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The effect of zinc supplementation on pregnancy outcome: a randomized controlled trial

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Abstract
Objectives: This study aimed to evaluate the impact of prenatal zinc supplementation on pregnancy outcomes.
Methods: A randomized controlled trial with equal randomization (1:1) was conducted on 540 pregnant women in Rasht, Iran from January 2010 to January 2012. Participants were randomly assigned to receive a daily supplement including 400 µg folic acid and 30 mg ferrous sulfate, with or without 15 mg zinc sulfate from the 16th week of gestation until delivery.
Results: Mean difference of birth weight between the two groups was not significantly different (3262 ± 390 g in the zinc, 3272 ± 403 g in the no-zinc groups) (p = 0.780). There were no significant differences between the two groups in terms of means of head circumference (p = 0.999), length (p = 0.848), and gestational age at birth (p = 0.057) incidences of low birth weight (p = 0.863), macrosomia (p = 0.642), and the Apgar score > 7 at 5 min (p = 0.999), incidences of preterm delivery (p = 0.999), pre-eclampsia (p = 0.835), premature rupture of membranes (p = 0.630), and spontaneous abortion (p = 0.772). Abruption of placenta, amnionitis, stillbirth, and intrauterine death were not observed.
Conclusion: Based on our findings, 15 mg zinc supplementation daily from 16 weeks of pregnancy until delivery cannot improve pregnancy outcomes.

Introduction
In pregnant women, poor zinc status can have adverse effects on maternal and neonatal outcomes [1], because zinc plays a key role in many biological functions including protein synthesis, cellular division, and nucleic acid metabolism [2]. It is also involved in neurological and proper immune function [3–5] and additional dietary zinc during pregnancy aids in reducing plasma and serum concentrations [6]. Zinc deficiency places women at risk for spontaneous abortion, congenital malformations, low birth weight (LBW), intrauterine growth retardation (IUGR), preterm delivery, and labor abnormalities [7,8] and is responsible for about 20% of prenatal mortalities worldwide [7]. In women with acrodermatitis enteropathica (an inherited defect in zinc absorption), poor pregnancy outcomes, fetal losses, and congenital malformations are common [1,9–11].

Although severe zinc deficiency is rare in humans, mild- to moderate- zinc deficiency is prevalent worldwide, especially in developing countries where consumption of zinc-rich animal-source foods are limited and cereals are high in phytate, which limits zinc absorption [12–14]. Based on World health organization’s (WHO) estimation, the global prevalence of zinc deficiency is 31% (range: 4–73%) and in the Eastern Mediterranean Region (EMR), which Iran is a part of, this prevalence is 25–52% [12]. Moreover, pregnant women are at highest risk of zinc deficiency. Worldwide, about 80% of pregnant women have insufficient zinc intake and consume less than the minimum recommended daily intake during the last two trimesters of pregnancy [7,12,15]. In a recent study done in Iran, the prevalence of zinc deficiency was reported at about 19% [16].

Studies conducted on healthy pregnant women to evaluate the effect of zinc supplementation during pregnancy have reported conflicting results [10]. This is reasonable because the effect of zinc supplementation varies among different populations based on their zinc status [17,18]. Although current available data have not provided enough evidence for routine zinc supplementation during pregnancy, supplementation intake may be beneficial in zinc-deficient populations [15,19,20]. Based on these facts, there is increased concern about the adequacy of zinc intake among pregnant women in developing countries [19]. WHO recommends the use of multiple micronutrient supplements including zinc for all pregnant women in developing countries [15]. Hence, in Iran all
pregnant women should be supplemented with folic acid (400-μg per day) from the beginning of their pregnancy, and iron (ferrous sulfate 30-mg per day) from the 16th week of pregnancy until delivery, but currently intake recommendations for zinc do not exist [21]. This study aimed to assess pregnancy outcomes on women who were administered zinc supplements from the 16th week of pregnancy until delivery.

Materials and methods

Trial design

A two-arm parallel randomized controlled trial with equal randomization (1:1) was conducted on pregnant women who presented at a private gynecologic clinic in Rasht, the capital of Guilan province, north of Iran from January 2010 to January 2012.

Participants

Inclusion criteria included all healthy women at 16 weeks of gestation who presented for antenatal care in the clinic, regardless of previously presenting at the clinic and did not have high-risk pregnancies [i.e. age under 18 and over 40 years, height under 145 cm, body mass index, BMI) under 15 kg/m² or over 30 kg/m² before pregnancy, smoking, multi-fetal pregnancy, pregnancies through assisted reproductive technology, uterine anomalies, leiomyoma, and any established medical risk for reduced or excessive birth weight (e.g. hypertension, renal disease, diabetes, and other underlying disease)], no history of miscarriage, intrauterine death, stillbirth, LBW, premature birth, pre-eclampsia, and/or macrosomia. Exclusion criteria included using any form of zinc supplements at any dosage, cervical shortening <30 mm, any surgical procedure within the abdominal cavity during pregnancy, and/or undergoing amniocentesis. Gestational age was determined by the date of the women’s last menstruation and confirmed by ultrasonography.

The protocol of this study was approved by the Ethical Committee of the Guilan University of Medical Sciences. All participants provided written informed consent before entry into the study.

Interventions

Participants were randomly assigned to receive a daily supplement including 400-μg folic acid and 30-mg iron (ferrous sulfate), with or without 15-mg zinc (zinc sulfate) from the 16th week of gestation until delivery. Because available pills containing 30 mg of zinc could not be cut in half, they were prescribed every other day. Zinc was administered according to its proper consumption, a daily dose between meals singly or with fruit juice and suitable time allotted between zinc intake and the other supplements, particularly iron, was observed. Zinc supplementation was manufactured by Nature Made (Mission Hills, CA). Supplements were packed and given to participants during each visit for the number of days until the next visit, plus 5 additional days. All participants visited the clinic every 4 weeks from enrollment to delivery. In each visit, adherence to supplementation intake was assessed by observing the number of tablets.

Outcomes

Birth weight was the primary outcome of this trial. Other neonatal outcomes including head circumference, length, gestational age at birth, incidence of LBW (<2500 g), macrosomia (≥4000), and Apgar scores at 5 min, and other maternal outcomes including weight gain during pregnancy, incidence of pre-eclampsia, premature rupture of membranes, and spontaneous abortion were secondary outcomes.

Data collection

At enrollment demographic data including age, educational level, residency, job, reproductive history, height, and weight, and blood pressure of the women were collected. At 20, 24, 28, 32, 36, and 38 weeks gestation, weight and blood pressure of the mother, fetal monitoring, and pregnancy complications were assessed. Maternal blood pressure and anthropometric measures during the study period were done by a trained midwife.

Baseline data of all participants were available. Maternal and neonatal outcomes of all participants were collected using data recorded in the participants’ medical records taken from clinic and maternity hospitals. Neonatal anthropometric measurements were conducted within 24 h of birth by maternity hospital nurses.

Sample size

To detect a difference in 100 g in birth weight between the two groups with an error probability of 5% and a power of 80%, assuming an SD of 390 g, at least 239 per group was necessary. To account for the possibility of 13% drop-out rate, we recruited 540 pregnant women.

Randomization

A computer-generated randomized list using a size four permuted block was used. Random sequences were prepared by a researcher with no clinical involvement in the trial. A gynecologist from the clinic allocated participants to each group by using random sequences.

Blinding

Outcome assessors and data analysts were kept blinded to the allocation.

Statistical methods

Data were analyzed using IBM SPSS software (Version 21, Armonk, NY). Intention-to-treat analysis was used and involved all women who were randomly assigned. We used descriptive and analytic statistics. For continuous variables, data were described as mean and standard deviation (SD) and for categorical variables data were shown as number and percentage. For statistical analysis, the two-tailed independent t-test was used to compare means between the two groups. The chi-square or Fisher’s exact tests were used to compare proportions between the two groups. A p-value less than 0.05 was considered as a significant difference.
Results

In each of the two groups, 270 pregnant women were randomly assigned and in the intervention group all women received at least one dose of zinc supplementation (Figure 1). Sixty-one women were lost to follow-up because they declined to continue participating, were traveling, or had a significant complication.

Baseline characteristics of the women in the two groups are shown in Table 1. Spontaneous abortion incidences were 2.6% (n = 7) in the zinc group and 1.9% (n = 5) in the no-zinc group and this difference was not significant (p = 0.772). Gender of the majority of neonates in the zinc (53%) and no-zinc (50.4%) groups were girls. The mean birth weights were 3262 ± 390 g in the zinc and 3272 ± 403 g in the no-zinc groups and this difference was not significant (p = 0.780). Also, there were no significant differences in mean of head circumference (p = 0.999), length (p = 0.848), and gestational age at birth (p = 0.057). The incidences of LBW (p = 0.863), macrosomia (p = 0.642), and the Apgar score >7 at 5 min (p = 0.999) did not differ significantly between the two groups (Table 2).

Mean weight gain during pregnancy was 14.15 ± 7.5 kg in the zinc group and 13.39 ± 4.8 kg in the no-zinc group and this difference between the two groups was not significant (p = 0.160). There were no significant differences between the two groups in terms of incidences of preterm delivery (p = 0.999), pre-eclampsia (p = 0.835), premature rupture of membranes (p = 0.630), and spontaneous abortion (p = 0.772) (Table 3). During the study period, there were no reports of abruption of placenta, amnionitis, stillbirth, and intrauterine death.

Discussion

This study showed that there were no significant difference in neonatal outcomes, including birth weight, gestational age, head circumference, length, gender, macrosomia, Apgar score, and incidence of LBW between the two groups. Also, maternal outcomes including weight gain during pregnancy, incidence of pre-eclampsia, premature rupture of membranes, preterm delivery, and spontaneous abortion between the two groups were not significantly different.

A previous randomized clinical trial conducted on 196 Iranian pregnant women showed 50-mg daily zinc sulfate from 16 to 20 weeks of pregnancy until delivery did not significantly affect infant length, head circumference, gestational age at birth, incidence of prematurity, pre-eclampsia, premature rupture of membranes, and abortion, but incidence of LBW and mean birth weight were significantly higher in the zinc group [22]. Another randomized clinical trial conducted on 84 Iranian pregnant women with a previous preterm delivery showed that in women who received 50-mg daily zinc sulfate from 12 to 16 weeks of gestation till delivery, infant mean birth head circumference was higher than in the placebo group. But there were no significant differences in terms of birth weight, length, Apgar score, intrauterine growth restriction, and gestational age at delivery [23]. Positive effects of zinc supplements on birth weight and head circumference that was reported from the two previous trials can be related to the use of higher doses of zinc than in our study. But in randomized trials in other developing countries, similar to our findings, zinc supplementation did not have any effects on maternal or neonatal outcomes. In a review study, it was shown that zinc supplementation trials have failed to find a benefit of zinc supplementation on pregnancy-induced hypertension, pre-term or post-term delivery, premature rupture of membranes, prenatal mortality, congenital malformations, and fetal growth [8].

Osendarp et al. carried out a double-blind, placebo-controlled trial on 559 women between 12 and 16 weeks of gestation and women in the intervention group received 30-mg elemental zinc daily until delivery. That trial showed no significant effect of zinc supplement on birth weight, gestational age, length, head circumference, incidence of LBW, prematurity, and smallness for gestational age, also gained weight during pregnancy between two groups was not significantly different [14]. In a randomized controlled trial that was conducted on 600 pregnant women in Ghana, Saaka et al. showed that receiving 40 mg of zinc gluconate and 40 mg of iron as ferrous sulfate versus 40 mg of elemental iron as ferrous sulfate had no significant effects on birth weight, length of gestation, incidence of LBW, preterm delivery, and intrauterine growth restriction [24]. A meta-analysis that included 17 randomized controlled trials showed significant effects of zinc supplementation on birth weight. Among the 17 included randomized controlled trials, 13 did not find an association between zinc supplementation and birth weight, three reported a positive association and one reported a negative association [10]. In a randomized double-blind
Absence of any positive effect of zinc supplementation in our study might be associated to dietary habits and multiple micronutrient deficiencies that can reduce absorption of zinc [5,6]. Also, homeostatic adjustment to meet the need for zinc during pregnancy can be another factor that masks the effect of zinc supplements [6].

Limitations

Compliance with intervention was assessed at the standard patterns of prenatal care and we did not monitor zinc usage at home based on the orders of the researcher. Also, our control group did not use a placebo.

Conclusion

In conclusion, based on our findings, 15-mg zinc supplementation daily from 16 weeks of pregnancy until delivery cannot improve neonatal and maternal outcome. Conducting further controlled trial conducted on 242 low-income Peruvian women, participants received supplements containing 60-mg iron, 250-mg folic acid with or without 25-mg zinc from 10 to 16 weeks gestation and there were no significant differences between the two groups in terms of duration of pregnancy, fetal sex, or birth weight [25]. In a systematic review of 8000 births, it was shown that zinc supplementation did not have a significant effect on means of birth weight, length at birth, gestational age at birth, or head circumference at birth [19]. A trial conducted on 2173 pregnant women in Indonesia showed zinc supplements can improve birth length, but did not have a significant effect on birth weight, the proportion of LBW, neonatal morbidity, or mortality [26]. In a systematic review including 20 randomized controlled trials, it was shown that zinc supplementation had a small, but significant effect on reduction of preterm birth. However, its effect on incidence of LBW and other primary maternal or neonatal outcomes were not significant [27].

Absence of any positive effect of zinc supplementation in our study might be associated to dietary habits and multiple micronutrient deficiencies that can reduce absorption of zinc [5,6]. Also, homeostatic adjustment to meet the need for zinc during pregnancy can be another factor that masks the effect of zinc supplements [6].

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Conclusion

In conclusion, based on our findings, 15-mg zinc supplementation daily from 16 weeks of pregnancy until delivery cannot improve neonatal and maternal outcome. Conducting further
studies in this area by using a higher dose of zinc or on zinc-deficient pregnant women can be useful to discover any positive effects of zinc supplementation.

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Declaration of interest
This study was based on a thesis submitted by the Sadeghi H., medical student at the Guilan University of Medical Sciences. The authors declare that they have no conflicts of interest.

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