Zinc supplementation during pregnancy and effects on mental development and behaviour of infants: a follow-up study.

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Background Zinc deficiency is widely prevalent in developing countries. Zinc supplements given to Bangladeshi pregnant women have been shown to reduce infants' infectious disease morbidity. We assessed these infants at age 13 months to establish the effect of antenatal zinc supplementation on infant development and behaviour.

Methods The study originally consisted of 559 pregnant women who were randomly allocated to zinc (30 mg daily) or placebo (cellulose) from 4 months' gestation to delivery. The effect of zinc supplementation on pregnancy outcome and on infant growth and morbidity in the first 6 months was assessed. We then randomly selected a subsample of 168 infants from 383 who completed the study at 6 months. When babies in this subsample reached age 13 months, we assessed mental development with Bayley scales of infant development-II, rated behaviour on a modified version of Wolke's scales, and measured weight and height.

Findings When we controlled for differences between tested and non-tested participants, infants in the placebo group had higher scores on mental development index (regression coefficient=3.3, SE 1.6, 95% CI 0.2-6.5, p=0.04) and psychomotor development index (5.1, 2.4, 0.2-9.9, p=0.04) than those in the zinc-supplemented group. Zinc supplementation had no significant effect on behaviour or growth. The children's nutritional status was poor, and weight-for-age at testing was strongly related to developmental levels, which accounted for some of the treatment effect.

Interpretation Prenatal supplementation with zinc alone in poor women from Bangladesh does not seem to confer benefit on infants' mental development. Such treatment should be considered with caution.

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The authors discuss a study of the effects of zinc supplements on newborns when given to their mothers during pregnancy. It had been previously known that zinc deficiency in children impedes their development and supplements are useful in those situations. In this test, however, they found that pregnant women who had been given zinc supplements gave birth to infants who were smaller and less well-nourished.

Introduction

Zinc deficiency is widely prevalent in the developing world, where diets contain low levels of animal protein and high fibre and phytate. Zinc supplementation improves growth (1) and reduces morbidity (2) in zinc-deficient children, and there is some evidence that it improves children's development, but findings are inconsistent. (3) Pregnant women are also thought to be at high risk of zinc deficiency because of an increased physiological requirement. (4) Some investigators have noted that maternal zinc intake or plasma zinc concentration is positively related to pregnancy outcome, whereas others have failed to show an association. (5,6) Trials during pregnancy have had inconsistent findings about the effects of zinc supplementation on birthweight and length of gestation. (7)

Does zinc deficiency in pregnancy adversely affect the mental development of offspring? Results of studies in animals have shown that severe zinc deficiency during pregnancy affects brain development (8) and behaviour of offspring. (9) In an observational study of pregnant women in Egypt, maternal intake of fibre and phytate, which are inhibitors of zinc absorption, was negatively related to infants' motor development. (10) Furthermore, maternal intake of foods from animal sources was a significant predictor of the newborn baby's speed of encoding information. (11) The investigators suggested that zinc bioavailability might play a part in this relation. Fetal neurobehavioural development improves when

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zinc is added to iron and folate supplement during pregnancy. (12) However, we are unaware of any trial to assess the effect of zinc supplementation in pregnancy on subsequent mental and motor development of offspring.

In 1997, pregnant Bangladeshi women took part in a randomised controlled trial to examine the effect of zinc supplementation from the fourth month of pregnancy to term, on the outcome of pregnancy (13) and subsequent growth and morbidity of the infants in the first 6 months of life. (14) There was no benefit with regard to birthweight or gestational age at birth, but low birthweight infants whose mothers received zinc supplements had a reduced rate of infections. We took the opportunity presented in that study to examine the effect of prenatal zinc supplementation on development. We postulated that zinc supplementation of pregnant women would benefit the psychomotor and mental development and behaviour of their offspring.

Methods

The study was done in slum areas of Dhaka, which are characterised by high population density, poor housing, multifamily latrines and water sources, poor sewerage and drainage facilities, and irregular rubbish collection. The study was approved by the research and ethical review committees of International Centre for Diarrhoeal Disease Research, Bangladesh (ICDDR, B). Prior informed consent was obtained from the parents of the children.

Sampling

In the original study, a house-to-house survey was done in selected clusters of city slums. 559 pregnant women were stratified by parity (primiparous vs multiparous) and randomly assigned at 4 months of gestation to treatment or placebo until delivery.

The treatment comprised 30 mg elemental zinc daily (twice the recommended dietary allowance) in the form of zinc acetate tablets, (15) and placebo as a cellulose substance that was similar in appearance and taste to the zinc supplement. Both zinc and placebo tablets were packaged in bubble packs to facilitate compliance and counting. Health workers delivered tablets to the pregnant women once a week and counted how many were taken the previous week. A detailed history of the socioeconomic conditions was taken on enrolment, and the mothers' weight, height, and haemoglobin were measured.

410 singleton infants were born alive and were weighed within 72 h of birth. Reasons for loss of participants were: 19 stillbirths or neonatal deaths, 113 babies who moved and could not be traced, and seven sets of twins, who were excluded. (13) The infants were visited every week, and details of feeding and morbidity were obtained during these visits. Weight and length measurements were recorded monthly. At 6 months, 383 infants had completed the original study. These results are reported elsewhere. (13,14)

From the total of 383 cases a subsample of 240 children were randomly selected, 120 from each group. Sample size calculations showed that 72 children were needed in each group to detect differences of 0.5 SD in mental development index and psychomotor development index, with a power of 90% and a type 1 error of 5%. We traced the infants at 13 months of age, measured their length and weight, and assessed their behaviour, mental and psychomotor development, and stimulation in the home.

Measurements

The infants' development was assessed with the Bayley scales of infant development (BSID-II), (16) which has two subscales: mental development index (MDI) and psychomotor development index (PDI). All the infants were brought at age 13.5 months (or 1 month earlier or later than this age) to the ICDDR,B, and tested in the presence of their mothers. Children who were unwell on the day of test were treated, and tested when they recovered. One female tester, who was unaware of the children's group allocations, did all tests. The interobserver agreement between tester and trainer on 21 infants was good (intraclass correlation r=0.94 for MDI and r=0.98 for PDI).

We rated the infants' behaviour during the tests with a modified version of five scales designed by Wolke. (17) Each of the scales were nine-point ratings and included infants' activity (very still 1, overactive 9), emotional tone (unhappy 1, radiates

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happiness 9), responsiveness to examiner in the first 10 min--ie, approach (avoiding 1, friendly and inviting 9), co-operation with test procedure (resists all suggestions 1, always complies 9), and vocalisation (very quiet 1, constant vocalisation 9). During the study, the interobserver reliabilities (k) on ratings during 10% of the tests were: approach 0.7; emotional tone 0.8; activity 0.7; cooperation with test procedures 0.8; and vocalisation 0.7.

We assessed stimulation in the home with the Caldwell home inventory (HOME), (18) which was modified for Bangladesh after piloting. The intent of the questions remained the same, and most changes were made to increase variability in the study population. For example, a question in the modified HOME asked whether there was one book for adults in the home, rather than ten books (all questions have a response choice of yes or no). The inventory was given to the mothers at home in the presence of their infants by one female interviewer. Before the study began, the trainer observed 20 interviews, and interobserver reliability was high (r=0.98).

We measured weight and length with standard techniques. (19) Z scores for weight-for-age, height for age, and weight-for-height were then calculated according to National Centre for Health Statistics reference data for age and sex. (20)

Statistical analysis

We used independent sample t tests or x2 tests to compare the treatment and placebo groups. Bivariate correlations between developmental outcome variables and socioeconomic measurements were examined. To examine the treatment effect, we did multiple linear regression analyses of each of the developmental and behavioural variables, and weight-for-age, length-for-age, and weight-for-length at 13 months. We controlled for any differences on enrolment and at birth between participants who were tested and those who were not tested, and differences between the treatment groups in socioeconomic variables.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The figure shows the trial profile. Of 240 randomly selected infants, four had died before our study began, one had epilepsy and was excluded, five refused to come for further assessment, and eight were ill and by the time they recovered had exceeded the age required by the selection criteria for testing. Another 54 infants could not be found. We therefore located a total of 168 children from our subset of 240 (zinc=83, placebo=85).

[FIGURE OMITTED]

We compared the characteristics at enrolment of the mothers of the tested and untested children in each treatment group in the original 559 women. There were no differences between the tested and untested children in parental education, household assets, and mothers' haemoglobin. However, mothers' body-mass index (BMI) was higher in the untested (mean 19.2, SD 2.6) than in the tested sample (18.3, 2.4) in the zinc group (p=0.01). We then examined the difference between the tested and untested sample for all children born in the study for their characteristics at birth: sex and length did not differ between the two samples, but the untested children tended to be lighter than the tested children in the placebo group (untested mean 2.52 kg, SD 0.4, tested 2.6 kg, 0.3, p=0.06). Additionally, growth and morbidity were much the same in tested and non-tested children in the first 6 months. Differences between lost and tested samples were taken into account in the analyses.

The zinc and placebo groups did not differ significantly in mothers' parity, parental schooling, paternal occupation, breastfeeding at 6 months, and age of introduction of complementary feeding. The placebo group tended to have more days ill with impetigo and dysentery than the zinc group, but this difference was not significant. The placebo group had significantly higher maternal BMI at 4 months of gestation (p=0.045) and more household assets on enrolment than the zinc group (p=0.02); this group was also less likely to have other children younger than 6 years in the home (p=0.002) (table 1). The quality of psychosocial stimulation at home (HOME), was slightly higher in the placebo group than in the tested group (p=0.1). Infants born to mothers in the placebo group were heavier at birth (p=0.02), and at 6 months of age (p=0.02) but their lengths for age were much the same. However, in the original study the differences between the placebo and zinc groups in weights at birth and at 6 months were not significant. (13,14)

Measurements of the childrens' weights and lengths at the time of Bayley tests also showed that the placebo group had better nutritional status. They had larger weights-for-age (p=0.005) and weights-for-length (p=0.02) than the zinc group. A significant difference in MDI (p=0.046), PDI (p=0.006), emotional tone (p=0.03) and cooperation with test procedures (p=0.03) was recorded in favour of the placebo group (table 2).

Bivariate correlations were calculated between Bayley scores and biological and social background variables. MDI correlated significantly with HOME (r=0.21, p=0.008), no other children less than 6 years old in the home (0.16, p=0.045), and weight at 6 months (0.2, p=0.009). PDI correlated significantly with HOME (0.19, p=0.02), assets (0.20, p=0.05), no other children less than 6 years old in the home (0.16, p=0.02), maternal BMI at 4 months (0.18, p=0.02), and birthweight (0.16, p=0.04) and weight at 6 months (0.34, p<0.0001)

To examine the treatment effect, we did multiple regression analyses of MDI, PDI, and each behaviour rating. Since there was a significant difference in maternal BMI in the original sample between the untested and the tested group, we entered maternal BMI in all regressions. We offered household assets, HOME, no other children younger than 6 years in the home, and birthweight and weight-for-age at 6 months (all of which were different between the treatment groups and significantly related to at least one of the Bayley indices) in a second step, and then entered treatment (model 1, table 3). Zinc had a significant negative effect on MDI and PDI. Weight-for-age at 6 months was the only other variable that had a significant effect on both MDI and PDI. Absence of other children under 6 years old in the home had a significant effect on co-operation and emotional tone, and the treatment effect was not significant.

Generally, the children's nutritional status deteriorated throughout the year, and 126 (73%) of them were moderately or severely underweight at testing. To examine the relation between weight at 13 months and Bayley scores and treatment, we did additional regressions of Bayley scores, which were similar to the above regressions but used only weight-for-age at both 6 and 13 months in the second step, and then entered treatment (model 2, table 3). Weight-for-age at 13 months had a significant effect on MDI and PDI, with a greater effect on PDI than on MDI. When weight-for-age was taken into account, the effect of zinc was reduced and no longer significantly associated with MDI or PDI.

We then assessed the effect of treatment on weight-for-age at 13 months in a multiple regression analysis. In the first step, we entered BMI, and then birthweight, assets, HOME, and presence of other children younger than 6 years; treatment was then entered. Birthweight (regression coefficient=0.7, SE 0.2, 95% CI 0.4-1.1, p=0.0001), no other children less than 6 years old in the home (0.04, 0.01, 0.01-0.06, p=0.004), HOME (20.5, 0.1, 20.8 to 20.3, p=0.0001), and BMI (0.07, 0.03, 0.01 to 0.1, p=0.02) all had a significant effect, but treatment did not. Similar regressions of weight-for-length also showed no significant effect of treatment.

Discussion

We have shown that zinc supplementation of pregnant women was associated with lower Bayley scores in their infants than in the placebo group. The difference remained significant when we controlled for differences between tested and non-tested participants, and between treatment groups. The deficit was small, about a third of 1 SD. Children of zinc-treated mothers were also less co-operative during the test and fussier than the placebo group, but this difference disappeared when we controlled for social background variables. The findings were surprising, since we had expected zinc supplementation to have a beneficial effect.

We achieved good quality control of developmental testing and behavioural ratings. However, the study of which this trial was an extension was a randomised treatment trial of pregnant women, and we took a random sample of offspring from the treated and placebo groups who remained in the study at age 6 months. Therefore, if we are to infer a causal relation between treatment and outcomes, the sample of children tested at age 13 months has to be equivalent to the original randomised samples in any factor that could affect children's development. We controlled for any difference between group characteristics on enrolment and at birth, between tested and untested children, and any background variables that

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differed between treatment groups. We were concerned that the placebo group was significantly heavier at birth and at age 6 months than the zinc-treated group in our subsample but not in the original sample. However, when we controlled for these variables, the significant effects of zinc treatment remained. Nevertheless, the treated and placebo samples might have varied in other unmeasured variables, which could have affected the children's development. For example, we recorded parental education, but there was little variation because many parents had not been to school. Parental intelligence quotient might have been a more sensitive measure than parental education, but was not assessed. Additionally, we had no information on what happened to the children between ages 6 and 13 months.

The Bayley test was standardised in the USA; however, it has been frequently used in other countries. Despite their poor environments, the scores of these Bangladeshi infants on the mental scale were in the normal range according to the test standards. We noted similar scores in a previous study in the same population. (21) Infants in traditional but poor societies often have high scores on developmental tests in the first year of life, and decline in the second year. (22) The motor scores of the infants were low and were more closely related to their weights than were the mental scores. Poor nutritional status is likely to affect motor development scores before it affects mental development. (23)

We could not locate any other study in which a negative effect of prenatal zinc supplementation on infants' development or behaviour was seen. Findings about zinc supplementation in early childhood have been inconsistent, but there is evidence of benefits to development and behaviour in some populations. (3) Research in animals has also shown that zinc deficiency might affect behaviour detrimentally. (9) However, further suggestion of a small negative effect of zinc treatment on infants' development comes from a companion study of zinc supplementation given to Bangladeshi infants from the same neighborhood. (21) In that study, infants were given zinc from 1 to 6 months of age, and a very small but significant negative effect on the children's mental development scores on the Bayley test at age 13 months was observed. Although the supplement was given to infants in one study and pregnant women in the other, the finding of a small but negative effect of zinc on children's development in both studies is worrisome.

The mechanism that links zinc treatment in pregnancy to children's development is unknown. Several hypotheses exist: zinc might have a direct effect on brain development in the womb, or could cause deficiencies or imbalances of other micronutrients secondary to competitive interactions. For example, absorption of iron and copper from the intestine is limited by zinc. (24-27) The iron status of the mothers might have been compromised, and the iron status of the mother could determine their child's iron status. (28) Iron-deficiency anaemia during infancy is associated with poor mental development. (29) However, haemoglobin concentrations in mothers did not differ between the zinc and placebo groups at 7 months of gestation. Unfortunately, we had no later measurements of haemoglobin in the mothers, and no information on the infants' iron or zinc status at the time of testing, and this absence of data seriously hinders any exploration of mechanism.

In this study, the children's nutritional status fell throughout the year. Weight-for-age had a significant detrimental effect on the children's mental and motor development, and this effect increased between 6 and 13 months of age. Although undernutrition is generally accepted to be detrimental to children's development, (30) our findings emphasise the serious nature of the difficulty in populations with high proportions of underweight children. Since zinc supplementation in infants has a beneficial effect on growth1 and morbidity, (2) and supplementation of mothers was associated with reduced morbidity in low birthweight infants in this study, (14) our findings complicate policy making. However, they could have arisen by chance, or might be specific to this population, which has a high rate of undernutrition. Undernourished pregnant women obviously require more than zinc alone. The next step would be to examine the effect of interventions (including supplementation) to improve maternal nutritional status during pregnancy on a broad range of outcomes including infants' development.

Table 1: Characteristics of families at enrolment and infants at birth

	Zinc group (n=83)	Placebo group (n=85)
Parental characteristics		
Mothers' body-mass index (kg/[m.sup.2])	18.3 (2.4)	19.0 (2.2)

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Mothers' haemoglobin (g/L)	114 (14)	116 (18)
Mothers with no schooling	55 (66%)	56 (66%)
Fathers with no schooling	42 (51%)	45 (53%)
Fathers occupation, unskilled	56 (68%)	49 (58%)
Social background		
Assets	1.7 (0.7)	2.0 (0.8)
Absence other children under 6 years in the home	28 (34%)	49 (58%)
HOME	68.3 (4.8)	69.6 (5.1)
Characteristics of infants at birth		
Sex (boys)	39 (47%)	45 (53%)
Gestational age (weeks) *	39.1 (2.0)	39.4 (1.8)
Weight (g)	2484 (375)	2614 (344)
Length (cm)	46.6 (2.0)	47.2 (1.8)
Ponderal index (g3100 per [cm.sup.3])	2.4 (0.2)	2.5 (0.2)

	95% CI of mean difference	p
Parental characteristics		
Mothers' body-mass index (kg/[m.sup.2])	-1.40 to -0.02	0.05
Mothers' haemoglobin (g/L)	-0.78 to 0.21	0.30
Mothers with no schooling	14 to 214	0.50
Fathers with no schooling	17 to 213	0.40
Fathers occupation, unskilled	25 to 24	0.10
Social background		
Assets	-0.49 to -0.04	0.002
Absence other children under 6 years in the home	29 to 240	0.0002
HOME	-2.76 to 0.26	0.10
Characteristics of infants at birth		
Sex (boys)	29 to 21	0.30
Gestational age (weeks) *	-0.88 to 0.29	0.30
Weight (g)	-239.3 to -20.1	0.02
Length (cm)	-1.1 to 0.08	0.08
Ponderal index (g3100 per [cm.sup.3])	-0.11 to 0.01	0.10

Data are mean (SD), unless otherwise indicated. * Assessed by history of last menstrual period at enrolment.

Table 2: Characteristics of the infants at ages 6 and 13 months

	Zinc (n=83)	Placebo (n=85)

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Age at test	13.7 (0.4)	13.7 (0.4)
Anthropometry		
6 months weight-for-age (Z score)	-1.5 (0.9)	-1.1 (0.9)
6 months weight-for-length (Z score)	-0.29 (0.8)	-0.08 (0.9)
6 months length-for-age (Z score)	-1.6 (0.9)	-1.4 (0.9)
13 month weight-for-age (Z score)	-2.7 (1.0)	-2.3 (1.0)
13 month weight-for-length (Z score)	-1.1 (0.8)	-0.8 (0.8)
13 month length-for-age (Z score)	-2.9 (1.1)	-2.6 (1.0)
Developmental outcomes		
MDI	99.34 (11.2)	102.64 (10.0)
PDI	88.7 (17.4)	95.7 (15.0)
Approach	6.63 (1.76)	6.53 (1.4)
Activity	5.1 (1.2)	5.2 (1.0)
Emotional tone	5.25 (1.9)	5.9 (2.0)
Cooperation	5.2 (1.8)	5.8 (1.9)
Vocalisation	4.9 (1.3)	4.98 (1.7)

	95% CI of mean difference	p
Age at test	-0.12 to 0.10	0.90
Anthropometry		
6 months weight-for-age (Z score)	-0.6 to -0.07	0.02
6 months weight-for-length (Z score)	-0.4 to 0.04	0.10
6 months length-for-age (Z score)	-0.5 to 0.04	0.10
13 month weight-for-age (Z score)	-0.67 to -0.12	0.005
13 month weight-for-length (Z score)	-0.54 to -0.05	0.02
13 month length-for-age (Z score)	-0.59 to 0.70	0.10
Developmental outcomes		
MDI	-6.54 to -0.06	0.05
PDI	-12 to -2.08	0.006
Approach	-0.39 to 0.58	0.70
Activity	-0.43 to 0.24	0.60
Emotional tone	-1.24 to -0.07	0.03
Cooperation	-1.17 to -0.05	0.03

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Vocalisation	-0.53 to 0.41	0.80

Data are mean (SD), unless otherwise indicated.

Table 3: Significant regression coefficients (B), standard errors (SE) and 95% CI from regression of MDI, PDI, cooperation and emotional tone (n=168)

	MDI B (SE, 95% CI)	p
Model 1 *		
Mothers' BMI	-0.7 (0.4, 21.4 to 0.04)	0.06
6 months weight (Z scores)	2.6 (0.9, 0.9 to 4.4)	0.004
No children <6 years	..	..
Treatment	3.3 (1.6, 0.2 to 6.5)	0.04
Model 2 ([dagger])		
Mother's BMI	-0.9 (0.3, -1.6 to -0.02)	0.009
13 months weight (Z scores)	4.4 (0.9, 2.7 to 6.1)	0.0001
Treatment	2.6 (1.5, -0.4 to 5.6)	0.09
	PDI B (SE, 95% CI)	**p**
Model 1 *		
Mothers' BMI	..	..
6 months weight (Z scores)	5.5 (1.3, 2.8 to 8.1)	0.0001
No children <6 years		
Treatment	5.1 (2.4, 0.2 to 9.9)	0.04
Model 2 ([dagger])		
Mother's BMI	..	..
13 months weight (Z scores)	8.7 (1.3, 6.2 to 11.1)	0.001
Treatment	3.8 (2.3, -0.7 to 8.2)	0.09
	Cooperation B (SE, 95% CI)	**p**
Model 1 *		
Mothers' BMI	..	..
6 months weight (Z scores)	..	..
No children <6 years	-0.7 (0.3, -1.3 to -0.1)	0.03
Treatment	0.5 (0.3, -0.01 to 1.1)	0.1
Model 2 ([dagger])		
Mother's BMI	..	..
13 months weight (Z scores)	..	..
Treatment	..	..
	Emotional tone B (SE, 95% CI)	**p**
Model 1 *		
Mothers' BMI	..	..
6 months weight (Z scores)	..	..
No children <6 years	-0.7 (0.3, -1.3 to -0.1)	0.03
Treatment	0.5 (0.3, -0.1 to 1.1)	0.09
Model 2 ([dagger])		
Mother's BMI	..	..
13 months weight (Z scores)	..	..
Treatment	..	..

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n=168. BMI=body-mass index; MDI=mental development index; PDI=psychomotor development index. * BMI entered, then birth weight, weight-for-age at 6 months, no children under 6 years, assets, and HOME, offered then treatment entered. ([dagger]) BMI entered, then weight-for-age at 6 and 13 months offered in second step, then treatment entered.

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Contributors

S McGregor and J D Hamadani designed and implemented the study, and gathered the data, with the help of G J Fuchs and S Osendarp. All authors analysed the data and wrote the report.

Conflict of interest statement

None declared.

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