IJPT
1735-2657/09/82-67-71
IRANIAN JOURNAL OF PHARMACOLOGY & THERAPEUTICS

IJPT 8: 67-71, 2009

RIDR

RESEARCH ARTICLE

Zinc Supplementation during Pregnancy: A Randomized Controlled Trial

N. AMINISANI, F. EHDAIVAND, S. M. SHAMSHIRGARAN, M. MOHAJERY, F. POURFARZI and M.D. SADEGHIYEH AHARI

For author affiliations, see end of text.

Received August 23, 2008; Revised January 21, 2009; Accepted February 26, 2009

This paper is available online at *http://ijpt.iums.ac.ir*

ABSTRACT

Zinc deficiency during pregnancy has been related to adverse pregnancy outcomes. However, the results of zinc-supplementation trials have not been consistent in improvement of pregnancies outcomes. This study was undertaken to investigate whether zinc supplementation was associated with pregnancy complications in Iranian women during the last 2 trimesters. It also assessed the anthropometric measurements of infants at birth. A double-blind placebo-controlled trial was conducted in Ardabil Province located in northwest of Iran. One-hundred ninty-six pregnant women between 16-20 weeks of gestation were recruited from urban healthcare centres. These women had no evidence of hypertension, diabetes, renal disease, history of prematurity, premature rupture of membranes (PROM) or low birth weight (LBW) infants. They were randomly assigned to receive zinc (50 mg daily) or placebo until delivery. Basic information was collected on socioeconomic status, reproductive and disease histories before randomization. The subjects were monthly followed during pregnancy and maternal complications were carefully recorded. The weight, length and head circumference of each infant was measured within 24h of birth. Of the 196 women, 17 were excluded from the study (9 in the zinc group and 8 in the placebo group, NS). The supplementation had no significant effect on prematurity, preeclampcia, PROM and stillbirth as well as gestational age, infant length and head circumference. The incidence of low birth weight was significantly lower in those under Zinc than placebo (p = 0.01). Meanwhile, pregnancy-induced hypertension and intrauterine growth retardation (IUGR) were observed only in the placebo group. The birth weight was also higher in the zinc group than that in the placebo group (p = 0.03). Supplementation with 50mg elemental zinc during pregnancy improved birth weight but did not reduce maternal complications.

Keywords: *Zinc supplementation, Pregnancy outcome, Maternal complications*

Zinc has received increasing attention since its deficiency may have grave consequences in humans [1, 2]. Zinc is an essential component of various enzymes and other proteins including bio-membrane components. It is necessary to maintain the normal structure and/or function of many enzymes, including some involved in gene transcription and translation and cell division [3]. The physiological role of zinc during periods of rapid growth and development emphasizes its importance during periods of gestation and fetal growth [4].

Maternal nutritional status is an important determinant of prenatal and neonatal well-being. Many nutritional programs have been established to prevent iron-deficiency anaemia during pregnancy. However, in the case of zinc, less has been done, although it is very important for maternal and infant survival. It was reported that 82% of pregnant women worldwide have an irregular and inadequate zinc intake. However, reports are inconsistent regarding association of maternal zinc status and birth weight in humans [5].

Recently, maternal zinc supplementation has been suggested as a possible nutritional intervention to improve the outcomes of pregnancies in developing countries [6]. Goldenberg et al. [7] found that 25mg of daily zinc supplementation in early pregnancy was related to greater infant birth weight and head circumference. Women who received 25mg zinc daily from the day of reporting pregnancy showed significant increases in serum zinc until delivery. In addition, their babies had higher birth weights and gestational ages than subjects under placebo [7]. Most of the studies about the effects of zinc supplementation on pregnancy

Table 1. Maternal baseline characteristics

	Zinc supplemented group	Placebo group
Age at enrolment	24.5 ± 4.8	23.9 ± 5.2
Parity	1.5 ± 0.8	1.6 ± 0.9
Education (yr)	7.7	8.2
Job housewife (%)	85 (95.6%)	84 (93.3%)
Weight (kg)	61.9 ± 8.9	63.5 ± 10.4
Height (cm)	160.2 ± 8.1	158.8 ± 6.1
BMI (kg/m^2)	24.1 ± 3.9	25.3 ± 4.0

outcome have been carried in industrialized countries and results have been inconclusive [8]. However, women from developing countries are more likely to be zinc deficient; therefore, they may be at higher risk of producing low birth weight infants. Despite these risks, few data are available from developing countries in this regard. In a review published in 2003, Osendarp et al. [6] discussed preliminary findings from eight recent randomized controlled intervention trials in less-developed countries. These findings indicated that maternal zinc supplementation has a beneficial effect on neonatal immune status, early neonatal morbidity and infant infections; with respect to labour and delivery complications, gestational age at birth, maternal zinc status and health, and neurobehavioral development of the foetus. However, these findings are conflicting and more researches are required [6]. The results of a national survey in Iran showed low plasma zinc is prevalent among pregnant women [9]. Zinc intake was shown to be low among women in both urban and rural areas [10]. We performed a double-blind, placebo-controlled zinc-intervention trial among pregnant women to find whether zinc supplementation can reduce risk of delivering low birth weight infants or not.

PATIENTS AND METHODS

A total of 196 pregnant women living in urban areas of Ardabil district located in North-west of Iran were recruited between April 2004 and March 2005. The final sample size required to enable detection of difference of 310 gram in birth weight, with 80% power and a type 1 error of 5%, assuming a S1=700 and S2=600 was calculated 92 in each group. They were identified while they were between 16 and 20 wk of gestation. Gestational age on enrolment was determined by the date of last menstrual period (LMP) as recalled by the women. The subjects were randomly selected from their health records kept in Ardabil's health care centers. (There are 14 urban health care centres in Ardabil city; we selected women from each centre). They were all resident in Ardabil, had no histories of diabetes, hypertension or renal disease, and provided informed consent. The study was approved by the Ethics Committee and Research Council of Ardabil University of Medical Sciences.

The study was double-blind and the women were randomly assigned to receive either 50 mg daily elemental zinc as zinc sulphate (n=98), or placebo (n=98). Basic information was collected on socioeconomic status, reproductive and disease history of each participant before beginning supplementation.

The zinc sulphate and placebo capsules were made by the Alhavi Company. The placebo capsules were similar to the zinc sulphate capsules in both shape and blister packing. The zinc sulphate was coded as "A" and the placebo as "B", however, both interviewers and participants remained blind of these codes until the study was completed. The women were followed during study until delivery. In addition to the zinc, all subjects received 1mg folic acid and 30mg ferrous sulphate tablets (Iron and folic acid at night, zinc sulphate or placebo at midmorning). Anthropometric measurements, blood pressure and information on compliance were assessed and recorded monthly by trained midwives working in each centre. Those with complications or other problems were referred to a gynaecologist who was co-investigator in the project. She was also blind to the subject allocation. Gestational age assessment, birth-weight and infant anthropometric measurements were performed by trained midwives within 24h of birth. In this study, low birth weight (LBW) was defined as body weight at birth of less than 2500g, preterm birth was defined those infants delivered prior to the completion of 37 weeks, intrauterine growth retardation (IUGR) defined as an infant whose birth weight is usually below 10th percentile for its gestational age [11].

Main delivery outcome variables were compared between trial and placebo group using chi-square, Fishers' exact test or ANOVA using SPSS 14 for Windows. The RR was calculated using EPI Info 2002.

RESULTS

A total of 196 subjects were recruited and randomly assigned in two groups. Six refused to participate (3 in zinc and 3 in placebo group), remaining (190) were included in the study. Subjects who consumed placebo or supplement irregularly (on fewer than 21 days per month or 70% compliance) were excluded; 11 (5.8%) were excluded (6.3% in the zinc group and 5.3% in placebo group NS), they withdrew prior to the outcome being measured, but 93.2% of the participants consumed Zinc supplement or placebo regularly (Fig. 1). Duration of supplementation was 20.2 ± 2.6 weeks in zinc group and 20.5 ± 2 weeks in placebo group. Both groups had similar maternal baseline characteristics (Table 1) and they were not different in socioeconomic status. Anthropometric measurements

Table 2. Infant characteristics by type of prenatal supplement consumed during pregnancy

	Mean ± SD	95% CI
Gestational age (week)		
Supplemented(n=87)	38.3 ± 1.8	37.9 - 38.7
Placebo(n=88)	38.2 ± 2.9	37.8 - 38.6
Birth weight (kg)		
Supplemented(n=87)	3513 ± 400	3427 - 3599
Placebo(n=88)	3352 ± 544	3238 - 3467
Height (cm)		
Supplemented(n=87)	49.7 ± 1.5	49.4 - 50
Placebo(n=88)	50.2 ± 3.2	49.5 -50.9
Head circumference (cm)		
Supplemented(n=87)	35.7 ± 2.7	35.2 - 35.8
Placebo(n=88)	35.5 ± 1.5	35.1 - 36.4
Low birth weight (<2500 g)		
Supplemented(n=87)	0	
Placebo(n=88)	6	

Table 3. Maternal complications

	Zinc group (n=89)	Placebo group (n=90)	RR (95% CI)
PROM	6 (6.7%)	6 (6.6%)	1.12 (0.38 - 3.36)
Preeclampcia & Eclampcia	3 (3.4%)	5 (5.6%)	0.61 (0.15 - 2.46)
Hypertension	0 (0.0%)	2 (2.2%)	-
Preterm delivery	9 (9.3%)	7 (7.8%)	1.30 (0.51 - 3.34)
Still birth	2 (2.3%)	2 (2.2%)	1.01 (0.15 - 7.20)

were compared within two groups of supplemented and placebo (Table 2). There was a significant difference in average birth weight between the zinc and the placebo groups (p=0.03). LBW infants were seen in women taking Zinc supplement, while six women in placebo group had LBW infants (p = 0.01). Two of six LBW infants were IUGR. All infants delivered prematurely were of >2500 g in the zinc group by exception of one infant who had died in the 28 wk of gestational age. However, the treatment did not significantly affect infant length, head circumference or gestational age at birth.

The average weight gain between the time of enrolment (usually 4-8 wk of pregnancy) and end of pregnancy was not significantly different between two groups (10.1 ± 4.03 in the zinc group and 10.3 ± 3.9 in the placebo group). Of the 179 women who completed the follow-up until delivery, 4 (2 in the zinc-supplemented and 2 in the placebo group, NS) delivered a stillborn fetus or an infant that died shortly after birth. Maternal complications were not different between the two groups (Table 3).

None of women taking zinc delivered infants with IUGR, whereas 2 subjects (2.2%) in the placebo group delivered infants with IUGR. Pregnancy-induced hypertension was also observed only in the placebo group (2.2%).

DISCUSSION

In this study, Infants born from mother under zinc supplementation had birth weights of 3513 ± 400 gram compared to 3352 ± 544 gram in the placebo group (p=0.03). None of women taking zinc delivered low birth weight infants. Zinc supplementation had no significant effect on neonatal head circumference and length. Zinc treatment also had no significant effect on gestational age or maternal complications. However, some complications (pregnancy-induced hypertension and IUGR) were observed only in those under placebo.

Castillo-Duran et al. [12] analyzed the effect of zinc supplementation on pregnancy outcomes among Chilean adolescents of low socioeconomic status. They found significantly higher birth weights, fewer infants with low birth weight and a lower rate of prematurity in the Zinc group compared to the placebo group, although they did not report any effects on pregnancy complications. In a study conducted in India by Garg et al. [13], Zinc supplements significantly improved foetal growth. The effect on birth weight was greater whenever the supplement initiated in the first trimester, than in the third trimester [13]. Goldenberg et al. [5] studied the effect of Zinc supplements on birth weight in a group of medically indigent African-American women. Women at risk of poor zinc nutrition were targeted for this intervention study. The supplement had a significant effect on increasing birth weight and head circumference only in non-obese women (BMI<26).

Some investigators have observed a significant reduction in preterm deliveries in Zinc-supplemented pregnant women [5,13,14]. This effect was only observed among normal-weight women in the group studied by Cherry et al. [14]. Among Indian women, the gestational age of the infant increased more with longer periods of Zinc supplementation; those who received the supplement from the first trimester had an average gestational age of 39.4 wk, while those supplemented only from the third trimester had a gestational age of 38.8 wk. The average gestational age among the placebo group was 38.3 weeks [13]. Goldenberg et al. [5]

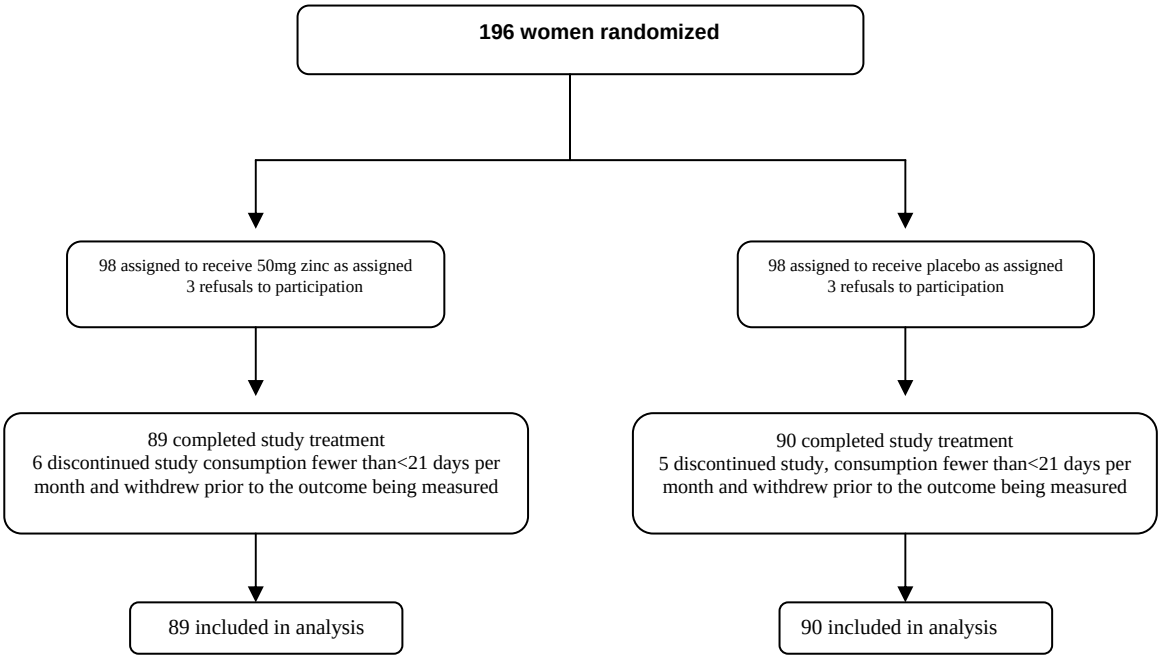

Fig 1. Flowchart of study

reported a tendency toward increased gestational age (p<0.08) among women with BMI <26.

Simmer et al. [15] studied mothers at risk of delivering infants with intrauterine growth retardation and reported reduced IUGR in 29 compliers. Hunt et al. [16] found that 20 mg daily Zinc supplements reduced the incidence of pregnancy-induced hypertension among adult Hispanic women but not among adolescent Hispanic women. These findings are in contrast with some studies in which no effect of zinc interventions on pregnancy outcomes was found [17-23].

Supplementation with 50 mg elemental zinc during pregnancy improved birth weight but did not affect maternal complications. The results of the study are consistent with those obtained from zinc supplementation trials conducted on pregnant women in other parts of the world. This may suggest beneficial effect of maternal zinc supplementation on size at birth. This controversy could be explained by three possible reasons. Firstly, a higher dose of zinc was given in this study (50 mg) which may affect fetal growth. Caulfeild et al. [18] used 15 mg supplementation. In the other study in which no difference was found, 30 mg of zinc was given [17]. Secondly, our subjects had higher BMI (24.7) compared to other in which no difference was seen [17]. The higher BMI would likely favour higher average birth weight. Thirdly, it may be true that in some populations, improvements in maternal zinc nutriture mostly occur before pregnancy or early in pregnancy to affect pregnancy. More evidence on this is required in other developing countries.

This study has several strengths that lend credence to the findings. First, compliance with supplementation was high. Second, the randomization of the women to prenatal supplement type formed comparable treatment groups at enrolment. Third, the outcomes were measured reliably, and all maternal complications were confirmed by a gynaecologist. Fourth, the loss to follow-up was minimal. Fifth, zinc supplementation was initiated between 16 and 20 weeks of pregnancy in all cases. The most important limitation of this study was the exclusion of women who took less than 70% compliance because they withdrew prior to the outcome.

CONCLUSION

This randomized double-blind study suggests that zinc supplements may improve infants' birth weight. Although, this finding needs to be confirmed in further studies with larger sample size, optimal micronutrient could be encouraged.

ACKNOWLEDGEMENT

This study was supported by the Research Fund of Ardabil University of Medical Sciences. We thank the women who participated in this study and fieldworkers, including midwives and other support staff who assisted in the study. We also thank Al-Havi Company for preparing the supplement and placebo.

REFERENCES

1. Hambidge M. Human zinc deficiency. *J Nutr* 2000; 130:1344S-9S.
2. Berg JM, Shi Y. The galvanization of biology: a growing appreciation for the roles of zinc. *Science* 1996; 271:1081-5.
3. McCall KA, Huang C, Fierke CA. Function and mechanism of zinc metalloenzymes. *J Nutr* 2000; 130:1437S-46S.
4. Bhatnagar S, Natchu UC. Zinc in child health and disease. *Indian J Pediatr* 2004; 71:991-5.
5. Caulfield LE, Zavaleta N, Shankar AH, Merialdi M. Potential contribution of maternal zinc supplementation during pregnancy to maternal and child survival. *Am J Clin Nutr* 1998; 68:499S-508S.
6. Osendarp SJ, West CE, Black RE. Maternal Zinc Supplementation Study Group. The need for maternal zinc

supplementation in developing countries: an unresolved issue. *J Nutr* 2003; 133:817S-27S.

7. Goldenberg RL, Tamura T, Neggers Y, Copper RL, Johnston KE, DuBard MB, Hauth JC. The effect of zinc supplementation on pregnancy outcome. *JAMA* 1995; 274:463-8.
8. King JC. Determinants of maternal zinc status during pregnancy. *Am J Clin Nutr* 2000; 71:1334S-43S.
9. Majidpour A, Adalatkhah H, Sezavar SH, Aminisani N, Shabani M, Nemati A, et al. Research Priorities in Health Field in Ardabil Province: An Experience. *JAUMS* 2004; 3:7-22.
10. Mohammadian S, Safavi SM, Sheikholeslam R, Naghavi M, Abdollahi Z. Assessment of zinc status among Iranian pregnant women. *JKMU* 2006; 13:196.
11. Fabre E, Gonzalez de Aguero R, de Augustin JL, Ezquerra A. Intrauterin growth restriction: concept and epidemiology. In: Kurjak K, Kurjak A, Chervenak FA, Editors. Textbook of Prenatal Medicine. CRC Press. 2006.
12. Castillo-Duran C, Marin VB, Alcazar LS, Iturralde H, Ruz MO. Controlled trial of zinc supplementation in Chilean pregnant adolescents. *Nutrition Research* 2001; 21:715-24.
13. 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.
14. Cherry FF, Sandstead HH, Rojas P, Johnson LK, Batson HK, Wang XB. Adolescent pregnancy: associations among body weight, zinc nutriture, and pregnancy outcome. *Am J Clin Nutr* 1989; 50:945-54.
15. Simmer K, Lort-Phillips L, James C, Thompson RP. A double-blind trial of zinc supplementation in pregnancy. *Eur J Clin Nutr* 1991; 45:139-44.
16. Hunt IF, Murphy NJ, Cleaver AE, Faraji B, Swendseid ME, Browdy BL, et al. Zinc supplementation during pregnancy in low-income teenagers of Mexican descent: effects on selected blood constituents and on progress and outcome of pregnancy. *Am J Clin Nutr* 1985; 42:815-28.
17. Osendarp SJ, van Raaij JM, Arifeen SE, Wahed M, Baqui AH, Fuchs GJ. A randomized, 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.
18. Caulfield LE, Zavaleta N, Figueroa A, Leon Z. Maternal zinc supplementation does not affect size at birth or pregnancy duration in Peru. *J Nutr* 1999; 129:1563-8.
19. Jonsson B, Hauge B, Larsen MF, Hald F. Zinc supplementation during pregnancy: a double blind randomized controlled trial. *Acta Obstet Gynecol Scand* 1996; 75:725-9.
20. Ross SM, Nel E, Naeye RL. Differing effects of low and high bulk maternal dietary supplements during pregnancy. *Early Hum Dev* 1985; 10:295-302.
21. Merialdi M, Caulfield LE, Zavaleta N, Figueroa A, DiPietro JA. Adding zinc to prenatal iron and folate tablets improves fetal neurobehavioral development. *Am J Obstet Gynecol* 1999; 180:483-90.
22. Mahomed K, James DK, Golding J, McCabe R. Zinc supplementation during pregnancy: a double blind randomized controlled trial. *BMJ* 1989; 299:826-30.
23. 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.

CURRENT AUTHOR ADDRESSES

N. Aminisani, Department of Epidemiology, Faculty of Health and Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran. E-mail: nami9910@usyd.edu.au (Corresponding author)

F. Ehdaivand, Department of Gynaecology, Faculty of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran.

S. M. Shamshirgaran, Department of Epidemiology, Faculty of Health and Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran.

M. Mohajery, Department of Gynecology, Faculty of Medicine, Azad University of Mashhad, Mashhad, Iran.

F. Pourfarzi, Deaprtment of Community Medicine, Faculty of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran.

M. D. Sadeghiyeh Ahari, Deaprtment of Community Medicine, Faculty of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran.