

## Original Article



# The effect of zinc supplementation in delayed preterm delivery and biometric of neonates suspected with preterm delivery in mothers suspected of having a preterm delivery

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## Abstract

**Background and aims:** Micronutrient deficiency in women of reproductive age is considered as a major health problem in many developing countries. Therefore, it is important to prevent micronutrient shortage before pregnancy. This study aimed to evaluate the effect of zinc (Zn) supplementation on delaying preterm delivery and biometric neonates with suspected preterm birth.

**Methods:** In this semi-experimental study, 140 women with preterm delivery were selected by a gynecologist in the Hajar hospital of Shahrekord University of Medical Sciences in 2016. The women were divided into four groups. Then, the serum Zn level of the mother's blood and the umbilical cord was measured. First group had a normal level; Zn level in the second group was between 50-70 mg/dL; in the third group between 20-50 mg/dL; and in the fourth group fewer than 20 mg/dL. Three groups received <20-70 mg/dL oral Zn and the normal group was given a placebo. Next, the serum Zn levels of mothers were measured and recorded at the end of the eighth month and delivery time. Infant anthropometric parameters at birth, 1 month to 3 months were measured as well. Overall, 71 (50%) and 69 (49.3%) infants were males and females, respectively. The data were analyzed using descriptive statistics and analytical statistics tests.

**Results:** The average age of 140 pregnant women was  $30.39 \pm 5.33$  years old and their age range was between 18 and 41 years. In addition, the maternal Zn serum level was  $56.52 \pm 33.38$  mg/dL on admission and the serum level on the cord blood at birth was  $53.22 \pm 66.94$  µg/dL. A significant relationship was reported between the level of serum Zn on cord blood and the maternal serum Zn level on admission with growth in babies at birth and the first, second, and third month ( $P < 0.05$ ).

**Conclusion:** In general, Zn is effective in children's growth and the use of Zn supplementation can be suggested during pregnancy.

**Keywords:** Zinc, Premature birth, Child development

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## Introduction

Preterm delivery, called the termination of pregnancy before 37 weeks of pregnancy, is a dangerous condition with a prevalence of approximately 10%-20% deliveries (1). This kind of delivery is now known as a syndrome that is caused by several mechanisms such as inflammation, infection, placental uterine ischemia, excessive uterine distension, stress, and other immunological processes. It is thought that the exacerbation of any of these risk factors may result in the transfer of the uterus from the onset to preterm delivery or the premature rupture of membranes.

Preterm delivery is responsible for 75% of prenatal mortality and over 50% of long-term infections. Primary prevention is not always possible due to unknown causes and mechanisms of preterm delivery (2). Diet is one of the most important environmental factors affecting maternal, embryonic, and fetal health. The type and amount of food by the mother in the following months have a direct impact on the growth and health of the fetus and the mother (3). Further, pregnancy is associated with an increase in the demand of all micronutrients, including zinc (Zn), and it seems that the deficiency of this element through the

development of changes in maternal embryonic metabolism can affect the outcome of pregnancy, including early delivery. Zn micronutrient also affects the development of the fetus and the baby, as well as the health of the pregnant mother (4). Furthermore, Zn is the second most abundant mineral in the body and plays an important role in the synthesis and metabolism of proteins, nucleic acid metabolism, and cell membrane stabilization. Moreover, this element is essential for many metabolic functions of the cell (5). The Zn level in pregnancy begins to decrease from early pregnancy and this decrease continues until the term so that the level of Zn in pregnant women is lower at least 35% compared to non-pregnant women (6).

Recent data suggest that Zn deficiency and serum Zn levels are less than 70 µg/dL in pregnant and non-pregnant women in urban and rural areas (7). Additionally, preterm infants have low Zn deficiencies due to their low physical reserves because 60% of Zn is injected into the baby during the last trimester of pregnancy (8).

The lack of micronutrients has a negative impact on the health of the mother and the developing fetus. Additionally, the important side effects of pregnant mother's malnutrition include low birth weight, early delivery, the increased prevalence of pregnancy poisoning, the birth of the baby with intrauterine growth retardation, and the mental impairment of the child. According to the listed items, this study aimed to investigate the effect of Zn supplementation in delaying preterm delivery and biometric neonates with suspected preterm birth.

## Methods

In this semi-experimental study, 140 women with preterm delivery were selected by a gynecologist in the Hajar hospital of Shahrekord University of Medical Sciences in 2016. The inclusion criteria included women who were diagnosed with preterm delivery by a gynecologist and those who had not any other disease. On the other hand, the exclusion criteria were patients who presented no written informed consent and those who suffered from other diseases. The sampling was conducted by the convenience sampling method and the statistical population of the current study was 230 preterm women. In addition, the samples were determined as 143 based on the Cochran's calculation formula as follows.

$$N = \frac{nz^2 pq}{nd^2 + z^2 pq} + \frac{nz^2 pq}{z^2 pq} = 143$$

They were divided into four groups each including 35 preterm women (N=230 statistical population, d= 0.05 permissible mistake amount, Z=1.96, and p=q=0. The level of Zn of the first group was normal and that of the second, third, and fourth group was within the range of 50-70 mg/dL, 20-50 mg/dL, and less than 20 mg/dL, respectively. The edible Zn was in the range of <20-70 mg/dL for three groups and the placebo was given to the normal group and

their serum Zn level was measured in hospital laboratories in Shahrekord University of Medical Sciences and recorded at the end of the eighth month and at the time of delivery. The administrator of Zn supplementation was unaware of the demographic characteristics of mothers and parameters to be measured in mothers and infants. At the time of delivery, the serum Zn level was measured from the embryonic cord and the infants with serum Zn levels below 70 were given 5 mg of Zn daily. Finally, the biometrics of these infants and the time delay of delivery in mothers were measured as well.

The benefits of the study were explained to women and informed consent was obtained before their selection. When registering a pre-natal clinical examination, women's personal, medical, familial, social-economic, and occupational records were entered on the checklist and the maternal blood from the cubital artery (5 mL) and the umbilical vein (1 mL) were taken immediately after delivery considering all health and aseptic measures. All tubes were ionized with the acid to remove any inappropriate elements and to test the conditions appropriately. The whole obtained blood was centrifuged and the serum was carefully collected in polyethylene containers that were well washed with the acid. In addition, anthropometric measurements were performed by the researcher using an electronic scale and height gauge for babies and the strip meter. These measurements at birth and 1 month to 3 months later were measured by the researcher. Eventually, the data were analyzed using descriptive statistics (i.e., frequency, percent, mean, and standard deviation) and the analytical statistics (i.e., Pearson's correlation coefficient, Kruskal-Wallis, and Mann-Whitney) tests.

## Results

The age of the pregnant women was  $30.39 \pm 5.33$  years in the range of 18 to 41 years old. Further, the mean age of gestational age was  $31.57 \pm 2.60$  weeks and at the time of delivery, it was  $37.99 \pm 1.43$  years based on early pregnancy ultrasound. Furthermore, the mean number of pregnancies was  $2.48 \pm 1.16$  and the rate of preterm delivery in the population was 19.3% (27 cases). In this study, maternal attending was reported as 12.9% due to the premature rupture of the amniotic membrane. As regards the baby's gender, 71 cases (50.7%) were males and 69 (49.3%) of them were females (Table 1).

**Table 1.** Frequency distribution of a baby's gender, preterm delivery history, and premature rupture of amniotic membrane in subjects under study

Variable	Group	No.	%
Baby's gender	Male	71	50.7
	Female	69	49.3
Preterm delivery history	No	113	80.7
	Yes	27	19.3
Premature rupture of amniotic membrane	No	122	87.1
	Yes	18	12.9

**Table 2.** Comparison of mean zinc concentrations of newborn umbilical cord serum in four groups

Group	Concentration of mother's serum zinc level at the time of admission n = 35	The Level of serum zinc concentration in the umbilical cord of the baby	P value
		Mean $\pm$ SD	
First	Above 70 mg/dL (normal)	91.94 $\pm$ 19.11	0.117
Second	Between 50 and 70 mg/dL (deficiency)	104.05 $\pm$ 27.76	
Third	Between 20 and 50 mg/dL (deficiency)	92.35 $\pm$ 19.56	
Fourth	Less than 20 mg/dL (deficiency)	90.25 $\pm$ 20.72	

Note. SD: Standard deviation.

Moreover, the concentration of Zn in the serum of the mother was  $56.22 \pm 33.38$  mg/dL (in the range of 9-138),  $88.36 \pm 22.20$  mg/dL (44-150), and  $94.66 \pm 22.53$  mg/dL (40-149) at the time of admission, the end of the eighth month, and at delivery, respectively. Additionally, the serum concentration of Zn in the umbilical cord of the baby during delivery was  $94.66 \pm 22.53$   $\mu$ g/dL (in the range of 40-149). In addition, the duration of receiving Zn supplementation by the mother was  $6.55 \pm 2.76$  weeks. According to the findings of Table 2, the mean serum Zn level of the newborn cord was higher in the second group compared to the third, first, and fourth groups, but this difference was not statistically significant ( $P=0.117$ ).

Based on the results of Table 3 and the Kruskal Wallis test, there was a significant difference between the growth indices of newborns in the four groups so that the mean of birth weight, head circumference, and head circumference at one month and two and three months was significantly more in the first group (normal group) compared to the second, third, and fourth group ( $P<0.01$ ). Further, the mean weight and head circumference of one month, and two and three months in the second group were significantly higher compared to the first, third, and fourth groups ( $P<0.01$ ), the details of which are provided in Table 3.

However, the results (Table 4) demonstrated no significant relationship between the premature rupture of the amniotic membrane and the studied groups ( $P<0.05$ ).

On the other hand, there was a significant and direct

relationship between serum Zn concentrations in the newborn's umbilical cord and the concentration of Zn in the mother at admission with the growth indices of the newborns at birth and one month, as well as two and three months old (Table 5).

According to the findings of the Mann-Whitney test, a significant relationship was observed between male gender with high levels of a serum Zn concentration of infant's umbilical cord ( $P=0.032$ ), the Zn level of the mother in the eighth month ( $P=0.001$ ) and the Zn of the mother during labor ( $P=0.016$ ).

Furthermore, there was a significant relationship between the low levels of the mother's Zn on admission and the mother's Zn level at the eighth month and a history of preterm delivery (Mean  $\pm$  SD =  $36.85 \pm 17.71$ , mean  $\pm$  SD =  $78.62 \pm 20.52$ ,  $P=0.001$ ,  $P=0.016$ ), related data are presented in Table 6.

## Discussion

In the present study, there was no considerable relationship between the maternal Zn level and the rupture of the amniotic membrane. Moreover, no significant difference was observed between serum Zn deficiency and preterm delivery ( $P>0.05$ ). However, the analysis of the results showed that the mother's Zn level in the eighth month and at the time of delivery had a direct and significant relationship with the gestational age ( $P<0.05$ ). The findings of this study indicated the effect of Zn on the growth indices of newborns.

**Table 3.** Comparison of mean growth rates of newborns at birth, one, two, and three months in four groups

Variable		First group Mean $\pm$ SD	Second Group Mean $\pm$ SD	Third Group Mean $\pm$ SD	Fourth Group Mean $\pm$ SD	P value
Weight (g)	Birth	378.26 $\pm$ 3298.85	395.78 $\pm$ 3205.42	411.91 $\pm$ 3114.00	259.86 $\pm$ 2942.57	0.002
	1 Month	4070 $\pm$ 500.02	569.67 $\pm$ 4094.28	501.66 $\pm$ 3874.28	380.28 $\pm$ 3674.28	0.003
	2 Month	4825.71 $\pm$ 554.84	548.90 $\pm$ 5170.85	674.07 $\pm$ 4673.14	495.08 $\pm$ 4465.71	0.001
	3 Month	57.92 $\pm$ 513.24	579.19 $\pm$ 6121.14	734.42 $\pm$ 5544.00	568.58 $\pm$ 5375.71	0.001
Height (cm)	Birth	49.71 $\pm$ 1.03	49.51 $\pm$ 1.50	49.45 $\pm$ 1.95	48.95 $\pm$ 1.44	0.161
	1 Month	53.17 $\pm$ 1.21	53.20 $\pm$ 1.60	52.25 $\pm$ 2.03	51.94 $\pm$ 1.63	0.002
	2 Month	56.57 $\pm$ 1.57	56.71 $\pm$ 1.97	55.64 $\pm$ 4	54.91 $\pm$ 1.68	0.010
	3 Month	60.44 $\pm$ 1.83	60.87 $\pm$ 2.21	58.58 $\pm$ 2.73	58.34 $\pm$ 3.57	0.001
Head circumference	Birth	35.38 $\pm$ 0.73	35.01 $\pm$ 0.75	34.85 $\pm$ 0.94	34.47 $\pm$ 0.98	0.001
	1 Month	37.14 $\pm$ 0.67	36.87 $\pm$ 0.89	36.60 $\pm$ 0.92	36.34 $\pm$ 0.82	0.001
	2 Month	38.58 $\pm$ 0.73	38.51 $\pm$ 0.64	38.25 $\pm$ 0.70	37.94 $\pm$ 0.70	0.001
	3 Month	40.30 $\pm$ 0.88	40.12 $\pm$ 0.67	39.94 $\pm$ 0.83	39.71 $\pm$ 0.90	0.035

Note. SD: Standard deviation.

**Table 4.** Frequency distribution of the premature rupture of amniotic membrane in four groups under study

Number		First Group		Second Group		Third Group		Fourth Group		P value
		No.	%	No.	%	No.	%	No.	%	
Premature rupture of amniotic membrane	Yes	6	82.9	3	91.4	6	82.9	3	91.4	0.513
	No	29	23.8	32	26.2	29	23.8	32	26.2	

**Table 5.** Correlation coefficient between the serum zinc concentration of an infant's umbilical cord and the serum zinc concentration of the mother with the infant's growth indices

	Serum Zinc Concentration of infant's Umbilical Cord	Zinc Level of Mother at the Time of Admission
Birth weight	r = 0.367 P=0.001*	r = 0.310 P=0.001*
Birth height	r = 0.460 P=0.001*	r = 0.195 P=0.021*
Head circumference at birth	r = 0.275 P=0.001*	r = 0.348 P=0.001*
One-month neonate's weight	r = 0.382 P=0.001*	r = 0.294 P=0.001*
One-month neonate's height	r = 0.476 P=0.001*	r = 0.308 P=0.001*
One-month neonate's head circumference	r = 0.340 P=0.001*	r = 0.358 P=0.001*
Two-month neonate's weight	r = 0.413 P=0.001*	r = 0.263 P=0.002*
Two-month neonate's height	r = 0.516 P=0.001*	r = 0.354 P=0.001*
Two-month neonate's head circumference	r = 0.384 P=0.001*	r = 0.324 P=0.001*
Three-month neonate's weight	r = 0.429 P=0.001*	r = 0.302 P=0.001*
Three-month neonate's height	r = 0.492 P=0.001*	r = 0.362 P=0.001*
Three-month neonate's head circumference	r = 0.429 P=0.001*	r = 0.233 P=0.001*

Based on the results, the mean serum Zn level was  $49.66 \pm 22.53$  and the mean Zn level of mothers was  $65.25 \pm 33.38$ . In a study on pregnant women in Jordan, Bawadi reported that the received Zn in 78% of pregnant women was less than the recommended rate (9). In countries where more than 20% of the population have Zn deficiency, researchers recommend enriching the food with this vital element (10).

In this study, the rupture of the amniotic membrane was reported 12.9% and there was no statistically significant relationship between the maternal Zn level and the rupture of the amniotic membrane. Similar to our study, the prevalence of preterm delivery was 12-13% in the USA and 5-9% in many other developed countries (11). Lotf Alizadeh et al also estimated the incidence of preterm delivery in Mashhad as 16.4%, which is more than that of the present study (12). The reason for this difference is probably the location of the research, the number of samples, and the difference in the socioeconomic status, food culture, and conventional habits (13).

The mean serum Zn level in the research units of this study was  $38.5 \pm 44.4$  mg/dL. Zn deficiency in the study of Borna on 675 pregnant women was estimated to be 16%

(14) and Noormohamadi et al reported the mean serum Zn level of 74 mg/dL in pregnant women as (15).

In this study, there was no significant difference between serum Zn deficiency and preterm delivery.

Concerning the relationship between the serum Zn level and preterm delivery, similar studies in Turkey (16) and the United States (17) showed no significant statistical relationship between serum Zn levels and preterm delivery. In addition, Danesh et al demonstrated that supplementation of pregnant women with 50 mg/day Zn had no significant effect on the gestational age at delivery (18). On the other hand, Scheplyagina found that serum Zn deficiency increases the risk of preterm delivery (19). This discrepancy in the sample size is probably attributed to the cutoff point, along with Zn measurement in other studies and the present study. It is also indicated that several factors are involved in preterm delivery, including age, education, occupation, and previous pregnancy intervals.

In the present study, there was a direct and significant relationship between the gestational age and the serum Zn level of the umbilical cord in newborns. Further, the mother's Zn level in the eighth month and at the time of delivery had a direct and significant relationship with the

**Table 6.** Comparison of mean serum zinc concentrations of the infant's umbilical cord, the mother's serum zinc concentration level in the eighth month and during delivery in terms of the infant's gender and history of preterm delivery

Variables		Serum zinc concentrations of infant's umbilical cord	Mother's zinc level on admission	Mother's zinc level at the eighth month	Mother's zinc level during delivery
		Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Infant's gender	Female	90.78 $\pm$ 21.68	54.81 $\pm$ 33.57	80.70 $\pm$ 20.09	90.78 $\pm$ 21.68
	Male	98.50 $\pm$ 22.85	58.18 $\pm$ 33.36	96.03 $\pm$ 21.71	98.50 $\pm$ 22.85
<i>P</i> value		0.032	0.621	0.001	0.032
History of preterm delivery	Yes	78.62 $\pm$ 20.52	36.85 $\pm$ 17.71	78.62 $\pm$ 20.52	93.51 $\pm$ 20.32
	No	90.75 $\pm$ 22.04	61.22 $\pm$ 34.57	90.75 $\pm$ 22.04	94.94 $\pm$ 23.11
<i>P</i> value		0.991	0.001	0.016	0.991

Note. SD: Standard deviation.

gestational age. In a similar study, a positive relationship was found between the gestational age and serum Zn level of umbilical cord and mother's Zn level (20). On the other hand, Iqbal and Shahidullah reported no significant relationship between the mother's serum Zn level and the umbilical cord of newborns with the gestational age (21).

Regarding the relationship between the serum Zn level and neonatal growth indices, the findings of this study indicated the effect of Zn on the growth indices of newborns. In other studies by Sadeghian et al (22), Lee et al (23), and Mahmudian and Rozbahani (24), it was shown that there was a significant relationship between the daily dietary intake of Zn and birth weight and linear growth in premature infants. Contrary to our study, Díaz-Gómez et al demonstrated that the addition of Zn supplementation to pregnant mothers' diet has no effect on the weight, height, and head circumference of the newborns (25). In the study by Hafeez et al (26), Zn administration to pregnant mothers failed to affect fetal growth (weight and height). In accordance with our study, Goldenberg et al reported that the size of the head circumference of the newborns was correlated with the plasma Zn level (27) while Nazari et al found no significant correlation between plasma Zn concentration and head circumference (28).

The report of Zn on the weight of the baby is different in developing and developed countries. The possible reason for this difference can be the effect of other foods, vitamins, and minerals on the growth of the baby. There are many differences in the nutrition of pregnant mothers in developed and developing countries. Thus, most people, especially pregnant women, do not receive enough protein, carbohydrates, and lipids in developing countries (29).

The mechanisms that make Zn precisely cause fetal growth are unclear, which is another reason for the controversy about the amount of mother's serum Zn level and the anthropometric factors of newborn infants. The mechanisms that make the fetus grow, including the effects on the immune system, specific enzymes, and growth hormones during pregnancy, require Zn, thus they may be important in postnatal growth pathways. Alkaline phosphatase requires Zn to stimulate DNA synthesis and cell proliferation during pregnancy and the low concentration of alkaline phosphatase reduces the intrauterine growth of

the newborn. Animal studies showed that Zn regulates the activity of the insulin-like growth factor in the formation of osteoblasts, and therefore regulates bone growth. These proposed mechanisms represent that the Zn element in the cell cycle is considered as an auxiliary factor in the growth of the neonate (30).

Despite the positive effects of Zn on the growth and development of the fetus and according to evidence from trials conducted in developed and developing countries (31) and the present study, there is still insufficient evidence for the routine Zn supplementation during pregnancy. Therefore, further studies are needed to complete the evidence. Due to the importance of Zn in growth, it is necessary to obtain enough knowledge in this regard for gynecologists and other related groups so that they can make recommendations to their clients.

## Conclusion

According to the findings of the present study, preterm delivery was 12.9% and did not correlate with the mother's Zn. However, the serum Zn level of the umbilical cord and mother's Zn affected the growth rates of the infants. Considering the role of the Zn element in the growth parameters of newborns, it can be suggested that pregnant women use Zn supplementation during pregnancy. Finally, more extensive studies should be conducted in this country in order to obtain definitive results in this regard.

## Conflict of interests

There is no conflict of interests.

## Acknowledgments

This article was obtained from a research project approved by the Research and Technology Deputy of the Shahrekord University of Medical Sciences (approval no 1987).

## Ethical considerations

This project was approved by the Ethics Committee of Shahrekord University of Medical Sciences under the code of IR.SKUMS.REC.1394.194 on January 31, 2016.

## Authors Contribution

SS: Reviewed the final manuscript and performed drafting. BM: designed the study, AK: designed the study ML: analyzed statistical studies. FB: Collected data.

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**Informed Consent**

140 women with preterm delivery were also satisfied with participating in the study and they declared their preparation by a written consent.

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