Zinc supplementation during pregnancy and effects on growth and morbidity in low birthweight infants: a randomised placebo controlled trial

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Summary

Background Infant malnutrition and mortality rates are high in less-developed countries especially in low-birthweight infants. Zinc deficiency is also widely prevalent in these circumstances. We aimed to assess the effect of daily zinc supplements given to pregnant mothers on their infants' growth and morbidity.

Methods We did a double-blind, placebo controlled, randomised trial in 199 and 221 Bangladeshi infants whose mothers took 30 mg daily elemental zinc or placebo, respectively, from 12 to 16 weeks' gestation until delivery. Infants were followed up until 6 months of age. We obtained data for morbidity every week by mothers' recall. Infants' anthropometric measurements were done every month, and their serum zinc was assessed at 1 and 6 months of age.

Findings Infants of mothers who received zinc during pregnancy had at age 6 months reduced risks compared with those in the placebo group for acute diarrhoea (risk ratio 0·84; 95% CI 0·72–0·98), dysentery (0·36; 0·25–0·84), and impetigo (0·53; 0·34–0·82). These reductions were seen in low-birthweight infants but not in those with normal birthweight. There were no differences in infant growth or serum zinc concentrations between treatment groups.

Interpretation Maternal zinc supplementation during pregnancy resulted in a reduction of the health risks in Bangladeshi low-birthweight infants, although this intervention did not improve birthweight. Whether zinc should be added to usual antenatal supplements in regions with high rates of low birthweight should be reviewed.

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Introduction

Micronutrient deficiency, including zinc, contributes greatly to impaired growth, health, and development of children in less-developed countries.[1] Zinc supplementation during infancy partly reverses the adverse effects of zinc deficiency, and is associated with a small improvement in growth,[2] improved immunity, and reduced morbidity due to infectious diseases.[3] These effects were especially pronounced in low-birthweight (ie, <2500 g) infants, who might be vulnerable to the effects of zinc deficiency because of their reduced stores of hepatic zinc metallothionein.[4,5]

Infants with a low-birthweight have high rates of morbidity and mortality because of infectious diseases and impaired immunity, and are at increased risk of growth failure and abnormal cognitive development as infants. They are also estimated to account for about a third of all deaths in the first year of life in less-developed countries.[6] The high prevalence of low birthweight, which is mainly attributable to intrauterine growth retardation in developing countries, is related to intergenerational cycles of malnutrition.[7] Thus, the adverse effects of nutritional deprivation and perhaps zinc deficiency might begin before birth, and the most effective time for an intervention might, therefore, be the antenatal period.

Low maternal blood zinc concentrations during pregnancy are associated with an increased risk of low birthweight and preterm delivery in some[8] but not all studies.[9] Results of studies in developed countries of zinc supplementation and pregnancy outcome are also inconsistent.[10] We have previously reported that zinc supplementation during pregnancy in a very poor, urban population of Bangladesh did not result in improved birthweights.[11] In rhesus monkeys, low maternal plasma zinc concentrations were associated with reduced infant growth.[12] Antenatal zinc deficiency in mice and rhesus monkeys resulted in reduced lymphoid organ sizes, IgG concentrations, and blood lymphocytes in the offspring.[13] Studies are required in man to investigate the relation between pregnancy and zinc status, prenatal zinc supplementation, and infant growth and health.

We, therefore, did a study in infants from poor urban areas in Bangladesh, whose mothers received either daily zinc supplements or placebo during pregnancy, and assessed the effect of supplementation on the infants' growth and morbidity from infectious diseases during the first 6 months of life. The study was done in a population in whom the proportion of babies with low birthweight was 43%.[11]

Methods

Study design and population

We did our study in selected poor urban areas of Dhaka, characterised by a very high population density, poor housing, inadequate sewerage, and low socioeconomic status.[14] The population is young and most people are illiterate.[14]

Pregnant women were enrolled between 12 and 16 weeks' gestation, stratified by parity, and randomly assigned to receive either daily zinc supplements or placebo until delivery. We used a computer-generated random letter to assign the mothers to each group. The codes remained unknown to investigators and participants until the study was completed. Singleton neonates were included in postnatal surveillance.[11] Doctors measured weight and length, and calculated gestational age of the babies within 72 h after delivery.[11]

We calculated gestational ages using date of last menstrual period as recalled by mothers at enrolment and with the Capurro method.[15] We classified the babies as small or appropriate for gestational age using the tenth percentile of a US fetal growth curve as a cutoff,[16] and recorded data on infant morbidity every week. Details of infant feeding were obtained every 2 weeks, and infants were classified as either exclusively (breastmilk only), predominantly (breastmilk and water or sugar water), or partly (breastmilk and other complementary fluids) breastfed, or not breastfed. We also recorded the age that complementary foods were introduced.

A total of 410 singleton infants with known birthweights (low birthweight <2500 g, normal birthweight ⩾2500 g) were included in the postnatal surveillance. We also included another ten infants whose mothers had taken supplements and were followed up throughout pregnancy, but for whom valid birthweight measurements were not available. Thus, 199 infants of mothers on zinc supplements and 221 of mothers on placebo were enrolled. Sample-size calculations had indicated that a minimum of 360 infants (180 in each group) was needed to detect a 15% difference in mean weight gain during the first 6 months of life, a 15% difference in mean number of episodes of diarrhoea, or a 20% difference in mean serum zinc concentrations between the groups, with 80% power and a type I error of 5%.

Supplements

During pregnancy, mothers on zinc supplements received 30 mg elemental zinc per day. The placebo was a cellulose substance indistinguishable from the zinc supplement in both appearance and taste. All supplements were prepared in bubble packs of ten tablets each (ACME Ltd, Dhaka, Bangladesh) and two laboratories independently confirmed the zinc content of both tablets. Health-care workers gave the women a week's supply of zinc tablets or placebo, every week. The women were instructed to consume 1 tablet daily between meals with no other vitamin or mineral supplements. Consumption of iron and vitamin or mineral supplements was uncommon in this population.[11] At baseline (12–16 weeks' gestation) only 11 (2%) women reported taking iron supplements and 45 (8%) reported taking other vitamin or mineral supplements during the past 14 days. According to general practice in Bangladesh, iron and folate supplements (200 mg ferrous sulphate and 200 μg folate per day) had been provided by the study team to women with a haemoglobin concentration of less than 90 g/L at 4 months' gestation (14 women, 2·5%) and 7 months' gestation (40, 8·5%). Compliance with zinc or placebo treatment was 86%, as assessed by counting the remaining tablets at the next weekly visit, and by monthly unannounced checks in a 10% subsample.

Blood analyses

We took blood samples from non-fasting infants at 1 and 6 months of age by antecubital venipuncture in the morning using trace-mineral-free plastic syringes, stainless steel needles, and plastic tubes. We separated the serum within 6 h after samples were taken and stored serum at −20°C. Before analysis we diluted the samples (1/12) with 0·03% polyoxyethylene 23 laryl ether and HNO_3 (10 mmol/L). Zinc concentration was measured by flame atomic absorption spectrophotometry. We established a standard curve with a commercial zinc reference (BDH Laboratory Supplies, London, UK), in concentrations of 0·1, 0·25, 0·5, and 1·0 mg/L, and used commercially obtained serum with known concentrations of zinc as a measure of quality control. The coefficient of variation of the measurements was always less than 5%.

Anthropometry

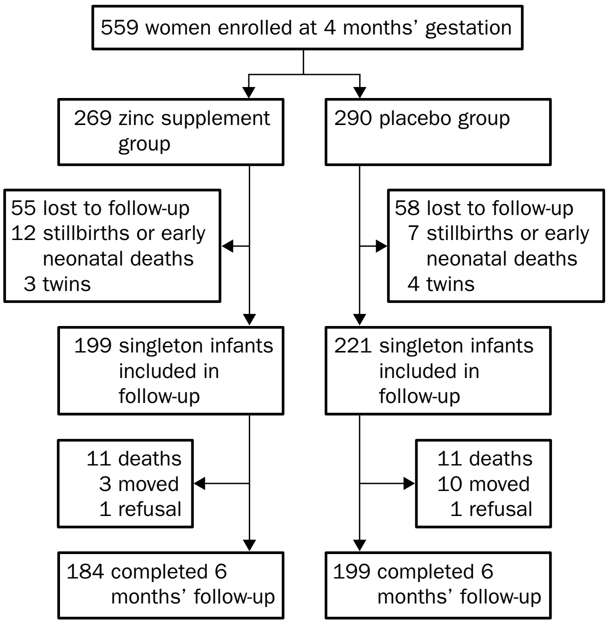
During monthly home visits, we weighed infants to the nearest 10 g on beam-balance scales (Seca 725, Hamburg, Germany) that were calibrated daily against standard weights. Recumbent lengths were measured to the nearest 0·1 cm on a length board, and head, chest, and arm circumferences were measured to the nearest mm with numeral insertion tapes. We recorded for all indices the mean of two readings as the measured value. Anthropometric measurements were done by trained field workers. Intra-observer and inter-observer variations were acceptable, with coefficients of variation less than 2% for all anthropometric indices. We defined underweight (low weight for age), stunting (low length for age), and wasting (low weight for length) as standard deviation scores (*Z* scores) of less than −2·00 compared with the US National Center for Health Statistics reference charts[17] using EPI Info software (version 6.1, 1994, Centers for Disease Control, Atlanta, GA, USA).

Morbidity assessment and outcome definitions

During home visits trained non-medical interviewers asked detailed questions on the infant's history during the past week of respiratory infections, diarrhoea, fever, skin infections, and other illnesses. To distinguish impetigo from other skin diseases, interviewers asked mothers whether the infants had any signs of this disease, using photographs showing clinical signs of impetigo of various degrees of severity as a guide. Infants were examined for signs of dehydration during monthly visits. The respiration rate was recorded, and a second record was taken for infants with a respiratory rate of more than 60 per min.

The same trained fieldworkers obtained the data, which registered nurses checked manually and coded. Doctors examined infants who required medical treatment using standard treatment protocols, and referred them to appropriate health-care facilities if necessary. Information was recorded about standard infant vaccinations received through the expanded programme of immunisation or other sources. We defined an infant as having acute lower respiratory infection if reported symptoms included cough, difficult breathing, or both, with or without fever lasting more than 1 day, and rapid breathing or chest indrawing. Upper-respiratory-tract infection was diagnosed if the infant had reported symptoms of cough or difficult breathing, with or without fever for more than 1 day, which was not associated wtih rapid breathing or chest indrawing, or a reported cough for more than 1 day with nasal discharge. Acute diarrhoea was defined as symptoms of unusually loose or unusually frequent stools, or both, as reported by the mother. If the stool contained blood the episode was classified as dysentery. Diarrhoea lasting for 14 days or longer was defined as persistent.

We calculated the actual number of surveillance days by subtracting the days on which no recall data were



Trial profile

available from the total days of follow-up. When a mother had been absent for more than 15 days (two consecutive visits), recall data was only obtained for 14 days before the previous interview. Infants were classified as recovered if they were symptom free for at least 3 consecutive days.

Statistical analysis

We did a multiple stepwise regression to identify variables that contributed significantly to the variation in the different outcome variables and those that required adjustment as confounders in the multivariate analysis on the effect of zinc supplementation. Possible interactions between treatment and infant's birthweight, sex, or serum zinc status were assessed by introduction of separate interaction terms in the linear regression models. On the basis of these outcomes, separate models were used for subgroups of birthweight.

We assessed differences in mean total weight and length gain between infants of mothers who took zinc supplements or placebo using ANCOVA with the outcome variables (eg, total weight gain) as dependent variables and treatment group (zinc or placebo group) as independent variable. Baseline values were added as covariates (SPSS version 7.5). We tested differences in anthropometric indices and *Z* scores at 1, 2, 3, 4, 5, and 6 months of age, with ANCOVA for repeated measurements.

To compare differences between treatment groups in frequency of diseases, we used a Poisson regression model with number of episodes as dependent variable, treatment group as independent variable, and total days of actual surveillance as off-set term included in the model. We added potential confounders to the regression models as additional independent variables (epidemiological graphics estimation and testing package, EGRET, SERC, Seattle, WA98105, 1991).

Duration of disease was calculated for all infants as percentage of actual surveillance days ill. We used the non-parametric Kruskal-Wallis test to compare differences in duration of illness between infants from zinc and placebo groups. Since the distribution of length of illness was highly skewed, we used log-transformed values in the multivariate regression models to enable control for

Maternal characteristic	Zinc supplement		Placebo	
	Lost to follow-up (n=15)	Follow-up completed (n=184)	Lost to follow-up (n=22)	Follow-up completed (n=199)
Maternal age (years)	22·0 (4·8)	23·8 (5·8)	23·5 (5·5)	22·4 (5·5)
Nulli parae	5 (31%)	35 (19%)	6 (27%)	48 (24%)
Socioeconomic status				
Poor	4 (25%)	72 (39%)	4 (18%)	82 (41%)
Very poor	8 (56%)	74 (40%)	12 (55%)	70 (35%)
Body mass index (kg/m²)	19·2 (2·8)	18·8 (2·5)	19·5 (3·4)	19·1 (2·3)
MUAC (mm)	224 (27)	227 (24)	231 (33)	226 (23)
Haemoglobin (g/L)	113 (15)	115 (15)	116 (12)	116 (14)
Serum zinc concentration (μmol/L)	14·4 (2·8)	16·1 (5·4)	15·0 (4·9)	16·4 (6·1)

Values are mean (SD) unless otherwise indicated; MUAC=mid upper arm circumference.

Table 1: **Selected baseline characteristics of 420 pregnant mothers**

covariates. Before log-transformation a constant was added to all duration values to eliminate zero values. P values less than 0·05 were regarded as statistically significant.

Results

After randomisation 139 women were lost to follow-up, including 7 twin births and 19 infant deaths. Of the infants that were included in the follow-up after birth 22 died and 13 were lost to follow-up because their families moved away from the study area. The mothers of two infants refused further participation in the study. No differences were recorded between the groups in numbers or reasons for not completing the study (figure 1). The maternal baseline characteristics were similar for infants lost to follow-up and those who completed follow-up (table 1). Mothers of infants who completed follow-up were significantly older (p=0·016) at enrolment in the zinc supplement group than the placebo group (table 1). No other differences in baseline characteristics were seen between the two treatment groups. 184 infants in the zinc and 199 in the placebo group completed 6 months' follow-up (figure 1). Infants lost to follow-up were included in the analysis of morbidity for the days on which observations were available.

All infants were breastfed throughout the study but the rate of exclusive breastfeeding was low because of early introduction of water given with breastmilk. At 24 weeks of age, 55 (13%) of all infants were exclusively or predominantly breastfed, and 353 (84%) were partly breastfed. There was no relation between breastfeeding status at 1 or 6 months of age and main outcome variables in stepwise multiple regression analysis to identify potential confounding variables. There was a relation with age at water introduction for some variables and with that at complementary food introduction for other outcome variables. Therefore, those variables were controlled for in the multivariate analysis. No differences in infant serum zinc concentrations were seen between the zinc and placebo groups at 1 month (15·1 μmol/L [SD 5·3] *vs* 15·8 μmol/L [5·5]) or at 6 months of age (11·4 μmol/L [2·5] *vs* 11·7 μmol/L [2·5]).

Between birth and 6 months of age changes in weight (3·49 kg [0·77] *vs* 3·56 kg [0·77]), length (15·2 cm [2·0] *vs* 15·4 cm [2·1]), and head circumferences (8·0 cm [1·2] *vs* 8·1 cm [1·3]) did not differ between infants of mothers on zinc or placebo. Average weight increase (0·58 kg/month [0·13] *vs* 0·59 kg/month [0·13]) and linear growth (2·5 cm/month [0·3] *vs* 2·6 cm/month [0·4]) did not differ between infants from the zinc or placebo

Disease	Zinc supplement	Placebo	RR (95% CI)	p
Acute diarrhoea				
Total episodes	267	346		
Episode/infant				
All infants*	1·5 (1·9)	1·9 (2·1)	0·84 (0·72–0·98)	0·037
Low-birthweight infants†	1·4 (1·8)	2·2 (2·3)	0·68 (0·53–0·87)	0·002
Normal-birthweight infants‡	1·6 (1·9)	1·6 (1·9)	1·04 (0·84–1·29)	NS
Persistent diarrhoea				
Total episodes	49	49		
Episode/infant				
All infants*	0·3 (0·7)	0·3 (0·6)	1·13 (0·76–1·68)	NS
Low-birthweight infants†	0·2 (0·5)	0·3 (0·6)	0·88 (0·46–1·71)	NS
Normal-birthweight infants‡	0·3 (0·8)	0·2 (0·6)	1·47 (0·86–2·50)	NS
Dysentery				
Total episodes	7	22		
Episode/infant				
All infants*	0·04 (0·2)	0·1 (0·4)	0·36 (0·25–0·85)	0·019
Low-birthweight infants†	0·04 (0·2)	0·1 (0·4)	0·26 (0·07–0·99)	0·049
Normal-birthweight infants‡	0·04 (0·3)	0·1 (0·4)	0·46 (0·14–1·44)	NS
Cough				
Total episodes	668	768		
Episode/infant				
All infants*	3·9 (1·9)	4·1 (1·8)	0·95 (0·68–1·06)	NS
Low-birthweight infants†	4·2 (2·4)	3·9 (2·1)	0·99 (0·84–1·16)	NS
Normal-birthweight infants‡	3·7 (1·7)	4·0 (1·8)	0·94 (0·82–1·08)	NS
Acute lower respiratory infection				
Total episodes	106	134		
Episode/infant				
All infants*	0·7 (1·2)	0·8 (1·3)	0·89 (0·69–1·15)	NS
Low-birthweight infants†	0·6 (1·2)	1·5 (6·6)	0·97 (0·64–1·45)	NS
Normal-birthweight infants‡	0·7 (1·1)	0·7 (1·0)	0·87 (0·62–1·24)	NS
Impetigo				
Total episodes	30	61		
Episode/infant				
All infants*	0·2 (0·6)	0·3 (0·8)	0·53 (0·34–0·82)	0·005
Low-birthweight infants†	0·1 (0·5)	0·3 (0·8)	0·39 (0·18–0·85)	0·018
Normal-birthweight infants‡	0·2 (0·7)	0·3 (0·8)	0·64 (0·37–1·10)	NS

RR=risk ratio estimated with Poisson regression adjusted for socioeconomic status, parity, baseline serum zinc, and age at introduction of water. Values are in mean (SD) unless otherwise indicated. *n=196 (zinc) and 214 (placebo). †n=88 and 214. ‡n=106 and 84. Birthweight was unknown in three infants.

Table 2: **Frequency of diseases for infants from zinc supplement and placebo groups during first 6 months of life**

Infant morbidity	Proportion of days ill (%)				
	Zinc supplement		Placebo		p
	Mean (SD)	Median (range)	Mean (SD)	Median (range)	
Acute diarrhoea					
All*	4·8 (6·0)	2·5 (0·0–29·7)	5·0 (6·3)	2·9 (0·0–36·1)	NS
Low birthweight†	4·4 (6·1)	1·5 (0·0–29·7)	6·0 (7·1)	3·5 (0·0–36·1)	0·008
Normal birthweight‡	5·1 (6·0)	3·1 (0·0–24·8)	4·2 (5·6)	2·3 (0·0–21·1)	NS
Persistent diarrhoea					
All*	3·2 (7·8)	0·0 (0·0–42·9)	2·9 (7·8)	0·0 (0·0–58·6)	NS
Low birthweight†	2·8 (6·7)	0·0 (0·0–30·3)	2·7 (6·2)	0·0 (0·0–29·5)	NS
Normal birthweight‡	3·6 (8·6)	0·0 (0·0–42·9)	2·6 (7·8)	0·0 (0·0–58·6)	NS
Dysentery					
All*	0·2 (1·2)	0·0 (0·0–10·5)	0·5 (2·0)	0·0 (0·0–14·8)	0·047
Low birthweight†	0·1 (1·0)	0·0 (0·0–8·8)	1·0 (2·3)	0·0 (0·0–14·8)	NS
Normal birthweight‡	0·2 (1·4)	0·0 (0·0–10·5)	0·4 (1·6)	0·0 (0·0–10·6)	NS
Cough					
All*	37·6 (24·1)	32·5 (0·0–91·8)	37·7 (24·2)	36·3 (0·0–100·0)	NS
Low birthweight†	39·5 (25·1)	36·4 (0·0–91·8)	36·5 (26·1)	36·2 (0·0–96·5)	NS
Normal birthweight‡	35·4 (22·8)	29·9 (0·0–91·1)	36·3 (22·9)	36·3 (0·0–100·0)	NS
Acute lower respiratory infection					
All*	7·7 (16·0)	0·0 (0·0–86·3)	8·8 (15·4)	0·0 (0·0–100·0)	NS
Low birthweight†	7·0 (13·4)	0·0 (0·0–60·5)	10·8 (18·5)	0·0 (0·0–100·0)	NS
Normal birthweight‡	8·0 (17·6)	0·0 (0·0–86·3)	7·2 (12·5)	0·0 (0·0–55·3)	NS
Impetigo					
All*	0·9 (3·2)	0·0 (0·0–24·1)	1·5 (4·4)	0·0 (0·0–39·0)	0·013
Low birthweight†	0·6 (2·5)	0·0 (0·0–18·1)	1·8 (5·4)	0·0 (0·0–39·0)	0·047
Normal birthweight‡	1·0 (3·6)	0·0 (0·0–24·1)	1·4 (3·6)	0·0 (0·0–21·2)	NS

p values are from linear regression analysis with log transformed values, controlled for birthweight, gestational age, age at introduction of complementary food, maternal baseline body mass index, household socioeconomic status, and maternal baseline serum zinc. *n=199 (zinc) and 221 (placebo). †n=90 and 88. ‡n=106 and 129. Only infants with known birthweight were included in subgroup analysis.

Table 3: **Proportion of days ill during first 6 months of life**

groups, respectively. At 6 months of age, *Z* scores for infants in the two groups were closely similar for mean length for age (−1·47 [0·91] *vs* −1·41 [0·96]), weight for age (−1·36 [0·87] *vs* −1·28 [0·92]), and weight for length (−0·29 [0·77] *vs* −0·28 [0·82]). There were no interactions with anthropometric outcomes and infant birthweight, sex, or serum zinc concentration.

The 420 infants were followed up for a total of 65 771 (93%) of a possible 70 560 days (31 378 days in the zinc supplement and 34 393 days in the placebo group). Infants of mothers taking zinc supplements had fewer episodes of acute watery diarrhoea, dysentery, and impetigo than those of mothers in the placebo group. For infants who were followed up for 15 days or longer the risk of these diseases was reduced by 16% for acute diarrhoea, 64% for dysentery, and 47% for impetigo (table 2). Infants of mothers on zinc had fewer days ill with dysentery and impetigo than those whose mothers were on placebo (table 3). Maternal zinc supplementation had no effect on frequency and duration of cough or acute lower respiratory infection in the infants.

When data were analysed separately for infants with low and normal birthweight (for whom birthweights were available) larger reductions were seen in low-birthweight but not normal-birthweight infants for the frequency of acute diarrhoea, dysentery, and impetigo in the zinc supplement than the placebo group. In low-birthweight infants of mothers receiving zinc, the risk of disease was reduced by 32% for acute diarrhoea, 74% for dysentery, and 61% for impetigo. By contrast, in normal-birthweight infants no differences in frequency of disease were seen between zinc and placebo groups. Likewise, low-birthweight infants in the zinc group had significantly fewer days ill with acute diarrhoea and impetigo than those in the placebo group, whereas no differences between the groups were seen in the normal-birthweight infants (table 3).

For low-birthweight infants born at term but with intrauterine growth retardation, we recorded significant reductions in zinc versus placebo groups for acute diarrhoea (risk ratio 0·59; 95% CI 0·44–0·79), all diarrhoeal episodes (0·61; 0·46–0·81), and impetigo (0·27; 0·10–0·76) whereas no differences between the groups were seen in preterm low-birthweight infants (<37 weeks' gestation n=46), for acute diarrhoea (1·19; 0·68–2·10), for all diarrhoea (1·10; 0·66–1·83), or for impetigo (0·95; 0·22–4·10).

Discussion

In our study population zinc supplementation during the last two trimesters of pregnancy reduced the frequency and duration of acute diarrhoea, dysentery, and impetigo especially in low-birthweight infants, but had no effect on infant growth during the first 6 months of life. Previously reported results from this study showed that prenatal zinc supplementation did not affect maternal weight gain during pregnancy or infant birthweight in this malnourished population.[11] 181 (43%) of our infants had low birthweight (<2500 g) and were, therefore, at increased risk of malnutrition and premature mortality mainly because of diarrhoea and respiratory tract infections.[6,18] The improvements in morbidity were substantial (32% and 74% reduced risk of acute diarrhoea and dysentery, respectively), and greater than the 18% reduction in frequency of diarrhoeal disease attributed to zinc supplementation during childhood.[3] The reductions in our study were also larger than the 28% in number of days ill due to diarrhoea reported with infant zinc supplementation in an intervention study in low-birthweight, full-term infants in Brazil.[4]

The improvements in morbidity in low-birthweight infants were due to reductions in intrauterine-growth-retarded and not preterm low-birthweight infants, although sample sizes for premature infants were too small for firm conclusions. Infants who are full-term with intrauterine growth retardation and those who are premature show different patterns of growth, morbidity, and mortality. Premature infants have better growth potential and gradually approach a normal weight.[7] By contrast, intrauterine-growth-retarded infants who receive optimum feeding achieve a limited catch-up growth only in the first few months of life.[19]

We noted effects on both frequency and duration of diarrhoeal diseases and impetigo, perhaps through enhancement of immune function in utero, as suggested by results in animals. Antenatal zinc deprivation in rats resulted in low immunoglobulin serum concentrations, especially IgA, IgG_2, and IgM in offspring at 6 months of age; these abnormalities can persist into adulthood.[13] Maternal zinc status during pregnancy might also affect in-utero acquisition of antibodies, because of the importance of zinc in placental transport.[20]

Zinc supplementation in infants and children is known to have beneficial effects on both prevalence and incidence of diarrhoeal diseases and pneumonia. These effects are thought to be attributable to improved immunity and intestinal mucosal regeneration and function, including decreased intestinal permeability.[3] The effects of zinc supplementation on impetigo might also be attributable to improved epidermal barrier function.[21]

Maternal zinc supplementation in our study population had an effect on postnatal morbidity but not on infant birthweight or postnatal growth. Maternal protein and energy supplementation in East Java also benefited infant growth but did not affect birthweight.[22] However, trials in Mexico[23] and Jamaica[24] of infant rather than prenatal zinc supplementation resulted in reduced infant morbidity and hospital admissions, but had no effect on infant growth. Results from a study in Peru also suggest that zinc supplementation during pregnancy has no effect on birthweight, but improves maternal and infant zinc status,[25] and might have enhanced immunity, as shown by increased concentrations of immunoglobulins in cord blood.

The effect of zinc on growth might be attributable to a direct role of zinc in protein synthesis and gene expression,[2] but may also result secondarily from reductions in morbidity and an increase in appetite.[26] In our study the 6-month follow-up might have been too brief to detect this effect.

Findings from studies of zinc supplementation during childhood have shown a small effect on growth, especially in children with low height for age or plasma zinc concentrations.[2,26] By contrast, in undernourished populations in Mexico,[23] Jamaica,[24] and Uganda,[27] zinc did not have an effect on infant growth. Zinc might not have been the primary growth-limiting nutrient in these populations, or in our study population.

Serum zinc concentrations at 1 and 6 months of age in our population were similar to those recorded in older infants and children in Ethiopia and Chile;[26,28] however, they were higher than those for children in India[29] and for infants who were small for gestational age in Chile.[5] Mothers in our study had high serum zinc concentrations during pregnancy. Although serum zinc is not a good measure of body zinc status,[30] these concentrations suggest that our infants were not profoundly zinc deficient. This possibility could account for the absence of a growth effect of zinc in our population. Most infants in our study were predominantly or partly breastfed. In more-developed countries, zinc deficiency is rare in full-term breastfed infants during the first few months of life.[31]

Our results suggest that infants of mothers supplemented with zinc during pregnancy are still born small, but might have a less compromised immune system than those of mothers who are not supplemented. Low birthweight, therefore, might be mainly an indicator of risk rather than direct cause of morbidity and mortality. In this respect, a small neonate would not be as disadvantaged if it were not for the adverse health outcomes later in life that are associated with low birthweight.[7] In intervention studies with the aim of reducing the frequency of low birthweight, investigators have restricted their assessments mainly to an effect on birthweight rather than the consequences of low birthweight.[10] Our findings suggest that future antenatal intervention studies should continue observations beyond the neonatal period.

Our results show a positive and clinically relevant effect of maternal zinc supplementation during pregnancy on infant morbidity, especially in low-birthweight infants, and might potentially contribute to a reduction in the disadvantaged health outcomes of these infants. Our findings could have important implications for child health and survival programmes in less-developed countries and, consequently, consideration should be given to the addition of zinc to regular antenatal supplements in regions with a high prevalence of low birthweight.

Contributors

All authors designed the trial and revised the manuscript. Saskia Osendarp was the principal investigator, implemented the study, and prepared the final paper with George Fuchs. Joop van Raaij, Joseph Hautvast, and Abdullah Bagui gave advice on design and analysis. Gary Darmstadt did the additional analysis on impetigo.

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