Evaluation of Zinc Supplementation Effect on Fetal Outcomes in Pregnant Women with Lower-than-Median Serum Zinc Concentration

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Abstract

Objective: Zinc is the second main element in the body after iron. Its importance in pregnancy is related to role in DNA and protein synthesis and consequently the necessity of its availability for the appropriate growth and development of the fetus and neonate. The purpose of this study was to assess the effect of zinc supplement on fetal outcomes (height, weight, head and chest circumference of the fetus, low birth weight, and pre-term birth) in pregnant women with lower-than-median serum zinc.

Materials and methods: Participants of this experimental double-blind clinical trial study were 263 healthy singleton pregnant women with a mean age of 26.46 (±4.52) years and gestational age of 14.52 (±4.51) weeks whose (non-fasting) serum zinc levels were lower than median of the study population. All eligible individuals were randomly divided into two groups of zinc supplement and placebo. Individuals in the zinc supplement group (128 participants) took one zinc supplement capsule including 25 mg elemental zinc and participants in the placebo group (135 people) took one placebo capsule per day until the end of pregnancy. All women were under control and supervision until the end of the pregnancy and their information about labor, delivery, and neonate measures were collected through their obstetric records and then compared.

Results: Findings of this study showed no significant difference in fetal measures at birth (weight, height, head and chest circumference), pre-term delivery, and low birth weight between zinc supplement and placebo groups.

Conclusion: According to our findings, administration of 25mg elemental zinc per day does not improve fetal measures in pregnant women with lower-than-median serum zinc concentration; however, more in-depth studies with larger sample sizes are recommended to achieve more reliable results.

Keywords: Zinc supplement, Serum zinc concentration lower than the median, fetal outcome

Introduction

The importance of zinc in pregnancy is due to its role in DNA and protein synthesis and as a result the necessity of its availability for the appropriate growth and development of the fetus and neonate (1). Zinc deficiency, in addition to reducing cell proliferation, protein synthesis, or rate of tubule polymerization, decreases growth in embryonic and fetal periods (2).

Findings of various animal studies have well showed a direct relationship between zinc deficiency

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and fetal growth restriction and fetal malformations; however, such a relationship has not been documented in human studies so far (3). Results of several studies indicate a direct and significant relationship between the maternal level of serum zinc and measures of the neonate (4-8) while some other studies have failed to find such a relationship (9-11). Moreover, there is evidence that lower levels of plasma zinc are associated with undesirable pregnancy outcomes such as fetal malformations, pre-term delivery, fetus growth restriction, pre-eclampsia, and bleeding after delivery (12-17); however, some other studies do not confirm these reports (3, 5,18). Although the differences in the findings of these studies have resulted in a controversial challenge regarding the necessity of zinc supplementation during pregnancy, at least one study has documented the desirable effects of zinc supplementation on fetal measures at birth in pregnant women with lower-than-median serum zinc levels (19).

Therefore, considering the high prevalence of zinc deficiency in Iranian pregnant women (20, 21) and findings of a study performed by Goldenberg in 1995 (19), it seemed that conducting this study was necessary to assess the effect of zinc supplementation on fetal outcomes (fetal measures, pre-term birth, and low birth weight) in pregnant women with lower levels of serum zinc.

Materials and methods

The ethics committee of Tehran University of Medical Sciences approved this experimental double-blind clinical trial in 2006 (registration number: 2719).

The participants of this study were selected among the eligible pregnant women who were admitted to the pre-natal clinic at MirzaKouchak Khan Hospital. Their maximum gestational age was 24 weeks and their serum zinc (proportional to the gestational age) was lower than median. They had no history of systemic, cardiovascular, proliferative, or endocrine diseases, neoplasm, and anemia. They did not smoke or consume alcohol and were not addicted to illicit drugs. Also, they did not use any medications except for acid folic (1 mg) and Ferrous sulfate (50 mg elemental iron) since the beginning of the second trimester.

In order to determine the median serum zinc level of the pregnant women who were admitted to the aforementioned clinic, 99 eligible pregnant women were randomly selected at the beginning of the study and their non-fasting serum zinc was assessed via the enzymatic method after obtaining their consent and drawing 2 ml of venous blood. Then, based on the median serum zinc level of these individuals, which was determined proportional to the gestational age, subsequent samples were chosen (following taking blood and measuring serum zinc) and randomly divided into two groups of zinc and placebo recipients. In addition to folic acid and Ferrous sulfate, individuals in the zinc group took one zinc sulfate capsule including 25 mg elemental zinc and participants in the placebo group received a similar capsule including starch daily until the end of the pregnancy.

All eligible women were under control and supervision regarding pregnancy complications until the end of the pregnancy. Finally, information about labor and delivery were collected through obstetric records and then compared.

In this study, gestational age was calculated at the beginning of the study based on the first day of last menstrual period and fundal height. If a woman did not remember the first day of her last menstrual period or her fundal height differed with her gestational age for more than two weeks, ultrasound was employed to accurately determine the gestational age (less than 20 weeks). Pre-term delivery was defined as delivery before 37 complete weeks and neonates weighing less than 2500 gr were considered as low birth weight (22). Statistical tests applied in this study included bivariate correlation, chi-squared, and t tests. All analyses were performed with a 95% confidence interval (α=0.05) using SPSS software version 17.

Results

Among 4194 pregnant women who were admitted to MirzaKouchak Khan Hospital during 2 years (from 2007 to 2009), serum zinc concentration of 619 eligible pregnant women (99 initially for determining the median of serum zinc and 471 in the next step) was measured and 312 with maximum gestational age of 24 weeks and lower-than-median serum zinc level entered this study; 157 women received zinc supplementation and 155 received placebo. At the end, after excluding 49 participants (due to different reasons such as development of diseases affecting pregnancy outcome and delivery in other centers), information of 128 individuals in the zinc group and 135 in the placebo group was compared. The exclusion of 49 participants did not affect our final results since there was no significant difference

between these individuals and the remaining participants.

Figure 1 represents changes in mean serum zinc level of all participants at the beginning of the study. As this figure shows, serum zinc concentration decreased until the 20th week of pregnancy and then increased. However, no significant correlation was noted between serum zinc concentration and the gestational week. Only some insignificant differences were noted in serum zinc concentration in the second (weeks 4-8) and fifth (weeks 16-20) months of pregnancy (P=0.075).

As Table 1 shows, the two groups were similar in age, weight at the beginning of pregnancy, height, body mass index at the beginning of pregnancy, parity, occupation, level of education, cesarean history, and gestational age, serum zinc at the time of entry to this study, hemoglobin concentration, and hematocrit on routine pregnancy tests. Moreover, the two groups did not differ significantly in the duration of pregnancy, fetus gender, and cesarean delivery.

Comparison of fetal outcomes showed no significant difference in fetal measures at birth (weight, height, head and chest circumference), pre-term delivery, and low birth weight (Table 2) between the two groups.

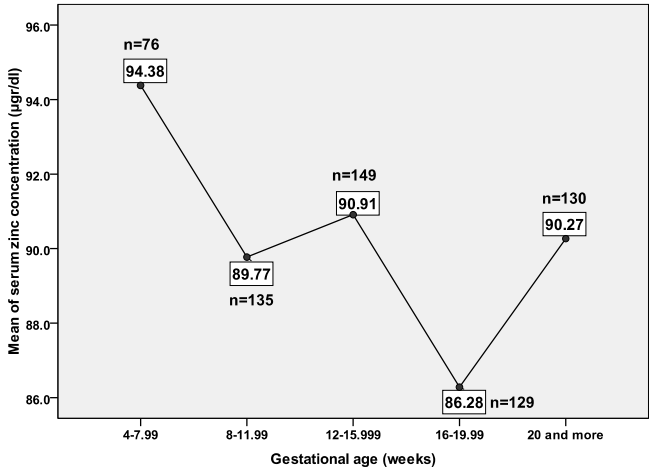

Figure 1. Mean of serum zinc concentration of total participants (619 individuals) at the beginning of the study proportional to the gestational age

Table 1: Characteristics of participants

		Groups		P-value
		Zinc n=128	Placebo n=135	
Age (Mean ± sd) (year)*		26.39 ± 4.1	27.21 ± 4.97	NS[1]
Weight at the beginning of pregnancy (Mean ± sd) (kg)*		62.24 ± 1.5	63.64 ± 10.88	NS
Height (Mean ± sd) (cm)*		160.57 ± 6.11	161.58 ± 6.22	NS
Body mass index (BMI)*		24.13 ± 3.57	24.36 ± 3.76	NS
Parity (Mean ± sd)*		1.66 ± 0.84	1.79 ± 1.05	NS
Occupation** Number(Percent)	Housekeeper	108 (86.5)	118 (87.3)	NS
	Employed	20 (13.5)	17 (12.7)	
Level of education**	Primary	9 (7)	10 (7.5)	NS
	Secondary	22 (17.2)	22 (16.5)	
	High school	74 (57.8)	72 (53.4)	
	University	23 (18)	31 (22.6)	
Cesarean history (Percent)**		20 (16)	24 (17.6)	NS
Serum zinc concentration (Mean ± sd) (µgr/dl)*		71.06 ± 13.41	67.51 ±16.39	NS
Gestational age (Mean ± sd) (week)*		14.44 ± 5.48	14.60 ± 5.37	NS
Hemoglobin concentration (Mean ± sd) (gr/dl)*		12.78 ± 1.21	12.56 ± 1.24	NS
Hematocrit (Mean ± sd) (percent)*		39.09 ± 6.22	37.74 ± 3.54	NS

* T-test ** Chi-squared test [1] Non-significant

Table 2. Comparison of the two groups of zinc supplementation and placebo regarding pregnancy outcomes

		Groups		P-value1
		Zinc n=128	Placebo n=135	
Duration of pregnancy (Mean ± sd) (day)*		265.46 ± 29.65	259.86 ± 39.04	0.196
Fetus gender (Percent)**	Female	63 (49.2)	69 (50.8)	0.899
	Male	65 (50.8)	66 (49.2)	
Cesarean delivery (Percent)**		75 (58.5)	83 (61.7)	0.607
Fetus birth weight (Mean ± sd) (gr)*		3142.56 ± 451.77	3230.16 ± 527.99	0.164
Fetus birth height (Mean ± sd) (cm)*		50.33 ± 3.52	50.22 ± 2.97	0.791
Fetal head circumference at birth (Mean ± sd) (cm)*		34.78 ± 1.71	34.11 ± 2.36	0.869
Fetal chest circumference at birth (Mean ± sd) (cm)*		32.74 ± 4.36	33.11 ± 2.36	0.553
Pre-term delivery (Percent)**		16 (12.5)	19 (14.07)	0.656
Low birth weight (Percent)**		7 (5.8)	9 (6.4)	0.840

* T-test ** Chi-squared test

Discussion

Although different studies have reported rarity of severe zinc deficiency, its low to moderate deficiency is prevalent worldwide. The average zinc intake in the developing and developed countries are 5 to 11 and 8 to 14 mg per day respectively and it is estimated that 82 to 100 percent of pregnant women around the world probably receive insufficient zinc considering the more need of mothers to zinc during the pregnancy and 55.5% suffer from zinc deficiency (23).

In spite of the fact that zinc deficiency is prevalent in pregnant women, findings of many experimental studies evaluating the effect of 15 to 40 mg elemental zinc during pregnancy have suggested no significant relationship in fetal measures (24-27). Results of our study also revealed that administration of 25 mg elemental zinc did not have any effects on fetal measures in women with lower-than-median serum zinc level. However, some limited studies have reported improvement in fetal measures in mothers who received zinc supplementation during pregnancy (19,28). Goldenberg concluded that administration of 25 mg elemental zinc significantly increased birth weight, head circumference, arm length, femur length, and skin fold thickness in neonates of mothers with lower-than-median serum zinc level (19). Similar to our study, they did not find any significant difference in the proportion of low birth weight (less than 2500 gram) and pre-term delivery (before 37 weeks). In other words, an increase of 126 gr in birth weight could not decrease the proportion of these two main indices. As different studies have reported, the importance of these indices is in predicting neonatal mortality rate which highly increases as birth weight (less than 2500gr) and gestational age (less than 37 weeks) decrease (29).

Our findings showed that administration of 25 mg elemental zinc did not increase fetal measures in Iranian pregnant women with low levels of serum zinc (lower than median); however, further studies with larger sample sizes are recommended to obtain more reliable results.

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References

1. World Health Organization. Trace elements in human nutrition and health [internet] 1996. Geneva; Available from:http://whqlibdoc.who.int/publications/1996/9241561734_eng_fulltext.pdf
2. Cetin I, Berti C, Calabrese S. Role of micronutrients in the periconceptional period; Human Reproduction Update 2010;16:80–95.
3. Tamura T, Goldenberg RL, Johnston KE, Dubard M. Maternal plasma zinc concentrations and pregnancy outcome. Am J clin Nutr 2000;71: 109-13.
4. Neggers YH, Cutter GR, Acton RT, Alvarez JO, Bonner JL, Goldenberg RL, et al. A positive association between maternal serum zinc concentration and birth weight. Am J Clin Nut 1990; 51: 678-84.
5. Ghosh A, Fong LY, Wan CW, Liang ST, Woo JS, Wong V. Zinc deficiency is not a cause for abortion, congenital abnormality and small-for-gestational age infant in Chinese women. Br J Obstet Gynaecol

1985;92:886-91.
6. Kirksey A, Wachs TD, Yunis F, Srinath U, Rahmanifar A, McCabe GP, et al. Relation of zinc nutriture to pregnancy outcome and infant development in an Egyptian village. Am J Clin Nutr 1994;60:782-92.
7. Crosby WM, Metcoff J, Costiloe JP, Mameesh M, Sandstead HH, Jacob RA, et al. Fetal malnutrition: an appraisal of correlated factors. Am J Obstet Gynecol 1977;128:22-31.
8. Mameesh MS, Hathout H, Safar MA, Mahfouz A, AL-Hassan JM. Maternal plasma proteins, magnesium, zinc and copper concentration at term associated with birth size in kuwait. Acta vitaminol enzymol 1985;7:183-7.
9. Aydemir F, Cavdar AO, Söylemez F, Cengiz B. Plasma zinc levels during pregnancy and its relationship to maternal and neonatal characteristics: a longitudinal study. Biol Trace Elem Res 2003;91:193-202.
10. Tamura T, Goldenberg RL, Freeberg LE, Cliver SP, Cutter GR, Hoffman HJ. Maternal serum folate and zinc concentration and their relationships to pregnancy outcome. AM J Clin Nutr 1992;56:365-70.
11. Higashi A, Tajiri A, Matsukura M, Matsuda I. A prospective survey of serial maternal serum zinc levels and pregnancy outcome. J pediator Gastroenterol Nutr 1988;7:430-3.
12. Roungsipragarn R, Borirug S, Herabutya Y. Plasma zinc level and intrauterine growth retardation: a study in pregnancy women in Ramathibodi hospital. J Med Assoc thai 1999;82:178-81.
13. Jain S, Sharma P, Kulshreshtha S, Mohan G, Singh S. The role of calcium, magnesium, and zinc in pre-eclampsia. *Biol Trace Elem Res 2010; 133:162-70.*
14. Cavdar AO, Bahceci M, Akar N, Erten J, Bahceci G, Babacan E, et al. Zinc status in pregnancy and the occurrence of anencephaly in turkey. J Trace Elem Electrolytes Health Dis 1988;2:9-14.
15. Atinmo T, Mbofung C, Osinusi BO. Relationship of zinc and copper concentrations in maternal and cord blood and birth weight. Int J Gynaecol Obstet 1980;18:452-4.
16. Kumru S, Aydin S, Simsek M, Sahin K, Yaman M, Ay G. Comparison of serum copper, zinc, calcium and magnesium levels in precclamptic and healthy pregnant women. Biol trac Elem Res 2003; 94:105- 12.
17. Jameson S. Zinc and copper in pregnancy, correlation to fetal and maternal complications. Acta Med Scand Suppl 1976;593:5-20
18. Bahadoran P, Zendehdel M, Movahedian A, Hasan Zahraee R. The relationship between serum zinc level and preeclampsia. Iran J Nurs Midwifery Res 2010;15:120-4.
19. Goldenberg RL, Tamura T, Neggers Y, Copper RL, Johnston KE, Dubard MB, et al. The effect of zinc supplementation on pregnancy outcome. JAMA 1995; 274:463-8.
20. Salimi S, Namai M. Assessment of prevalence of zinc deficiency in pregnant women in Zahedan. Zahedan University of medical science, Zahedan, Iran. 1380.
21. Shashahan Z, Habib zadeh A. Evaluation of plasma Zinc concentration in pregnant in Isfahan women. Esfahan University of medical science, Esfahan, Iran. 1380.
22. Cunningham G, Gant NF, Leveno KJ. Gilstrap LC, Hauth JC, Wenstrom KD. Williams Obstetrics. 21st ed. New York: Mc Graw- Hill companies, 2010.
23. Caulfield LE, Zavalenta N, Shankar AH, Merialdi M. Potential contribution of maternal zinc supplementation during pregnancy to maternal and child survival. Am J Clin Nutr 1998; 68 :4995- 5085.
24. Caulfield LE, Zavaleta N, Figueroa A, Leon Z. Maternal zinc supplementation does not affect size at birth or pregnancy. J Nutr 1999;129:1563-8.
25. Hafeez A, Mehmood G, Mazhar F. Oral zinc supplementation in pregnant women and its effect on birth weight: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2005;90:F170-1.
26. Osendarp SJM, Raaij JMA, Arifeen SE, Wahed MA, Baqui AH, Fuchs GJ. Arandomized, placebo-controlled trial of the effect of zinc supplementation during pregnancy on pregnancy outcome in Bangladeshi urban poor. Am J Clin Nutr 2000;71:114-9.
27. Saaka M, Oosthuizen J, Beatty S. Effect of prenatal zinc supplementation on birthweight. J Health Popul Nutr 2009;27:619-31.
28. Garg HK, Singhal KC, Arshad Z. A study of the effect of oral zinc supplementation during pregnancy on pregnancy outcome. Indian J Physiol pharmacol 1993; 37: 276- 84.
29. Alexander GR, Kogan M, Bader D, Carlo W, Allen M, Mor J.US birth weight/gestational age-specific neonatal mortality: 1995-1997 rates for whites, hispanics, and blacks. Pediatrics 2003;111:e61-6.