Maternal gestational zinc supplementation does not influence multiple aspects of child development at 54 mo of age in Peru[1–3]

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ABSTRACT

Background: Zinc is necessary for central nervous system development, and maternal zinc status has been associated with developmental differences in offspring.

Objective: The objective was to evaluate differences in cognitive, social, and behavioral function in Peruvian children at 54 mo of age whose mothers participated during pregnancy in a zinc supplementation trial.

Design: We attempted to follow up 205 children from a prenatal zinc supplementation trial and present data on 184 (90%) children—86 whose mothers took 25 mg zinc/d in addition to 60 mg iron and 250 μg folic acid and 98 whose mothers took iron and folic acid only. Following a standardized protocol, we assessed children's intelligence, language and number skills, representational ability, interpersonal understanding, and adaptive behavior and behavioral adjustment. We also assessed aspects of the mother (eg, age, education, verbal intelligence, stresses, and social support in parenting) and the home environment [HOME (Home Observation for the Measurement of the Environment) inventory].

Results: No differences were observed between any of the tests used to characterize cognitive, social, or behavioral development ($P > 0.05$). Child sex, parity, or treatment compliance did not modify the effects of supplementation on any outcomes.

Conclusion: The addition of zinc to prenatal supplements did not influence developmental outcomes in Peruvian children when assessed at 4.5 y of age. *Am J Clin Nutr* 2010;92:130–6.

INTRODUCTION

The role of zinc for healthy pregnancy outcomes has long been recognized (1, 2), but the public health importance of inadequate intakes of zinc observed in women living in resource-poor settings has not been clear (3, 4). Severe maternal zinc deficiency has been associated with spontaneous abortion and congenital malformations (eg, anencephaly), whereas milder forms of zinc deficiency have been associated with low birth weight in earlier studies but not in the majority of subsequent randomized controlled trials (5). Studies in animals and humans suggested a role of maternal zinc status in cognitive and behavioral development of the offspring (6, 7), but the literature is not consistent (8, 9).

We have conducted 2 zinc supplementation trials in Peru, where usual maternal zinc intakes are 8 mg/d (10). Although we did not observe differences in birth weight or gestational age associated with supplementation (11), we found differences in fetal neural development, assessed using electronic fetal monitoring. In study 1, which involved 55 fetuses studied at 32 and 36 wk gestation (12), fetuses of mothers receiving 15 mg supplemental zinc/d (in addition to 60 mg iron and 250 μg folic acid) showed greater fetal heart rate range, more accelerations, fewer epochs of low variability, and increased fetal movement and time spent moving. In study 2, which involved 195 fetuses monitored monthly from 20 to 38 wk gestation, fetuses of mothers receiving 25 mg supplemental zinc/d (in addition to iron and folic acid) showed steeper declines in mean fetal heart rate over gestation and steeper inclines in heart rate variability and accelerations in late pregnancy (13). This pattern of effects indicates improved neurobehavioral development in fetuses of mothers taking supplemental zinc on a regular basis.

These fetal results further suggest that zinc supplementation alters the developing nervous system in a way that may generate persistent effects on development postpartum. Significant predictive associations between aspects of fetal heart rate and motor patterns have been documented with developmental outcomes through the third year of life (14). To evaluate whether maternal zinc supplementation influenced child development, we conducted a follow-up study of the children from study 2 at 4.5 y of age to evaluate their cognitive, social, and behavioral development. We used a broad measurement array designed to evaluate both conspicuous aspects of child cognitive functioning (eg, intelligence and mathematical ability) as well as more subtle

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indicators of developmental performance (eg, indexed by linguistic ability and concept formation).

SUBJECTS AND METHODS

We conducted a double-blind randomized controlled trial of prenatal zinc supplementation in women receiving prenatal care at Centro Materno Infantil "San Jose," in Villa El Salvador, a peri-urban community in Lima, Peru. The trial was conducted between 1998 and 2000, and the main findings have been reported (13, 15). In 2003 we began a follow-up study designed to evaluate the health, nutritional status, and cognitive, social, and behavioral development of these children who, at the time of follow-up, were 54 mo of age.

In the original study, 242 women were enrolled at 10–14 wk gestation and were randomly assigned within strata (on the basis of week of gestation and parity) to receive daily supplements containing 60 mg iron (as ferrous sulfate) and 250 μg folic acid, with or without an additional 25 mg zinc (as zinc sulfate). Compliance with supplementation was high (157 $\pm$ 27 tablets during pregnancy with no difference by supplement type). Of those enrolled, 222 (90.1%) completed the pregnancy protocol, and 195 (80.6%) were included in the formal analysis of uncomplicated pregnancies (10). For the follow-up study, we attempted to locate those 195 mother-child pairs as well as 10 additional women with complicated pregnancies whose babies had survived the neonatal period and were free of congenital malformations. From this final pool of 205, we located and conducted evaluations of 184 (90%) children—86 whose mothers had received zinc supplements during pregnancy and 98 whose mothers had not. Of the 10 mother-infant pairs not included in the original analysis, we conducted evaluations on 7 pairs: 3 in the zinc group and 4 in the control group.

Protocols for the original study and the follow-up were approved by the institutional review boards of the Instituto de Investigación Nutricional (Lima, Peru) and the Johns Hopkins Bloomberg School of Public Health (Baltimore, MD).

Follow-up study

The primary outcome in this report was children's developmental status. We used a protocol developed at the Child and Family Research Section of the Eunice Kennedy Shriver National Institute of Child Health and Development for studying multiple facets of cognitive, social, and behavioral functioning in 4–5-y-old children. Specifically, we assessed intelligence, language and number skills, representational ability, interpersonal understanding, as well as adaptive behavior and behavioral adjustment. Because maternal and environmental factors influence child development, we assessed aspects of the mother (eg, age, education, verbal intelligence, stresses, social support in parenting) and the home environment to evaluate as statistical controls.

Children were evaluated at the clinic on 2 occasions within a 1-wk period and were administered the protocol tasks in a fixed order; we administered the protocol over 2 sessions so that it would not burden the children. The tests were administered by 1 of 2 Peruvian psychologists who were trained in the protocol and coding at the Eunice Kennedy Shriver National Institute of Child Health and Development and who were blinded to supplementation condition. A third psychologist recorded the sessions with a video camera for subsequent behavioral coding. Occasionally, a child would refuse to cooperate with an activity or part of an activity that would render it uncodable. As a result, the number of participants in each group varied slightly by task. In the following paragraphs, the assessments used in the current analyses are described briefly. The instruments used were either published Spanish versions or were translated and adapted to Spanish from English by using standard forward- and back-translation techniques and evaluated for "adapted equivalence" by bilingual and bicultural researchers (16–18).

Intelligence

Children's intelligence was measured by using the Spanish adaptation of the Wechsler Preschool and Primary Scale of Intelligence (19), a standardized measure of verbal and performance abilities in young children aged from 3 to 6.5 y. The verbal subtest includes scales for information, comprehension, arithmetic, vocabulary, similarities, and sentences. The performance subtest includes scales on object assembly, geometric design, block design, mazes, picture completion, and animal pegs.

Language development: bear story

The goal of this activity is have the child tell a story about a bear family to obtain indications of the child's language development and narrative ability. The child was presented with props in a consistent order (bear family, living room, kitchen, park with rabbit and duck, policeman, and doctor). The child played with the props for 10 min and was then asked to tell a story "with a beginning, a middle, and an end." Structured prompts were given if the child faltered in telling a story. For the purposes of coding, the child's bear story was divided into 3 or 4 segments: *1*) the first 5 min of play, *2*) the second 5 min of play, *3*) the child's formal story, and *4*), the child's prompted story (if needed). Each segment of the child's story was coded, and the highest rated segment was used for *1*) narrative cohesion (20) on a scale from 0 to 11 based on the complexity and elaboration of the story; *2*) narrative structure (21) on a scale from 0 to 11, which considers the presence of aspects of a mature story such as main characters, a major theme, or a temporal setting of the story; and *3*) proposition counts, or units of meaning, in the child's story. These 3 scores were standardized (mean = 0, SD = 1) and averaged to yield the narrative scale. Coder reliability [intraclass correlation (ICC)] was 0.77.

Number concepts: the counting game

A novel board game was used to investigate children's number concepts. The game involves 3 number concepts: *1*) counting, *2*) cardinality and one-to-one correspondence, and *3*) the ability to integrate 2 dimensions (counting and spatial direction). To quantify child performance in one game, the coder counted the number of times the child moved the game piece the correct number of spaces and made the correct number of moves divided by the number of turns taken per game. A second game incorporated the same skills and added the element of direction the game piece was moving on the board (ie, toward the goal or away from the goal). To quantify performance in the second game, the coder gave credit for each turn in which the child moved the correct number of spaces in the correct direction.

Scores for game 1 and game 2 were standardized (mean = 0, SD = 1) and averaged to yield the counting game scale. Coder reliability (ICC) was 0.99 for game 1 and 0.98 for game 2.

Concept formation: draw a person

The child was asked to draw a person following the standardized procedures of the Goodenough & Harris Draw-A-Person Test (22). Evaluation of the child's drawing of the human figure served as a way of measuring the complexity of his or her concept formation ability. The scoring system indicated the presence or absence of specific components (eg, head, hair, eyes, trunk, legs, and arms) as well as the detail of each part (23), and scores could range from 0 to 20. Coder reliability (ICC) was 0.99.

Interpersonal understanding: the friendship interview

To assess interpersonal understanding, the child was asked open- and close-ended questions about their best friend and friendships in general. The friendship interview was set in the context of a pretend play date. This setting provided the opportunity to probe the child's knowledge of friendship concepts within the context of the child's own friends. The questions and the coding system were developed on the basis of research by Selman (24) and Serafica (25). A single a priori scale was computed as the average of 7 items rated to reflect the child's concept of friendship: no friendship concept (0), physical interaction friendship (1), one-way friendship (2), fair-weather friendship (3), mutual relation (4), and autonomous interdependence friendship (5). Coder reliability (ICC) for 3 coders ranged from 0.88 to 0.89.

Adaptive behavior

While the child was being tested, the mother (in one case, the father) was administered the Spanish adaptation of the Vineland Adaptive Behavior Scales (26) to obtain measures of the child's current level of adjustment and functioning. In this assessment, the parent is asked to indicate to what extent the child has mastered a variety of skills in 4 major domains (communication, daily living skills, socialization, and motor behavior).

Behavioral development

We also administered the Preschool Behavior Questionnaire (27), which is a 30-item instrument designed to assess the child's behavior problems. Mothers rate items on a 3-point scale (0–2) as to the current frequency of behavior problems. The original factor structure included 3 subscales: hostile-aggressive (11 items), anxious-fearful (9 items), and hyperactive-distractible (4 items). However, Trembley et al (28) observed that a 2-factor solution (externalizing and internalizing) was a better fit to the data. Consequently, the hostile-aggressive, hyperactive-distractible, and anxious-fearful scale scores were converted to z scores (mean = 0, SD = 1), the hostile-aggressive and hyperactive-distractible z scores were averaged to produce an externalizing score, and the anxious-fearful z score was used as an internalizing score.

Covariates

We collected child and maternal age and education data from a demographic questionnaire. In addition, we administered questionnaires to assess maternal verbal intelligence, stress, and social support and the home environment because they have known relations to child development.

Maternal verbal intelligence

Mothers were administered the Peabody Picture Vocabulary Test–Revised (29). Up to 175 vocabulary words were presented verbally by a trained administrator, and for each word presented the mother chose 1 of 4 pictures to indicate the meaning of the word. Standard scores within a possible range of 40–160 (mean = 100, SD = 15) were obtained on the basis of the mothers' age.

Maternal stress

Cohen et al's (30) Perceived Stress Scale was used to measure maternal stress. The 14 items were rated for the frequency of occurrence over the last month on a scale from never (0) to very often (4). Seven of the 14 items were reverse-scored, and then all items were summed to produce a total stress scale.

Maternal social support

The Social Network Form (31) was designed to assess maternal social supports. Following Weinraub and Wolf (31, 32), we derived 2 scales: *1*) parenting support (the sum of 6 questions about the value the mother places on the parenting advice she receives from her social contacts and the amount of parenting support received from parenting/organized groups) and *2*) emotional support (the sum of 10 questions about the degree to which the mother confides in her social contacts, emotional support received from social contacts, and emotional support received from parenting/organized groups). All items were rated on 10-point scales (eg, never-always, not at all–totally).

Home environment

The Home Observation for the Measurement of the Environment (HOME) Scale (33) was used to measure both the quality and the quantity of stimulation and support that is available to a child in his or her home environment. The full HOME scale score, composed of 45 items, was adapted for use in this population. It was scored after a home visit conducted by a psychologist and involved observations of the household structure and maternal interview.

Data analyses

To assess comparability of the treatment groups, the characteristics of women and children in each group were compared by t test or chi-square analysis. Analysis of variance (ANOVA) was then used to estimate the effects of zinc supplementation on child functioning, before and after adjustment for covariates and potentially confounding factors. To examine whether the effects of zinc supplementation on the outcomes varied depending on child sex, we included sex as a factor in the ANOVA and tested the interaction between treatment group (zinc compared with no zinc) and sex (male compared with female) and also tested for effect modification by parity and treatment compliance. In all tests, statistical significance was defined as $P < 0.05$. The analyses were conducted by using SPSS version 17 (SPSS Inc, Chicago, IL).

RESULTS

Selected characteristics of the 184 children and their mothers at enrollment in the pregnancy study are presented in **Table 1**. There were no significant differences in the presented variables between the 2 groups.

A post hoc power analysis was computed before data analysis to determine whether the sample size of 186 provided sufficient power to detect a medium-sized effect in a one-factor ANOVA design (34). With an effect size of $f = 0.25$ (31), $\alpha = 0.05$, and $n = 186$, the power estimate was 0.92, indicating adequate power to detect a medium or large effect. Performance scores on child development outcome measures by treatment group are presented in **Table 2**.

No significant main effects of treatment group were observed for any child development outcome. Effect sizes (η_p^2) ranged from 0.00 to 0.02. We explored adjustment for child sex, age and birth order, selected maternal and family characteristics, and interactions of zinc with these covariates. Adjustment for these variables did not alter our conclusions with respect to treatment, and no statistically significant interactions were found. Finally, we explored the effect of supplement compliance within the zinc treatment group on child outcomes. Compliance was not significantly related to any child outcome measure (shared variance ranged from 0% to 4%).

DISCUSSION

There is continuity in neural development between pre- and postnatal periods (35, 36), and in the synactive organization of behavioral development, functioning results from increasing

TABLE 1
Selected characteristics of Peruvian women and children by type of prenatal supplement[1]

	Prenatal supplement type			
	Iron + folate + zinc		Iron + folate	
Characteristic	n	Values	n	Values
Maternal				
Total no. of tablets[2]	86	154 ± 27[3]	98	157 ± 26
Compliance (%)	85	84.4 ± 10.9	96	86.7 ± 9.7
Age (y)	83	28.3 ± 4.9	94	28.6 ± 5.1
Schooling (y)	86	11.0 ± 2.2	97	10.5 ± 2.6
Single (%)	86	20.9	98	14.3
Employment (%)	86		97	
None		69.8		73.2
Worker		16.3		20.6
Employee		14.0		6.2
Verbal IQ	84	98.1 ± 17.6	96	93.3 ± 20.8
Child				
Age (mo)	85	53.8 ± 0.2	96	53.8 ± 0.2
Girl (%)	85	48.2	96	50.0
Weight (kg)	85	17.3 ± 2.1	97	17.5 ± 2.5
Height (cm)	85	102.8 ± 3.8	97	102.5 ± 3.4
Hemoglobin (g/L)	85	122.2 ± 10.2	97	120.1 ± 9.7
Firstborn (%)	86	58.1	98	58.2
Has younger sibling(s) (%)	83	26.5	94	34.0
In preschool program (%)	86	87.2	98	81.6
Months in preschool (%)	86		98	
0		18.6		26.5
1–11		34.9		28.6
12–23		30.2		37.8
24–36		16.3		7.1
Family				
Family better off now (%)	86		96	
No		27.9		17.7
Same		20.9		27.1
Yes		51.2		55.2
Economically better off now (%)	86		98	
No		40.7		31.6
Same		20.9		25.5
Yes		38.4		42.9
Persons per room in household	86	1.7 ± 0.9	98	1.8 ± 1.3
HOME inventory	84	34.0 ± 6.7	94	32.7 ± 7.1

[1] IQ, intelligence quotient; HOME, Home Observation for the Measurement of the Environment. No significant differences by type of prenatal supplement were observed ($P > 0.05$, as assessed by t test or chi-square analysis).

[2] Assessed by observing the supplement blister packs during biweekly home visits.

[3] Mean ± SD (all such values).

TABLE 2
Children's cognitive, social, and behavioral development at 54 mo of age by type of prenatal supplement consumed by their mothers[1]

	Prenatal supplement type			
	Iron + folate + zinc		Iron + folate	
	n	Values	*n*	Values
Intelligence	85		96	
Full IQ		91.9 ± 10.0[2]		92.3 ± 10.1
Verbal IQ		85.3 ± 9.8		86.2 ± 10.3
Performance IQ		100.6 ± 11.7		100.0 ± 12.8
Language development, bear story	82	0.01 ± 0.85	96	−0.01 ± 0.91
Number concepts, counting game	78	0.01 ± 0.88	94	−0.01 ± 0.88
Concept formation, draw a person	80	8.5 ± 3.6	88	8.9 ± 3.4
Interpersonal understanding, friendship interview	74	0.33 ± 0.21	92	0.37 ± 0.28
Adaptive behavior	85		96	
Communication		86.3 ± 8.3		87.2 ± 8.4
Daily living skills		87.7 ± 9.6		87.1 ± 10.8
Socialization		102.1 ± 13.8		101.1 ± 16.7
Motor skills		96.2 ± 12.4		95.6 ± 14.9
Behavioral development	85		96	
Internalizing		0.07 ± 0.98		−0.06 ± 1.02
Externalizing		0.03 ± 0.74		−0.02 ± 0.92

[1] All values are means ± SDs. IQ, intelligence quotient. There were no significant differences by type of prenatal supplement ($P > 0.05$, as assessed by ANOVA).

[2] Mean ± SD (all such values).

hierarchical organization, progressing from autonomic control, motor activity, and behavioral states to periods of attention and interaction with environmental stimuli. Thus, as children approach school age (as is the case here), interindividual differences in play and social responsiveness, language, mechanical and math ability, and problem solving would reflect underlying differences in organization. For this reason, we chose a comprehensive approach to identify differences in functioning in these children associated with the type of supplement consumed by their mothers during pregnancy.

Zinc is a critical nutrient for central nervous system development, with multiple roles including direct roles in brain growth, brain structure for neurotransmission, and neurotransmitters involved in brain memory function (37). Zinc is found predominantly in the hippocampus, cerebellum, and prefrontal cortex, which are the areas of the brain responsible for learning and memory, posture and balance, and higher intellectual functioning. Neural influences on heart rate variability originate in the medulla oblongata and are connected with the cortex via the hypothalamus. Zinc-containing neuron systems form connections between the cortex and other brain structures, including the hypothalamus (37), and thus zinc may play an important role in the establishment of functional connections between different brain structures.

Despite this strong biological rationale, the results here indicate that the addition of zinc to the regular iron and folic acid prenatal supplements consumed by Peruvian women did not influence any developmental outcomes in their children when assessed at 54 mo of age. This lack of treatment effect was robust after adjustment for child, maternal, and environmental characteristics, and we found no evidence of treatment effects for subgroups of children (no treatment × characteristic interactions). In separate analyses, we did find continued treatment differences in autonomic function in these children when assessed at rest (LE Caulfield, N Zavaleta, F Lazarte, et al, unpublished observations, 2010). The significance of differences in child autonomic function awaits further exploration, because, as shown here, they did not translate into observable cognitive, social, or behavioral differences across children.

There are notable strengths of this study that lend credence to the reported findings. First, we have been working in a population with usual zinc intakes during pregnancy of about half that recommended, and we have shown that multiple measures of zinc status in the mother and newborn are improved with supplementation (10, 38). Indeed, compliance with supplementation was high. Second, randomly assigning women to prenatal supplement type adequately formed equivalent treatment groups at enrollment, and our ability to evaluate 90% of the sample during the follow-up suggests that selection bias did not likely affect our findings. Third, the outcomes assessed were psychometrically valid and broad, and thus selectivity, bias, and random error are not likely to have obscured any underlying differences. Fourth, the sample size per group was adequate to detect relevant differences in child functioning, and we observed no evidence that the effect of zinc supplementation differed depending on maternal or fetal characteristics or methodologic aspects of the study. The results indicate almost completely overlapping distributions of the outcome variables by prenatal supplement type. Thus, it is unlikely that our focus on measures of central tendency obscured important differences between groups at specific points in the distributions (eg, at the lower tails).

In comparison with US intelligence quotient (IQ) norms (mean = 100, SD = 15), children's full IQ and verbal IQ were between 0.5 and 1 SD below average. Children's performance IQ, however, was average. Similarly, children were rated by their mothers as ≈1 SD below average on communication and daily living skills, but socialization skills and motor skills were near average. These comparisons indicate that the children in our sample performed comparably to typical US children in some domains (eg, spatial, socialization, and motor skills) but below average in others (eg, communication and daily living skills). Direct comparisons are difficult, but these results are not inconsistent with what is known about the effects of persistent poverty on child cognitive development (39).

Our findings are also consistent with the only other such evaluation involving 5-y-old low-income US children whose mothers received 25 mg zinc/d or placebo during the latter half of pregnancy (9). In that study, supplemental zinc was associated with increased head circumference and weight at birth, but no differences were observed in mental or psychomotor development at age 5 y. Although the studies are quite different in terms of population and methods for assessing child development, together the findings suggest that maternal zinc supplementation during pregnancy does not appear to have lasting effects on child cognitive, social, or behavioral development. However, 2 other explanations are also possible. First, in both of these studies, very little is known about potential intervening factors during early childhood that may have led to findings of no difference in development at 4–5 y of age. We studied factors collected retrospectively but did not identify any that might have differentially influenced development by treatment group; however, the possibility for such influences remains. Differences in child development by supplement type could have been evident earlier during the postnatal period but were not studied systematically. The information we have from abstraction of the clinical records, however, do not provide evidence of earlier developmental differences. Second, the 2 studies were conducted in populations in which average maternal zinc intakes were 50% and ≈90% of recommended intakes. Thus, it may be true that this amount of maternal zinc intake is adequate to support child development, and differences in child development would only be detected in populations with more severe maternal zinc deficiency.

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