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### RESEARCH ARTICLE

#### THE EFFECT OF ZINC SUPPLEMENTATION ON GROWTH AND DEVELOPMENT IN PRETERM NEONATES.

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Development, growth, preterm, zinc.

#### Abstract

**Objective:** This study aimed to show the effect of zinc supplementation on growth and development in preterm neonates in the first 4 months of life.

**Background:** Preterm infants have impaired zinc status because of low body stores as 60% of fetal zinc is acquired during the third trimester of pregnancy in addition to their limited capacity to absorb and retain micronutrients, coupled with increased endogenous losses associated with organ immaturity.

**Subjects and methods:** The present study was carried out at Pediatric and Clinical Pathology departments, Benha University hospital, in the period between March 2015 to September 2015. on 80 healthy preterm infants between 32 and 36 weeks of age divided into two groups : zinc-supplemented group fed with breast milk, and supplemented with multivitamins and zinc (2 mg/kg/day) since the first day of life, and a non-zinc-supplemented group fed breast milk with multivitamins only (without zinc supplementation). Both groups were followed for 4 months for growth with assessment of development by the Age and Stage Questionnaire at 4 months of corrected age and serum levels of zinc at 2 and 4 months and hemoglobin at 4 months were measured.

**Results:** In our study , it was found that the zinc-supplemented group had a significantly higher increase in weight and length at 2 and 4 months of chronological age ( $p < 0.001$ ), and non significant increase in head circumference at 2 and 4 months of chronological age ( $p > 0.05$ ) compared with the non-zinc-supplemented group. Also our study found that the zinc supplemented group had significantly higher weight, length centiles ( $p < 0.001$ ) and significant increase in head circumference centile ( $p < 0.05$ ) than that of the non-zinc-supplemented group. There was a highly significant increase in the serum zinc levels of the zinc-supplemented group at 2 and 4 months ( $p < 0.001$ ) compared with the non-zinc-supplemented group, in addition the zinc supplemented group had significantly higher level of HB at 4 months ( $p < 0.001$ ) than that of non zinc supplemented group. Also, the developmental score of the zinc-supplemented group was

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significantly higher ( $P < 0.001$ ) than that of the non-zinc-supplemented group in all tested domains.

**Conclusion:** Zinc supplementation in the first 4 months of life was found to be an effective enhancer for both the growth and the development of preterm infants.

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## **Introduction:-**

Liveborn infants delivered before 37 wk from the 1st day of the last menstrual period are termed premature by the World Health Organization [1]. Low birth weight (LBW) neonates are neonates with birth weight of 2,500 g or less, is a consequence of prematurity, poor intrauterine growth (IUGR, also referred to as SGA), or both [2]. More than 5% of deaths in children <5 yr of age occur within the 1st month of life, with about half of the deaths attributable to prematurity. Approximately 8% of liveborn neonates in the United States weigh < 2,500 g. The incidence of preterm births in the United States continues to rise and is mainly a result of multiple gestation pregnancies and increased reporting as live births of the most immature babies [1].

Preterm infants are especially susceptible to zinc deficiency because of low body stores, limited capacity to absorb and retain micronutrients, coupled with increased endogenous losses associated with organ immaturity, high nutrient demand to support catch-up growth, and inadequate intakes because of exclusive breastfeeding [3].

Zinc is involved in numerous aspects of cellular metabolism [4]. It is required for the normal structure and function of zinc-containing enzymes involved in the production of growth hormones and in transcribing and translating DNA and therefore cell division [5]. Zinc plays an essential role in neurodevelopment as zinc-dependent enzymes are involved in brain growth, zinc-finger proteins participate in brain structure and neurotransmission, zinc-dependent neurotransmitters are involved in brain memory function, and finally zinc is involved in the precursor production of neurotransmitters [6]. This study aimed to show the effect of zinc supplementation on growth and development in preterm neonates in the first 4 months of life.

Oral informed consents were obtained from the parents of the preterm infants studied. The ethics committee of the Faculty of Medicine, Benha University, approved the study.

## **Subjects and methods:-**

### **Subjects:-**

This randomized controlled study was carried out on 80 healthy preterm infants attending Pediatric department, Benha University hospital, in the period between March 2015 to September 2015. 80 preterm infants with gestational age <37 weeks and they were divided into 2 groups. Both groups fulfilled the same inclusion and exclusion criteria. The inclusion criteria were as follows: GA between 32 and 36 weeks, birth weight (BW) between 1800 and 2600 g appropriate for GA (BW between the 10<sup>th</sup> and the 90th percentile for GA), and in a stable clinical condition without any evidence of disease likely to influence growth and neurodevelopment. The exclusion criteria were as follows: term neonates (>37 weeks of gestation), intrauterine growth restriction, congenital malformations, chromosomal abnormalities, suspected inborn errors of metabolism, multiple gestations, congenital heart disease, perinatal asphyxia (APGAR < 3, longer than 5 min) and neonatal sepsis. The two groups were as follows : a zinc-supplemented group, which included 40 healthy exclusively breast-fed preterm neonates, gestational age (GA)  $35.75 \pm 1.98$  weeks, weight  $2.36 \pm .21$  kg, 22 (55%) were males, 18 (45%) were females, supplemented with zinc ( 2 mg/kg/d) and multivitamins as the following ( adequate intake of vitamin A 400 mg/d, vitamin C 40 mg/d , vitamin E 4 mg/d , vitamin B1 0.2 mg/d , vitamin B2 0.3 mg/dl , vitamin B6 0.1 mg/d , nicotinamide 2 mg/d ,vitamin D 400 IU ) [7] from day 1 to age of 4 months, and a non-zinc-supplemented group, which included 40 healthy exclusively breast-fed preterm neonates, GA  $35.14 \pm 2.33$  weeks, weight  $2.28 \pm .43$  kg , 28 (70%) were males, 12 (30%) were females, supplemented with multivitamins only (without zinc) for the same period. In study group syrup zinc was administered by nursing staff till discharge. After discharge from hospital , zinc syrup was administered by the mother .The mothers were given two bottles When the neonates were discharged from the hospital one bottle containing zinc ( zinc sulphate syrup 2mg/ml ) and instructed to give it to her baby at a dose of 2 mg/kg/day orally with multivitamin drops till the age of 4 months . In control group, the mothers were given only multivitamins bottle for the same duration.

**Methods:-**

**All neonates were subjected to:-**

**Medical examination, immediately after birth.**

**Anthropometric measurements** (weight, length, and occipitofrontal circumference). At birth, 2 and 4 months of chronological age, anthropometric measurements for all infants were recorded plotted on TNO (Netherlands Organization for Applied Scientific Research) preterm growth charts [8] to follow their growth on centiles.

**Blood samples for basal serum hemoglobin (Hb) and zinc levels** were withdrawn on the first day, blood samples for serum zinc at 2 and 4 months of age and for HB at 4 months were measured and all results were recorded for comparison between study and control group.

**Sampling:-**

4 ml venous blood samples were withdrawn from each subject and were divided into 2 specimens:

1. 2 ml venous blood specimen were withdrawn on EDTA tube for HB assay at birth, 2 and 4 months .
2. 2 ml venous blood specimen were withdrawn on plain tube from newborn at birth, 2 and 4 months- Blood samples left to clot at room temperature for 30-60 minutes, centrifuged for 15 minutes. Then serum was transferred to Eppendorf's tube and frozen at  $-20^{\circ}\text{C}$  until analysis .

**Methods of assay:-**

1. **HB assay** : HB was assayed by using colorimetric test by BIOSYSTEM BTS-310
2. **Serum Zn assay** : Zn level was determined by using colorimetric assay by **BIOSYSTEM BTS-310**.

Using commercially available spectrophotometric assay by **BioSystems S.A. Costa Brava, 30. 08030 Barcelona (Spain)** with lower limit of detection 7.7 micro gm /dl and normal reference range 80-120 ug/dl obtained by manufacturer instructions.

Linearity limit : up to 1250 ug /dL .

**Principle of the test:-**

Zinc in the sample reacts with 5-Br-PAPS in alkaline medium forming a coloured complex that can be measured by spectrophotometry.

**Age and Stage Questionnaire (ASQ)** was applied for all parents of the infants at 4 months of corrected age. This involved detailed questions to the parents for previous aspects of development at 4 months of age of their infants after correction of the age as postnatal age should be corrected for prematurity before application [i.e. corrected age = postnatal age in weeks - (40 weeks - GA)] [9] . Then, the results were recorded for assessment of the score of every aspect [10].

**Statistical analysis:-**

This phase included the following: coding of collected data and data entry into the computer and statistical analysis of the collected data. The collected data were entered into the computer using the statistical package for social sciences (SPSS) program version16 for statistical analysis. Two types of statistical analyses were carried out: descriptive statistics [e.g. number, %, mean ( $\bar{X}$ ), and SD] and analytical statistics (e.g. Student's  $t$ -test, Mann-Whitney test, paired  $t$ -test, and Pearson's correlation coefficient). A  $P$  value  $<0.05$  was considered statistically significant (S). And a  $P$  value  $<0.0001$  was considered highly significant (HS) in all analyses.

**Results:-**

The 80 healthy exclusively breast-fed preterm infants were divided equally into two groups zinc supplemented group and non-zinc-supplemented group.

In the present study, on comparison between both groups for anthropometry, it was observed that the zinc-supplemented group had highly significant increase in weight and length at 2 and 4 months of chronological age ( $p < 0.001$ ) and non significant increase in head circumference at 2 and 4 months compared with the non-zinc supplemented group, indicating a significant effect of zinc supplementation on the growth of preterm infants (**Tab: 1**). Also, the zinc-supplemented group had higher significant increase in weight, length centiles ( $p < 0.001$ ) and

significant increase in head circumference centiles ( $p < 0.05$ ) at chronological ages of 2 and 4 months compared with the non-zinc-supplemented group (**Tab: 2**).

Our study also found that the zinc supplemented group had highly significant increase in the levels of serum zinc at 2,4 months and HB at 4 months ( $p < 0.001$ ) compared with the non-zinc-supplemented group (**Tab: 3**). In our study on comparison between both groups for developmental milestones using the ASQ, it was found that the developmental score of the zinc-supplemented group was significantly higher ( $P < 0.001$ ) than that of the non-zinc-supplemented group in all tested domains (**Tab: 4**).

**Table 1:-** Comparison between studied groups as regards their Anthropometry (weight, length and head circumference):

	Cases		Control		t	p-value
	Mean	S.D	Mean	S.D		
Weight at birth (Kgs)	2.36	0.21	2.28	0.43	1.1	>0.05
Weight 2 months (Kgs)	4.55	0.39	4.13	0.38	4.7	<0.001
Weight 4 months (Kgs)	6.26	0.29	5.98	0.28	4.4	<0.001
length at birth (Cms)	45.21	1.71	45.53	1.36	0.9	>0.05
length 2 months (Cms)	54.65	1.55	52.15	1.35	7.7	<0.001
length 4 months (Cms)	63.50	2.20	60.08	2.06	7.2	<0.001
HC at birth (Cms)	31.79	1.14	31.83	1.05	0.2	>0.05
HC 2 months (Cms)	37.83	1.08	37.84	1.09	0.1	>0.05
HC 4 months (Cms)	40.14	1.07	40.05	0.99	0.4	>0.05

HC: head circumference

**Table 2:-** Comparison between studied groups as regards their centiles weight, length and head circumference:

	Cases		Control		t	p-value
	Mean	S.D	Mean	S.D		
Weight at birth centile	47.53	12.61	47.08	13.44	0.2	>0.05
Weight 2 months centile	48.58	11.88	35.23	10.63	5.3	<0.001
Weight 4 months centile	48.24	11.47	36.00	11.10	4.9	<0.001
length at birth centile	48.85	11.72	48.58	10.58	0.1	>0.05
length 2 months centile	43.90	11.06	34.88	7.38	4.3	<0.001
length 4 months centile	49.65	10.06	35.08	8.17	7.1	<0.001
HC at birth centile	50.58	10.18	49.15	10.93	0.6	>0.05
HC 2 months centile	48.03	9.67	42.68	10.01	2.4	<0.05
HC 4 months centile	50.38	9.57	45.50	10.62	2.2	<0.05

**Table 3:-** Comparison between studied groups as regards their serum zinc, Hemoglobin.

	Cases		Control		t	p-value
	Mean	S.D	Mean	S.D		
HB at birth (gm/dl)	16.17	0.95	15.94	1.33	0.9	>0.05
HB at 4 mn (gm/dl)	11.83	0.71	10.40	0.78	8.5	<0.001
Zn at birth (ug/dl)	63.66	6.42	63.74	6.97	0.1	>0.05
Zn 2 months (ug/dl)	91.07	6.15	66.71	5.31	18.9	<0.001
Zn 4 months (ug/dl)	115.62	5.51	81.54	7.91	22.4	<0.001

**Table 4:-** Comparison between studied groups as regards their developmental milestones, at 4 months according to Age and Stage Questionnaire:

	Cases		Control		t	p-value
	Mean	S.D	Mean	S.D		
ASQ score 4m (Communication )	53.13	2.45	42.25	2.76	18.6	<0.001
ASQ score 4m	48.13	3.87	39.75	4.23	9.2	<0.001

( Gross motor )						
ASQ score 4m	48.63	3.92	40.13	4.16	9.4	<0.001
( Fine motor )						
ASQ score 4m	49.75	4.07	40.13	4.16	10.5	<0.001
( Problem solving )						
ASQ score 4m	50.63	3.95	40.25	4.23	11.3	<0.001
( Personal - social )						

ASQ: Age and Stage Questionnaire

### Discussion:-

The aim of our study was to assess the response of preterm infants after supplementation with zinc for 4 months of age in terms of their growth parameters, developmental milestones, and serum levels of zinc and Hb. There were no significant side effects of the supplements. These findings could have important implications for child health survival program especially in developing countries with high incidence of preterm infants. The strengths of that study included its randomized, and minor differences in initial anthropometric status of the studied groups, thus any differences in study outcomes were likely due to the supplements of zinc that were provided. The adequate intake (AI) for zinc is 2mg/kg/d for 0-6 months infants [11]. The side effects of zinc overdose are very rare and none were reported with doses <25 mg/day [12] and they include vomiting, diarrhea, abdominal cramps, loss of appetite, and manifestations of copper and iron deficiency [13]. None of our babies developed any of these known side effects.

Our study observed that there were no significant difference in weight, length and head circumference between the control & zinc groups at birth. However, we found a highly significant effect of zinc on increasing body weight and length ( $P < 0.001$ ) at 2 and 4 months of follow-up, but did not find a similar significant effect on head circumference ( $p > 0.05$ ). This was understandable as zinc has a profound role on cellular growth and proliferation and performs various metabolic functions [14]. Many studies and systematic reviews of trials have reported improved weight gain and linear growth in preterm infants supplemented with Zinc in different dosage regimens and for different durations. This is in agreement with **Abdul-karem J. et al. [14]** who found that zinc supplementation to preterm babies for 4 weeks resulted in improved weight gain and linear growth and in contrary to us head circumference also showed improved growth. Also this is in agreement with **Ravindra Sonawane, et al. [15]** who shows in their study that zinc supplementation at 2 mg/kg/day for 8 weeks in LBW infants have significantly higher weight gain, length, linear growth velocity and head circumference at 8 weeks, but in our study head circumference showed no improvement in relation to control group.

Our results also come in concordance with **Friel et al. [16]** where this study showed that increased zinc intake in early infancy may be beneficial to preterm infants. This also comes in agreement with **Aminul et al. [17]** who reported that zinc supplementation in preterm infants led to greater weight gain and fewer problems such as infections, convulsions, and jaundice; there was no adverse effect in the zinc-supplemented group.

Also **Islam et al. [18]** reported improved weight gain and linear growth and reduced incidence of diarrhea after zinc supplementation to 100 preterm infants. Our results also come in concordance with **Aminisani et al. [19]** who show in their study that zinc supplementation between 4 and 24 wk of age has been effective in weight and length gain in preterm and low birth weight infants. Also **TV Ram Kumar et al. [20]** in their study on 134 VLBW infants supplied with zinc at a dose of 10 mg/day for 8 weeks also found significant effect of zinc supplementation on weight and length and unlike us head circumference in their study showed better growth on zinc supplementation. Like in our study, however they used a higher dose of Zn in their study. Also in **Caecilia N. et al. [21]** study on 61 LBW were given 5 mg of zinc syrup daily for 3 months concluded that in the preterm and SGA infants, median percentages of weight, length, and head circumference increase after 3 months of zinc supplementation better than control group this agrees with us except for head circumference.

Also comes in agreement with **Sur et al. [22]** who found in their study significant effect of zinc supplementation on weight, length and linear growth velocity at the end of 1 year only. Also **Surkan PJ, et al. [23]** who considered as a fact that preventive zinc supplementation in populations at risk of zinc deficiency increases linear growth and weight gain among infants and young children and **Hoque et al. [24]** in a study of 200 LBW infants also found significant effect of Zn supplementation on weight gain. However, authors did not study the effect of Zn on other growth parameters.

In our study HC measurement was increased in both the groups after supplementation at 2 m and 4 mo follow-up , But the difference was not statistically significant. This result was consistent with the results of **Lind, et al. [25]** , **Diaz-Gomez, et al. [26]** , and **Islam et al. [18]** who found the same result when HC was increased in both groups after zinc supplementation at 1st and 2<sup>nd</sup> follow-up and they found the difference was not statistically significant. But this was in disagreement with **TV Ram Kumar et al. [20]** and **Abdul-karem J. et al. [14]** where there is significant difference in head circumference gain between the two groups, p value is statistically significant ( $p < 0.05$ ) .

On the contrary to us, **Taneja et al. [27]** in their randomized, placebo-controlled trial of Zn supplementation on 52 LBW infants did not find any significant effect of zinc supplementation (5 mg/d for those infants between ages 2 wk and 6 mo and 10 mg/d for those infants aged >6 mo up to 1 year of age), on the growth of LBW infants in their study although a positive effect on plasma zinc concentration was observed . on contrary to us **Anjan a. et al. [28]** and **Mazariegos et al. [29]** also found no significant effect of zinc on linear growth.

In our study, there was a highly significant increase ( $P < 0.001$ ) in the serum levels of zinc values in the zinc supplemented group and not in the control group. This indicated that zinc supplementation was successful in improving the zinc status of these infants . This is in agreement with **Friel et al. [16]** , **Díaz-Gómez et al. [26]** in which 5mg zinc supplementation was given to preterm infants. After three months of supplementation, the serum zinc level increased significantly and also **Islam et al. [18]** concluded that significant improvements were noted in serum zinc values in the zinc supplemented group and not in the control group with ( $P < 0.001$ ). This indicates that zinc supplementation was successful in improving the zinc status of these infants. In contrary to **Caecilia N. et al. [22]** in their study on 61 LBW who were given 5 mg of zinc syrup daily for 3 months. the post-supplementation serum zinc levels were not different compared to pre-supplementation level within each group.

In our study ,there was a significant increase in the serum levels of Hb in response to increased serum zinc, indicating the role of zinc in improving Hb level in preterm . This is in agreement with **Hyun-Ju et al. [30]** , **Díaz-Gómez et al. [31]** and **Islam et al. [18]** who found that hemoglobin levels were significantly higher in Group I than Group II after supplementation of zinc ( $P < 0.05$ ).

In our study, we found that the developmental score of the zinc supplemented group was significantly higher in all tested domains ( $P < 0.001$ ) than the non-zinc supplemented group using the ASQ at 4 months of corrected age. This is in agreement with **Friel et al. [16]** who reported improved motor development in preterm infants supplied with zinc supplement up to 6 months and in agreement with **NB Mathur and Devendra Kagarwal [31]** who concluded that zinc supplementation to preterm breastfed infants till 3 month corrected age improves alertness and attention pattern, and decreases signs of hyper-excitability and abnormal patellar and bicipital reflex. In contrary to us **Ashworth A. et al. [32]** study on low birth weight infants using Bayley Scale of Infant Development found that zinc supplementation did not improve the mental and psychomotor scores at 6 and 12 months and also **Pamela et al. [33]** reported that zinc supplementation in preterm low BW infants did not lead to better achievement of motor and language milestone.

### **Conclusion:-**

Our study concluded that zinc supplementation for 4 months to preterm infants enhances their growth ( weight and length) . Also oral zinc supplementation has positive effect on serum zinc and Hb level indicating the role of zinc in improving Hb level in preterm . Zinc also is essential for maturation of the central nervous system, which was indicated by a significant increase in the achievement of developmental milestones in preterm infants during the first 4 months of life.

### **Recommendations:-**

Zinc supplementation can be recommended with other vitamins to preterm infants for their better growth and development.

### **Conflicts of interest:-**

The authors declare no conflict of interest.

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