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# Exchangeable zinc pool size at birth in Pakistani small for gestational age and appropriate for gestational age infants do not differ but are lower than in US infants

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# Exchangeable Zinc Pool Size at birth in Pakistani SGA and AGA Infants Do Not Differ but Are Lower than in US Infants

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| **Abstract:** | Objectives: Small for gestational age (SGA) infants are more susceptible to infectious morbidity and growth faltering compared to their appropriate for gestational age (AGA) counterparts. Zinc supplementation of SGA infants may be beneficial but the underlying susceptibility to zinc deficiency of SGA infants has not been examined.<br><br>Methods: In a community-based, observational, longitudinal study in a peri-urban settlement of Karachi, Pakistan, we compared the size of the exchangeable zinc pools (EZP) in term SGA and AGA infants at birth and at 6 months of age, hypothesizing that the EZP would be lower in the SGA group. To measure EZP size, a zinc stable isotope was intravenously administered within 48 hours of birth (n=17 and 22) at 6 months (n=11 and 14) in SGA and AGA infants, respectively. Isotopic enrichment in urine was used to determine EZP.<br><br>Results: No significant difference was detected in the mean (± SD) EZP between SGA and AGA infants at birth, with values of 9.8 ± 3.5 and 10.1 ± 4.1 mg/kg, respectively ($p=0.86$), or at 6 months. Longitudinal EZP measurements demonstrated a significant decline in EZP relative to body weight in both groups at 6 months ($p<0.001$). Mean EZP (adjusted for body weight) size at birth for the combined Pakistani groups was significantly lower than U.S. AGA infants at birth ($p=0.017$). |

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Melvin Heyman, MD, MPH
Editor, Journal of Pediatric Gastroenterology and Nutrition

Dear Dr. Heyman:

On behalf of all of my co-authors, I am pleased to submit the attached manuscript entitled "Exchangeable Zinc Pool Size at birth in Pakistani SGA and AGA Infants Do Not Differ but Are Lower than in US Infants" for consideration for publication in JPGN. We believe the results of this study will be of interest to the Pediatric Nutrition community, including especially those with a global Nutrition perspective. None of the authors have any conflicts of interest, and ethical adherence of the study was maintained. We have provided suggestions for potential reviewers. Please let me know if there are any technical or formatting issues with our submission. Thank you in advance for your consideration of this manuscript.

With kindest regards,

Nancy F. Krebs, MD, MS
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List each author and his/her respective roles in the submitted work, documenting appropriate input for authorship.

Dr. Ariff oversaw the clinical and field operations at AKU and contributed to data analysis and manuscript writing. Drs. Krebs and Hambidge developed protocol, provided training to the field team, performed data analysis and interpretation, and wrote final manuscript. Ms Westcott contributed to study design and oversaw laboratory analyses at UC; Mr. Miller oversaw and conducted statistical analysis of data; A. Rizvi contributed to data management and analysis at AKU; and Dr. Bhutta contributed to study development, acquisition of funding, and oversight of study implementation.

**Abstract:**

Objectives: Small for gestational age (SGA) infants are more susceptible to infectious morbidity and growth faltering compared to their appropriate for gestational age (AGA) counterparts. Zinc supplementation of SGA infants may be beneficial but the underlying susceptibility to zinc deficiency of SGA infants has not been examined.

Methods: In a community-based, observational, longitudinal study in a peri-urban settlement of Karachi, Pakistan, we compared the size of the exchangeable zinc pools (EZP) in term SGA and AGA infants at birth and at 6 months of age, hypothesizing that the EZP would be lower in the SGA group. To measure EZP size, a zinc stable isotope was intravenously administered within 48 hours of birth (n=17 and 22) at 6 months (n=11 and 14) in SGA and AGA infants, respectively. Isotopic enrichment in urine was used to determine EZP.

Results: No significant difference was detected in the mean (± SD) EZP between SGA and AGA infants at birth, with values of 9.8 ± 3.5 and 10.1 ± 4.1 mg/kg, respectively ($p=0.86$), or at 6 months. Longitudinal EZP measurements demonstrated a significant decline in EZP relative to body weight in both groups at 6 months ($p<0.001$). Mean EZP (adjusted for body weight) size at birth for the combined Pakistani groups was significantly lower than U.S. AGA infants at birth ($p=0.017$).

Conclusions: These results did not support a difference in zinc endowment between SGA and AGA Pakistani infants. However, they do suggest lower *in utero* zinc transfer to the fetus in a setting where poor maternal nutritional status may confer a high susceptibility to postnatal zinc deficiency.

- What is known?
    - Zinc supplementation trials in small for gestational age (SGA) infants in low resource settings have reported improvements in growth and reduction in morbidity and mortality.
    - The potential benefit of zinc supplementation may reflect lower zinc endowment at birth or a higher postnatal zinc requirement in SGA infants.
    - The size of the exchangeable zinc pools (EZP) at birth may reflect intrauterine zinc status
- What is new?
    - The significantly lower EZP size at birth in both SGA and AGA groups of infants born to undernourished women compared to EZP size in infants born in a westernized setting provides evidence of very early vulnerability to postnatal zinc deficiency.

Keywords: nutrition, malnutrition, micronutrient deficiency, zinc deficiency

**Introduction:**

Zinc is an essential micronutrient for human health, and requirements are relatively high for young infants. Globally, zinc deficiency has been demonstrated to be an important contributor to increased infant and young child mortality, as well as having detrimental effects on health indicators such as growth, diarrhea, and other infectious morbidity[1]. The various physiologic roles of zinc are critical in metabolic pathways involved in gene expression, growth, immunologic and reproductive functions[2].

Small for gestational age (SGA) infants represent a particularly vulnerable population that is at risk for infectious morbidity, growth faltering, and neurodevelopmental deficits. Recent estimates indicate that there are more than 30 million infants born SGA, the vast majority being born at term and the highest rates being in Asia[1]. Zinc supplementation in primarily breastfed SGA infants over the first year of life has been associated with improved growth and reduction in mortality[3,4]. It is unknown whether the improvements in these infants' clinical course with zinc supplementation reflected correction of a deficiency acquired during fetal development or improvement in postnatal zinc intake that was otherwise insufficient to support catch up growth and optimal immune defenses.

Stable isotope studies have proved to be a useful tool in the evaluation of zinc homeostasis and of pool sizes in the body[2,5]. The size of the rapidly exchangeable zinc pools (EZP) is considered to be potential marker of zinc status in adults[2], with less clear utility in young children[5]. A study using zinc stable isotopes in an affluent country reported lower EZP size in premature SGA infants compared to appropriate for gestational age (AGA) premature infants at birth[6]. Those results provided plausibility for the hypothesis that SGA infants are born with relatively low stores of zinc. However, no such study has been performed in areas where the prevalence of maternal malnutrition and the burden of SGA are high.

The objective of this study was to compare the size of the EZP between SGA and AGA term infants born in Pakistan at birth and 6 months, and to compare the EZP results to those of US newborns. We hypothesized that size of the EZP at birth would be significantly smaller in absolute size and relative to body weight in SGA compared to AGA infants.

**Methods:**

*Study Design:* This was a community-based, observational, longitudinal study design carried out in a low socioeconomic, multi-ethnic peri-urban slum area of Karachi, Pakistan. The size of the EZP was measured by stable isotope methodology at birth and at six months of age in infants who were born with birthweights SGA and AGA, as described previously[6]. Isotope administration was conducted at Bilal Research Centre affiliated with the Aga Khan University in Karachi. Anthropometric measures were obtained by trained research workers at home visits approximately every three months through 6 months of age; breast milk and blood samples were obtained at birth and 6 mo.

*Study Site:* The study area has a population of approximately 63,270, with a high rate of SGA births, accounting for approximately 25% of births[7]. The population living around the catchment area of Bilal Research Centre was our study population. The research centre, in addition to carrying out research activities, also provides ambulatory Maternal Neonatal and Child Care services to the community.

*Study Subjects:* All newborns in the catchment population delivered either at home or community hospital who fulfilled the inclusion criteria of SGA and AGA were recruited. SGA was defined as term infants (≥ 37 wks) with birthweight < 2500 grams, and AGA as term infants weighing ≥ 2500 grams. We ensured the recruitment of SGA due to intrauterine growth retardation; low birthweights due to prematurity were excluded. Determination of gestational age was conducted by the research physician (SA) by determination of mother's reported last

menstrual period and by a combination of physical and neurological criteria by modified Ballard examination[8].

Recruitment procedures included identification of healthy pregnant women between the ages of 18 to 40 years through the household survey; enrollment into the study was obtained following their consent. Enrolled pregnant women were followed through last trimester until birth by trained community health workers (CHW) who were resident of the study area. All mothers with history of tobacco intake, HIV, and chronic infections were excluded. A written informed consent was taken from parent within 24 hr of birth to recruit infant into the study. The study and consent forms were approved by the ethical review committee (ERC) of the Aga Khan University and by the Colorado Multiple Institutions Review Board (COMIRB). The study was registered with the clinical trial registry NCT01140256.

Prior to initiation of the study, the research physician and the community health worker underwent a 5-day training workshop in which they were trained in newborn head to toe examination, anthropometry, and study procedures, including isotope administration and biospecimen collections and handling. Following delivery, a newborn examination was performed by the research physician (SA) and all infants with congenital anomalies were excluded from the study. A repeat newborn examination and gestational age assessment by trained neonatologist (SA) was carried out for eligibility criteria and for assignment to SGA or AGA cohort based on weight and gestational age assessment.

Sample size estimates were based on EZP data at birth obtained from previous study[6]. In that study, we observed a mean difference of approximately ±3.5 mg/kg of EZP between SGA and AGA. Using similar effect size and standard deviation for each group and an alpha = 0.05, a sample size of 14 infants per group provided a power of 0.80 for a 1-sided determination that EZP/kg is lower in the SGA group, and 17/group would be required for two-sided determination of difference.

*Dietary Intake*: Breastfeeding promotion was performed by CWH at each post-partum visit to encourage optimal breastfeeding practices. Qualitative data regarding feeding practices were also obtained by trained CHW at follow-up visits by use of food frequency and dietary recall tools.

*Anthropometry:* Home visits were performed by the CHW and research physician at the time of enrollment (within 24-48 hours of birth) and at 3 and 6 months. Anthropometric measurements included length, weight and head circumference. The procedures were all standardized and included naked infant weights (Seca scales, sensitivity 10 g); length by infantometer (AHRTAG-London); and head circumference measured with a laminated tape. Measurements were done in triplicate according to standardized procedures described by the World Health Organization[9].

*Isotope Dose Preparation and Administration:* Enriched stable isotopes of zinc were obtained from Trace Science International (Richmond Hill, Canada). Accurately weighed quantities of each isotopically enriched preparation were dissolved in 0.5 mol/L $H_2SO_4$ and then diluted with deionized water to prepare stock solutions of $^{67}Zn$ or $^{70}Zn$. Solutions were diluted with 0.45% saline, adjusted to a pH 6.0 and then filtered through a 0.22-μm filter to ensure sterility. The pharmaceutical quality of the sterile solution (i.e., sterility and pyrogenicity) was certified by the University of Colorado Hospital pharmacy and the core laboratory of the General Clinical Research Center, respectively. An accurate weight of approximately 40 μg/kg of stable isotope was administered to each subject at 0 and 6 months of age. Doses were prepared in Colorado and were based on estimated approximate newborn weights of SGA and AGA at birth and at 6 mo. Alternate isotope ($^{67}Zn$ or $^{70}Zn$) for each group was used at 6 months to avoid complexity in calculations to account for residual urine enrichment of isotope infused at birth.

Recruited infants were brought to the pediatric unit of the Aga Khan University hospital where the study neonatologist administered the stable isotope. A peripheral intravenous

catheter was placed by aseptic techniques and isotope was administered over a period of approximately two minutes. A 3-way stopcock was placed on the catheter to allow two rinses of catheter and syringe, each with a volume of saline equal to that of the isotope solution. Ashless filter paper was used to collect any losses during the infusion[6].

*Specimen Collection:* Milk samples (5-10 ml) were collected by hand expression at the pediatric unit after cleaning the nipple with deionized water; expressed milk was placed in zinc free plastic vials. Twice daily spot urine samples (am & pm) were collected from days 3 to 7 after isotope administration. CHW collected the urine samples of approximately 20 ml each in subjects' homes. A baseline urine sample was collected prior to first dose of intravenous isotope at both birth and 6 months of age. CHW washed the perineum with zinc free soap and water, then attached the zinc-free urine bag (Briggs, Des Moines, IA, USA) and waited for urine to collect. Once urine was passed, it was drained into a zinc free urine collection container. All precautions were taken throughout specimen collections and handling to avoid contamination of samples from environmental zinc. The urine samples were brought to the research lab of Aga Khan University, and were stored at -20 Cº until shipment in batches to University of Colorado Anschutz Medical Campus (CUAMC) for isotope ratio measurements.

Blood specimens were collected immediately before the isotope infusion at baseline and 6 months of age for assessment of hemoglobin (Hb) and plasma zinc concentrations. Precautions were taken to avoid zinc contamination during collection, handling, and storage of specimens.

*Sample Processing and Analysis:* Zinc concentrations in milk samples were determined by AAS using previously described methods[10]. Urine samples were purified and analyzed for zinc isotope ratios at CUAMC Pediatric Nutrition Laboratory. Urine samples were digested, as previously described[10], using a MARS microwave sample preparation system (CEM Corp, Matthews, NC). The remaining liquid from the digested sample was placed into a 50 mL beaker

and evaporated to dryness on a hotplate. The dried sample was reconstituted in 2 mL ammonia acetate buffer (pH 5.6) and zinc was purified by first chelating it with trifluoroacetylacetone and then extracting the chelate with hexane.

Isotope enrichment was determined by measurement of the isotope ratios $^{67}Zn/^{66}Zn$ and $^{70}Zn/^{66}Zn$ by ICP-MS (VG Plasma Quad 3, VG Elemental, Thermo Electron Corporation, Waltham, MA) and conversion of ratios to enrichment using a mathematical matrix. Tracer enrichment was defined as all of the zinc in the sample that was derived from the isotopically enriched tracer preparation divided by the total zinc in the sample[11].

Hemoglobin concentration was determined at birth and 6 months of age by Hemocue technique (Hemocue 201+ Hemoglobin Analyzer HemoCue® AB Kuvettgatan, Sweden). Plasma zinc concentrations were measured at AKU by AAS.

*Data Processing and Statistical Analyses:* Prior to data entry, all forms were checked for completeness and consistency. In case of inconsistency or missing responses, study personnel were consulted for possible explanations and corrections. For data entry, databases and entry screens were developed using Microsoft Visual Fox Pro 7.0. A subsample of the data was manually checked to examine data entry errors and to monitor error rates of data entry operators.

Anthropometric Z-scores were determined from the WHO Multicentre Growth Reference Study for breastfed infants[12].

The EZP is defined as the estimate of the total size of the combined pools of zinc that exchange with zinc in plasma within approximately 3 days. The size of EZP was calculated by dividing the mass (µg) of intravenous isotope dose ($^{67}Zn$ or $^{70}Zn$) by the enrichment value at the y intercept of the linear regression: EZP = IV dose/y-intercept. The intercept is estimated from

linear regression of a semi-log plot of urine enrichment data from study days 3-7 days after isotope administration[13].

The mean size of the EZP at birth for Pakistani infants was compared to that of SGA and AGA infants born in the U.S.[6] Methods were identical between the two studies, and all isotope enrichment analyses were conducted in the investigators' laboratory in Colorado.

We used GraphPad Prism 7.0 (GraphPad Software, Inc. La Jolla, CA) for data processing and statistical analyses, which included unpaired t-test to compare groups, and paired t-test to examine changes in EZP (relative to body weight), and hemoglobin from birth to 6 months. Data were checked for normality, and are presented as mean ± SD unless otherwise noted. Statistical significance was defined at $p \leq 0.05$ level.

**Results**

We initially recruited 22 infants in each group, keeping in view the nature of the study and anticipated high rate of attrition. Seventeen term SGA infants and 22 AGA infants were able to successfully complete the study procedures at birth. Of these, 11 SGA and 14 AGA infants completed the studies at 6 months of age. Reasons for incomplete follow-up measurements primarily included study burden for collections and being lost to follow-up due to leaving study area. Two infants' urine collections at 6 months (1 SGA, 1 AGA) were not useable for EZP determinations, likely due to contamination with natural abundance zinc. By study design, the mean birthweight of the SGA infants was significantly lower than that of the AGA infants ($p < 0.0001$); ponderal index was also lower in the SGA group ($p = 0.02$) (**Table 1**). Additional descriptive data of the SGA and AGA cohorts are provided in **Table 1**. As per Z-scores, 65% of SGA infants were wasted (weight/length Z-score < -2) at birth vs. 15% of AGA infants. At 6 months follow-up, wasting was observed in 17% of SGA group and < 5% of AGA group.

Less than 20% of SGA infants were exclusively breastfed until 6 months (mean duration 4.6 ± 2.1 months), while less than 5% in AGA group were exclusively breastfed until 6 months (mean duration 5.3 ± 2.0 months). Milk zinc concentrations did not vary by group; overall means were 2.32 ± 0.82 and 0.96 ± 0.93 µg/ml at 1 week and 6 months, respectively, which was a significant decline for both groups ($p < 0.001$). (Group data for milk zinc concentrations not shown). Many infants (28%) in the SGA group received formula or fresh milk in addition to breast milk, and weaning was started with initiation of complementary foods by 6 mo in 64% of SGA babies. Almost 90% of AGA infants were on complementary foods at 6 months. Feeding questionnaires at 6 mo indicated that complementary foods consumed were comprised predominantly of carbohydrate based foods (e.g. biscuits, wheat-based local bread (paratha/roti), sweet potatoes, rice kitchri, and local porridge (dalia). Intakes of protein foods were negligible, with 3 infants (2 AGA, 1 infant SGA) reported to have consumed chicken, red meat or liver once in the previous 24 hours. Fresh fruits were consumed by both groups and there was significant intake of beverages, e.g. teas, in both groups.

No significant differences in the sizes of the EZP between SGA and AGA groups were observed at either birth or 6 months of age (**Table 2**). For those subjects with measurements at both time points, EZP declined significantly from birth to 6 months for both groups ($p < 0.0001$). The mean of the EZP (adjusted for body weight) for the combined groups of Pakistani infants were significantly less than those of the AGA US cohort at birth. Specifically, the mean for U.S. AGA infants was 13.9 ± 4.5 mg/kg ($n = 11$)[6] vs 9.94 ± 4.75 mg/kg ($n = 39$) in the Pakistani infants combined groups ($p = 0.017$).

No significant differences were observed in the mean hemoglobin concentrations between SGA and AGA infants at birth or at 6 months (**Table 3);** the means at 6 months were significantly lower ($p < 0.001$) and indicate the high prevalence of anemia by this age (> 50% for both groups). Plasma zinc concentrations did not vary by group or time **(Table 3).**

**Discussion:**

The size of the EZP has been proposed as a biomarker reflecting host zinc status[2], as it has been correlated in infants with dietary zinc intakes and with the amount of zinc absorbed[10]. The EZP sizes at birth in our SGA cohort were not less than those of the AGA group as we had postulated, in contrast to those previously reported for SGA and AGA preterm infants in the U.S. at birth[6]. Thus, these results are not consistent with relatively lower levels of zinc accrual in the SGA fetus, nor was there any indication that the EZP sizes were lower in SGA infants than those of AGA infants at 6 months postnatal age. The lack of quantitative dietary data in this community-based study and the small percentage of exclusively breastfed infants limited the interpretation of the 6 month EZP data. Had all or most of the infants been exclusively breastfed, any differences in zinc intakes would primarily have been presumed to be driven by differences in total volume of intake, since zinc concentrations in milk are essentially independent of maternal zinc intake[14] and do not differ for women delivering SGA vs AGA infants[15]. Notably, the lower mean EZP size for both groups of Pakistani infants at birth compared to AGA infants in the U.S. raises the possibility that the underweight status of many of the Pakistani women was associated with generally poor nutritional status during pregnancy and suboptimal zinc transfer to the fetus. In such a scenario, multiple factors in addition to zinc would likely have contributed to the intrauterine growth restriction observed in the SGA group. This is consistent with recent analyses that have not demonstrated a benefit of maternal zinc supplementation alone on SGA births[16], but with those supporting a critical role of maternal undernutrition contributing to poor fetal growth[17].

The similar declines in EZP size (relative to body weight) for both SGA and AGA infants over the first 6 months are also not supportive of the need for further Zn supplementation in the SGA over the AGA infants, although the small sample sizes preclude definitive conclusions. The 6 month EZP values in this study were similar to those reported recently for another cohort of

poor Pakistani infants who had received zinc-containing micronutrient powder for several weeks prior to being studied[18]. A recent analysis of combined EZP data from infants and young children (8 – 120 months of age) found that age and body size are significant predictors of EZP size, increasing in absolute size but declining relative to body weight (ie, mg/kg)[5]. Although the summative analysis did not include infants as young as those in the present study, our observation that the absolute EZP sizes did not increase for either group with age and increasing body size raises the possibility that the 6 month levels are less than optimal. This could be due to marginal zinc intake from breast milk, from zinc – poor breast milk substitutes, and/or from zinc-poor complementary foods.

The strengths of this study are the prospective identification of term infants with and without evidence of intrauterine growth restriction and the measurement of the EZP size prior to any substantial zinc intake. This allowed comparison of primarily the fetal accrual of zinc in a vulnerable population with high rates of maternal undernutrition and low birthweight infants. Additionally, the availability of comparable data of EZP size at birth from a high resource setting provided an important comparison. The follow-up measurements at 6 months of age provided unique information, but the non-exclusive breastfeeding and lack of detailed dietary data limit the interpretation of EZP size in the older infants.

**Conclusions**

Contrary to our hypothesis and to our observations in premature infants in a westernized setting, we did not observe any difference in EZP size between the SGA and AGA cohort either at birth or at 6 months. The absence of an expected increase in mean total EZP size by 6 months of age, and the substantial and significant decline in the EZP sizes (adjusted for weight) in virtually all subjects from birth to 6 months of age may provide early evidence of deterioration in zinc status. The lower size (relative to body weight) of the EZP at birth in the Pakistani

infants, regardless of group, compared to prematurely born AGA infants in US supports the possibility of a lower zinc endowment at birth. The implications of these findings for understanding the potential risk of zinc deficiency in infants born to mothers at risk of poor nutrition in low resource settings, and for the utility of EZP as a biomarker of such risk, remain to be determined, ideally in controlled intervention studies with larger sample sizes and longer follow-up.

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**Table 1:** Demographic features of mother and infant pairs (small for gestational age and appropriate for gestational age)**.***

| **Characteristics** | **SGA (n=22)** | **AGA (n=22)** | **P value** |
|---|---|---|---|
| Age of mother (y) | 26.1 ± 5.9 | 25.9 ± 4.2 | 0.90 |
| Parity | 2.8 ± 2.2 | 3.6± 2.3 | 0.25 |
| Maternal height (cm) | 151.3 ± 5.0 | 153.3 ± (5.2) | 0.20 |
| Maternal weight (kg) | 48.1 ± 6.2 | 52.8 (7.9) | 0.05 |
| BMI | 21± 2.3 | 22.5 ± 3.7 | 0.14 |
| Antenatal care received (%) | 20.0 | 27.3 | 0.72 |
| Birthweight (g) | 2174 ± 228 | 3047 ± 349 | < 0.001 |
| Ponderal Index at birth | 228 ± 47.4 | 257 ± 31.2 | 0.02 |
| Gender (male %) | 68.2 | 59.1 | 0.53 |
| Exclusive breastfeeding at 6 months | 18.2% | 4.5% | |

*Data are presented as mean ± SD

**Table 2.** Mean ± SD exchangeable zinc pool size at birth and 6 months for small for gestational age and appropriate for gestational age infants

| | EZP (mg) | EZP (mg/kg) |
|---|---|---|
| **Birth** | | |
| SGA (n = 18) | 24.9 ± 19.2 | 9.78 ± 5.12 |
| AGA (n = 22) | 30.4 ± 14.8 | 10.1 ± 4.57 |
| **6 months** | | |
| SGA (n = 12) | 29.2 ± 17.8 | 4.77 ± 2.96 |
| AGA (n = 14) | 31.0 ± 16.1 | 5.59 ± 4.32 |

**Table 3:** Mean ± SD hemoglobin and plasma zinc concentrations at birth and 6 months for small for gestational age and appropriate for gestational age infants

| | **Hemoglobin (g/dl)** | **Plasma Zinc (µg/dl)** |
|---|---|---|
| **Birth** | | |
| SGA | 15.7 ± 2.8* (21) | 126 ± 97.6 (19) |
| AGA | 16.6 ± 3.0 (21) | 95.3 ± 41.6 (12) |
| **6 months** | | |
| SGA | 10.2 ± 2.3* (12) | 125 ± 47.8 (19) |
| AGA | 10.7 ± 1.7 (14) | 101 ± 54.2 (13) |

*No significant differences for comparison of group means for either variable; paired comparison indicates significant time effect ($p < 0.001$) for hemoglobin.