Maternal zinc and cord blood zinc, insulin-like growth factor-1, and insulin-like growth factor binding protein-3 levels in small-for-gestational-age newborns

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Summary

Purpose: To determine the relationship between maternal serum zinc (Zn) levels and birth weight of the offspring and their correlation with cord blood Zn, insulin-like growth factor (IGF-1) and insulin-like growth factor binding protein-3 (IGFBP-3) levels.

Method: 22 term small-for-gestational-age (SGA) and 34 term appropriate-for-gestational-age (AGA) infants and their mothers were included. Maternal and cord blood Zn levels and cord blood IGF-1 and IGFBP-3 levels were measured.

Results: Eighteen percent of mothers had Zn deficiency (< 75 mcg/dl). No significant difference between IGF-1 and IGFBP-3 levels and birth weight of infants of the mothers with and without Zn deficiency was found. Maternal and neonatal Zn levels correlated ($r = 0.38$, $p < 0.01$). Mean IGF-1 and IGFBP-3 levels were significantly lower in the SGA group compared to the AGA group (42.3 ± 16.8 ng/ml, 1.2 ± 0.2 mcg/ml, and 62.4 ± 22.7 ng/ml, 1.5 ± 0.4 mcg/ml, $p < 0.001$). A correlation was found between birth weight, IGF-1 and IGFBP-3 levels, and weight gain of the mother during pregnancy ($p < 0.01$).

Conclusions: Zn deficiency was not observed to be a risk factor for low birth weight. The significant difference between the SGA and AGA babies' IGF-1 and IGFBP-3 levels emphasizes function of the IGF system in intrauterine growth.

Key words: Zinc deficiency; IGF-1; IGFBP-3; SGA.

Introduction

Dietary zinc deficiency causes postnatal growth retardation and is associated with reduced circulating insulin-like growth factor 1 (IGF-1) concentrations in both animals and humans [1]. IGF-1 has an important role in both fetal and postnatal growth [2]. IGF-1 production is regulated mainly by insulin and fetal nutrition during intrauterine life [3].

Zinc deficiency during pregnancy may affect embryonic and fetal growth in experimental animals, however the studies are controversial in humans [4-7]. The presence of coexisting nutritional deficiencies, patient characteristics, timing and duration of zinc supplementation are among the factors that may explain the contradictory results of zinc supplementation during pregnancy [7, 8].

The aim of this study was to determine the relationship between maternal serum zinc levels and birth weight of the offspring and the correlation of these with cord blood Zn, IGF-1 and IGFBP-3 levels.

Materials and Methods

The study population consisted of mothers (n = 22) who delivered a small-for-gestational-age (SGA) infant after 37 weeks of gestation. Thirty-four mothers and their appropriate-for-gestational-age (AGA) newborns were included as controls. Exclusion criteria were babies with congenital malformations, chromosomal anomalies and congenital infections. SGA was defined as birth weight below the 10^{th} percentile for gestational age.

An informed consent was obtained from the mothers about the procedures and purpose of the study. A short history comprised of obstetric characteristics, socioeconomic status, dietary habits and general health was taken. Umbilical venous cord blood samples and venous blood from the mothers were collected. Blood samples were centrifuged and the sera were stored at –20°C for future analysis. Birth weight, length and head circumference of the infants were measured. Nutritional status of the newborns was also evaluated with the ponderal index based on birth weight (BW) and birth length (BL). (Ponderal index= $BW \times 100/ BL^3$).

Zinc levels in the cord blood and maternal serum samples were analyzed with atomic absorption spectrophotometry. Zinc deficiency was defined as Zn < 75 ug/dl. IGF-1 and IGFBP-3 were analyzed by using immulite 1000 chemiluminescent assay (DPC, Los Angeles, CA, USA)

Statistical analysis of the results, which were all parametric, was done via the standard computer programs SPSS version 11 using the Student's t and Mann-Whitney U tests for quantitative data and chi-square analysis for qualitative data in addition to the Spearman's correlation test. The numerical data are represented as mean ± SD and the differences were considered significant if the p value was less than 0.05.

Results

Demographic characteristics and IGF-1, IGFBP-3 and Zn levels of study and control groups are given in Table 1. Obstetric history of the mothers of SGA infants revealed preecleampsia (13%), smoking (10%) and

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Table 1. — *Characteristics of study population*.*

	AGA[1] (n = 34)	SGA[2] (n = 22)	p
Male/female	15/19	8/14	0.370
Vaginal delivery (%)	93.1	82.6	0.387
Birth weight (g)	3315 ± 315	2242.6 ± 238	0.0001
Gestational age (wks)	38.4 ± 0.9	38 ± 0,9	0.09
Mothers' age (yrs)	27.7 ± 6.9	25 ± 6,7	0.096
Mothers' weight gain (kg)	13.2 ± 4.5	11.3 ± 3.6	0.095
Mothers' BMI (kg/m²)	23 ± 3.3	22.6 ± 4.2	0.482
Ponderal index (g/cm³)	2.76 ± 0.28	2.32 ± 0.32	0.0001
Zinc (mcg/dl)	150.5 ± 43.8	165.2 ± 51.8	0.259
IGF-1 (ng/ml)	62.1 ± 22.7	42.3 ± 16.8	0.001
IGFBP3 (mcg/ml)	1.5 ± 0.4	1.2 ± 0.2	0.001

*Values are given in means with standard deviations.
[1]Appropriate-for-gestational-age; [2]Small-for-gestational age.

failure to gain weight (< 12 kg) during pregnancy (60%) and anemia in one mother.

Serum levels of IGF-1 and IGFBP-3 in SGA infants were significantly lower when compared to AGA infants. There was no significant difference between the cord blood zinc levels in SGA and AGA infants.

Mean serum zinc level of mothers of SGA infants was not (121.8 ± 54.3 mcg/dl) statistically different than zinc levels of mothers of AGA infants (103.8 ± 34.3; p = 0.287 mcg/dl). Infants' zinc levels were correlated with mothers' zinc levels (r = 0.351, p < 0.008) (Figure 1). In our study population 18% of mothers had zinc deficiency, whereas only one infant had a low zinc level. Infants of zinc deficient mothers did not have significantly different IGF-1 or IGFBP3 values (70.2 ± 29.8 ng/ml and 1.6 ± 0.5 mcg/ml, respectively) when compared to infants of mothers with normal zinc values (51.2 ± 20.2 ng/ml and 1.4 ± 0.4 mcg/ml, respectively). Birth weights of these infants were not affected by mothers' zinc deficiency either (2845 ± 600 gr vs 3065 ± 587 g in zinc deficient and sufficient mothers, respectively).

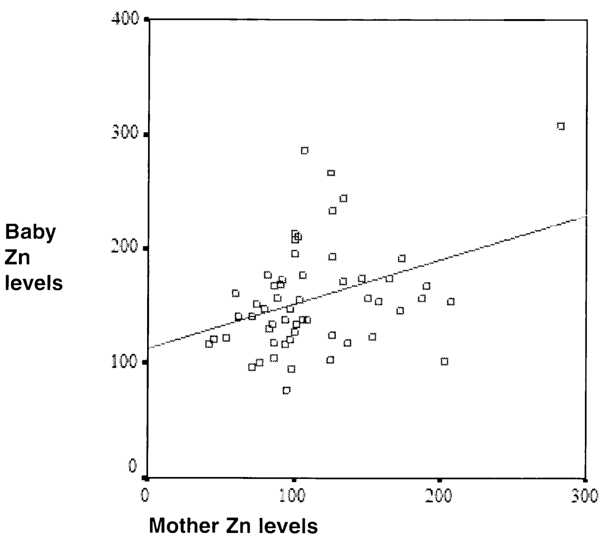

Figure 1. — Regression line graph of Baby Zn levels and Mother Zn levels.
A significant correlation exists between mothers' and infants' zinc values (power of Spearman 35.1%, p = 0.008).

In this study, birth weight was correlated with cord IGF-1 and IGFBP-3 values ($r_{\text{Sperman rho}}$ = 58.1%, p = 0.0001, $r_{\text{Sperman rho}}$ = 55.3%, p = 0.0001), and also mean weight gain of the mother during the pregnancy ($r_{\text{Sperman rho}}$ = 32.7% p = 0.009).

Discussion

It has been demonstrated that IGF-1 plays an important role in the regulation of fetal growth [2] and has positive correlations with BW and gestational age. IGFBP-3 is a carrier protein that extends the half-life and bioavailability of IGF-1. IGFBP3 levels of SGA infants were lower than those of AGA infants. Our results have also shown that SGA infants had lower IGF-1 levels than AGA infants.

IGF-1 synthesis and its release into the circulation have been shown to be under the influence of growth hormone, insulin, protein intake and micronutrients like zinc [9-11]. However the data is lacking regarding the effect of zinc on the regulation of IGF-1 production during fetal life.

In our study, we did not find a relationship between maternal serum zinc levels and IGF-1 and IGFBP-3. This may be due to the fact that the mothers in our study did not have severe zinc deficiency.

Pregnant women have increased zinc requirements and zinc deficiency is a common problem in developing countries. In our study we found that 18% of pregnant women had mild zinc deficiency. Severe Zn deficiency has a negative effect on birth weight of experimental animals, but the effect is less consistent with mild zinc deficiency. Maternal zinc levels were not associated with intrauterine growth retardation in another study from India [4]. In our study although maternal serum zinc levels correlated with cord blood zinc levels, maternal marginal zinc deficiency did not have any effect on birth weight of the offspring.

In infants improved growth performance after zinc supplementation is the most accurate measure of preexisting zinc deficiency [12-14]. Similarly supplementation of pregnant women at risk for zinc deficiency (young age, low socioeconomic status, low weight at the onset of pregnancy) might have a positive effect on the birth weight of the offspring [8, 13, 15].

Zinc supplementation during the first months of life has beneficial effects on growth of infants born small for gestational age or premature [11, 14]. This may suggest a prenatal depletion or insufficient zinc intake to support catch-up growth postnatally.

Growth retardation related to zinc deficiency is not only caused by low serum IGF-1 concentrations but also by inhibition of the metabolic actions of IGF-1 [1, 9].

Nihn *et al.* [9] reported that zinc-deficient rats had decreased circulating IGF-1 concentrations. These rats were given exogenous IGF-1 which restored circulating IGF-1 concentrations to normal but this intervention failed to reserve the growth retardation induced by zinc deficiency.

In conclusion, maternal mild zinc deficiency is not a risk factor for having a SGA baby in this study. However future trials should focus on Zn and IGF-1 levels in pregnant women who receive supplemental zinc or placebo and determine if zinc supplementation decreases fetal growth retardation in high-risk groups.

References

[1] Lefebvre D., Boney C.M., Ketelslegers J.M., Thissen J.P.: "Inhibition of insulin-like growth factor-I mitogenic action by zinc chelation is associated with a decreased mitogen-activated protein kinase activation in RAT-1 fibroblasts". *FEBS Lett.*, 1999, *449,* 284.

[2] Diaz E., Halhali A., Luna C., Diaz L., Avila E., Larrea F.: "Newborn birth weight correlates with placental zinc, umbilical insulin-like growth factor I, and leptin levels in preeclampsia". *Arch. Med. Res.*, 2002, *33,* 40.

[3] Rosenfeld R.G., Cohen P.: "Disorders of GH/IGF secretion and action". In: Sperling M.A. (ed.). Pediatric Endocrinology. Philadelphia: Saunders, 2002, 211.

[4] George S.S., Swaminathan S., Kanagasabapathy A.S., Seshadri L.: "Maternal zinc indices and small babies". *Natl. Med. J. India,* 1998, *11,* 120.

[5] Pitt J.A., Zoellner M.J., Carney E.W.: "Developmental toxicity of dietary zinc deficiency in New Zealand white rabbits". *Reprod. Toxicol.*, 1997, *11*, 781.

[6] Wells J.L., James D.K., Luxton R., Pennock C.A.: "Maternal leucocyte zinc deficiency at start of third trimester as a predictor of fetal growth retardation". *Br. Med. J. (Clin. Res. Ed.),* 1987, *294,* 1054.

[7] Castillo-Duran C., Weisstaub G.: "Zinc supplementation and growth of the fetus and low birth weight infant". *J. Nutr.,* 2003, *133,* 1494S.

[8] Cherry F.F., Sandstead H.H., Rojas P., Johnson L.K., Batson H.K., Wang X.B.: "Adolescent pregnancy: associations among body weight, zinc nutriture, and pregnancy outcome". *Am. J. Clin. Nutr.*, 1989, *50,* 945.

[9] Ninh N.X., Maiter D., Verniers J., Lause P., Ketelslegers J.M., Thissen J.P.: "Failure of exogenous IGF-I to restore normal growth in rats submitted to dietary zinc deprivation". *J. Endocrinol.,* 1998, *159,* 211.

[10] Ninh N.X., Thissen J.P., Maiter D., Adam E., Mulumba N., Ketelslegers J.M.: "Reduced liver insulin-like growth factor-I gene expression in young zinc-deprived rats is associated with a decrease in liver growth hormone (GH) receptors and serum GH-binding protein". *J. Endocrinol.*, 1995, *144*, 449.

[11] Diaz-Gomez N.M., Domenech E., Barroso F., Castells S., Cortabarria C., Jimenez A.: "The effect of zinc supplementation on linear growth, body composition, and growth factors in preterm infants". *Pediatrics*, 2003, *111,* 1002.

[12] Domenech E., Diaz-Gomez N.M., Barroso F., Cortabarria C.: "Zinc and perinatal growth". *Early Hum. Dev.*, 2001, *65* (suppl.) S111.

[13] Costello A.M., Osrin D.: "Micronutrient status during pregnancy and outcomes for newborn infants in developing countries". *J. Nutr.,* 2003, *133,* 1757S.

[14] Castillo-Duran C., Perales C.G., Hertrampf E.D., Marin V.B., Rivera F.A., Icaza G.: "Effect of zinc supplementation on development and growth of Chilean infants". *J. Pediatr.*, 2001, *138,* 229.

[15] Prentice A.: "Micronutrients and the bone mineral content of the mother, fetus and newborn". *J. Nutr.,* 2003, *133,* 1693S.

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