral supplements for 5 months during pregnancy had babies with higher birth weight and head circumference.

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