Zinc Deficiency in Pregnancy and Fetal Outcome
Dheeraj Shah, MD, DNB, and H.P.S. Sachdev, MD, FAMS

Maternal zinc deficiency during pregnancy has been related to adverse effects on progeny, and there are data showing that mild to moderate zinc deficiency (as assessed by available indicators) is quite common in the developing world. Observational data relating zinc deficiency to adverse fetal outcome have produced conflicting results, mainly because of the lack of a valid indicator of zinc deficiency in pregnancy. Studies of human pregnancy and zinc supplementation, including those from developing countries, have failed to document a consistent beneficial effect on fetal growth, duration of gestation, and early neonatal survival. Preliminary results from unpublished studies in developing countries have also proven to be discouraging. However, recent data and some preliminary findings indicate a beneficial effect of maternal zinc supplementation on neonatal immune status and infant morbidity from infectious diseases, and there is also preliminary evidence that zinc supplementation may prevent congenital malformations (cleft lip/palate). With respect to neurobehavioral development, the evidence is conflicting, with only one study reporting a positive outcome. More research is required to assess the benefits of the large-scale introduction of zinc supplementation during pregnancy on congenital malformations, immune functions, neurobehavior, and overall neonatal survival in countries where zinc deficiency is a problem. Currently available information does not support the routine use of zinc supplementation to improve pregnancy outcome.

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INTRODUCTION

Zinc is a constituent of more than 70 metalloenzymes and plays a critical role in normal growth and development, cellular integrity, and many biological functions, including protein synthesis and nucleic acid metabolism. Zinc is believed to be important for fetal growth, development, and immune function. This review examines the possibility that a deficiency of zinc during pregnancy can adversely affect outcome.

There is scant reliable information regarding the magnitude of zinc deficiency in pregnant women, largely because of a lack of consensus on the appropriate indicators of zinc status during pregnancy. Although severe zinc deficiency is rare, it is estimated that mild to moderate deficiency is common in several regions of the world. However, in the absence of a reliable marker for zinc deficiency, there is no direct evidence for this estimate.

Zinc nutriture, which is most commonly assessed by plasma zinc concentrations, is different in pregnant women than in non-pregnant women. Plasma zinc concentration begins to decline in early pregnancy and continues to decline until term, when it is about 35% below that in non-pregnant women. There are discrepancies concerning the rate of decline, which may reflect the varying zinc status among the women studied. This decline in zinc levels has been attributed to hemodilution, decrease in the level of zinc binding protein, hormonal changes during pregnancy, and the active transport of zinc from the mother to the fetus. All of these factors make serum zinc a less reliable indicator of zinc nutriture during pregnancy. Using serum zinc as an indicator of body zinc nutriture, recent data showed that zinc deficiency (serum zinc < 70.0 µg/dL) is common in both pregnant and non-pregnant urban, rural, and tribal women in India. Dietary zinc intake in pregnant women has also been used as an indicator of deficiency. In 1996, Tamura and Goldenberg reported mean dietary zinc intakes in pregnant non-vegetarians to be around 10.0 mg/d in 27 studies from various parts of the world. At that time, the US Recommended Dietary Allowance (RDA) was 16 mg/d. Most of these studies were conducted in the...
United States and the United Kingdom; the intake in developing countries, where many people are vegetarians, is usually much lower.\cite{8-10} Caulfield et al.\cite{11} estimated that 82% of pregnant women worldwide are likely to have inadequate intakes of zinc.\cite{11} This estimate was derived from the usual intakes reported in the literature and from an estimated distribution of zinc required by women to meet their normative needs during pregnancy (11.5 ± 1.75 mg/d).\cite{7} However, this derivation is a crude overestimate, since it is based on higher body weights and greater usual intakes of zinc in pregnant women from developed countries.

Recently, the US RDA of zinc for pregnant women was revised to 12 mg/d for women up to the age of 18 years and 11 mg/d for women above 19 years of age.\cite{12} This recommendation accounts for the zinc accumulation by maternal and embryonic/fetal tissues, particularly during the latter part of pregnancy. This calculation assumes average fractional absorption of zinc to be 27%, with no significant increase during pregnancy. However, the absorption of zinc from predominantly vegetarian diets in developing countries is lower than that from non-vegetarian diets. The variations in these status indicators are most likely due to the amount of phytate, fiber, calcium, or other inhibitors of zinc absorption in the vegetarian diets. The requirement for dietary zinc may be as much as 50% greater for vegetarians—particularly for strict vegetarians, whose major food staples are grains and legumes and whose dietary phytate to zinc molar ratio exceeds 15 to 1.\cite{12} Lack of sufficient data precludes separate recommendations for zinc for vegetarians on the basis of the presence and concentration of other nutrients and food components.\cite{12}

It has been suggested that supplementation trials should be used to provide a reliable estimate of the magnitude of maternal zinc deficiency, since currently available methods do not. However, currently available supplementation studies in the literature do not permit even an approximate estimate.

**CONSEQUENCES OF ZINC DEFICIENCY**

Animal experiments indicate that maternal zinc deficiency upsets both the sequencing and efficiency of parturition. An increased incidence of difficult and prolonged labor, hemorrhage, uterine dystocia, and placental abruption has been documented in zinc-deficient animals.\cite{13-15} These effects may be mediated by the defective functioning of estrogen via the estrogen receptor, which contains a zinc-finger protein.\cite{16} The dysfunction of estrogen impairs uterine contractions, cervical ripening and dilatation, maintenance of fetal membrane, and amniotic fluid integrity,\cite{17,18} all of which adversely affect fetal outcome. Zinc is also essential for the normal growth and development of the fetus,\cite{19,20} so it is plausible that maternal zinc deficiency may cause increased fetal loss, congenital malformations, low birth weight, intrauterine growth retardation, and preterm delivery.

**Survival**

Studies in experimental animals and case reports of acrodermatitis enteropathica have documented increased fetal loss and neonatal mortality with severe maternal zinc deficiency.\cite{15,21,22} However, observational studies linking maternal zinc deficiency with fetal outcome are scarce and have produced conflicting results. There is very little information on the effect of zinc supplementation on fetal loss or neonatal mortality, as most zinc supplementation trials were not designed to study this problem. The Cochrane review of zinc supplementation trials during pregnancy did not document a significant effect of zinc supplementation on neonatal survival.\cite{23} A recent cluster-randomized trial from Nepal evaluated the effect of maternal micronutrient supplementation (in various combinations) on fetal loss and neonatal mortality.\cite{24} None of the supplements reduced fetal loss. Among preterm infants, folic acid alone or in combination with iron reduced mortality in first 3 months of life, but there was no additional benefit of adding zinc to the combination.

From what little evidence is available, it appears that subclinical zinc deficiency, which is prevalent in the developing world, is unlikely to influence fetal loss and neonatal mortality to any significant effect. However, improvement in subsequent childhood survival may be plausible: recently emerging data document better immunocompetence and lower infectious disease morbidity in children receiving perinatal zinc supplementation.

**Congenital Malformations**

In 1966, Hurley et al.\cite{25} documented a teratogenic effect, particularly on the central nervous system, of zinc deficiency in pregnant rats.\cite{25} Since then, numerous studies have confirmed the important anti-teratogenic role of zinc in animals. Experimental data indicate that even in zinc-sufficient or borderline-deficient animals, stressful events such as infection can result in the sequestration of body zinc, making it unavailable for the growing fetus. If this happens during a critical period of organ development, the “sequestration-induced deficiency” can prove teratogenic for the fetus.\cite{26}

Epidemiological data and case reports in humans support the experimental observations that severe zinc deficiency can cause fetal malformations that can be reversed by supplementation with oral zinc.\cite{22,27-29} Hambridge et al.\cite{22} reviewed pregnancy outcomes in women
with acrodermatitis enteropathica and reported that out of every seven pregnancies, there was one abortion and two malformations, suggesting that the human fetus is also susceptible to the teratogenic effect of severe zinc deficiency. Brenton et al. suggested that these malformations could be prevented by treating the mothers with zinc antenatally.

There are few well-controlled studies in humans evaluating the causal relationship between zinc deficiency and fetal malformations. Most of the data in this context are retrospective and have produced mixed results (Table 1). In the largest of these investigations, 430 fetuses and infants with neural tube defects (NTDs) were compared with 429 normal controls. Maternal intake of pre-conceptional vitamins, minerals, and food supplements was recorded. The authors reported a reduced risk of NTDs with increased total pre-conceptional zinc intake (odds ratio [OR] = 0.65; 95% confidence interval [CI] 0.43–0.99). These benefits were independent of other confounders such as folate intake and sociodemographic factors. However, these data should be interpreted with caution, as zinc nutriture in this study was assessed by the recall method, and it remains unclear whether increased zinc intake, or another nutrient or combination of nutrients highly correlated with zinc intake in the diet, is causally associated with reduced risk of NTDs. A study from India evaluated serum and scalp hair zinc levels in mother-baby pairs from 80 newborn babies with NTDs and 80 healthy controls. There was no significant difference in maternal serum zinc levels, but the hair zinc levels of the affected babies and their mothers were significantly lower (P = 0.003 and P = 0.02, respectively) red blood cell zinc concentrations than controls.

The supplementation trials are inadequate to validly assess any effect of zinc supplementation in reducing congenital malformations. In a Cochrane review of supplementation trials, 6 out of 350 babies in the supplemented group and 10 out of 333 in the control group had congenital malformations (OR = 0.56; 95% CI 0.21–1.53). However, this meta-analysis did not have a sufficient sample size to reliably assess the effect on congenital malformations. Also, none of the trials commenced supplementation sufficiently early or were of sufficient magnitude to effectively address the outcome of congenital malformations.

Preliminary results from a large study being conducted in East Timor, Indonesia to specifically address the problem of congenital malformations suggest a significantly lower incidence of cleft lip/palate in children of mothers who were given zinc supplementation compared with mothers given placebo (1.18% vs. 0%). The final analyses and publication of the results of that study will be extremely useful.

Based on the data available to date, a definite conclusion cannot be drawn as to whether the deficiency of zinc alone during pregnancy is teratogenic in humans. The studies are mostly retrospective and have not been well controlled. Further, no reliable method of estimating mild to moderate zinc deficiency in pregnant women is available. Thus, the effectiveness of zinc supplementation in preventing fetal malformations remains unclear.

**Fetal Growth and Duration of Gestation**

Many studies have reported an association between maternal zinc nutriture and birth weight of babies, both in animal and human populations. In humans, there is no consensus as to whether maternal zinc nutriture is associated with fetal growth. Of 46 studies reporting an association between maternal plasma, serum, or leukocyte zinc concentration and fetal growth (expressed either as birth weight or above a cutoff point such as the 10th percentile), 23 (50%) reported a positive relationship; however, the other half found no such relationship. Of the 18 studies from developing countries, 10 showed a positive relationship between maternal zinc nutriture and birth weight of the babies. In a study from Tamil Nadu, India, there was no significant difference in the mean plasma, red blood cell, or white blood cell zinc levels between mothers who gave birth to small-for-gestational age babies and those who delivered appropriate-for-gestational age babies. The presence of predisposing factors for intrauterine growth retardation also did not influence the maternal zinc levels. This lack of agreement may be due to differences in timing of sampling, laboratory methods and quality, sample size, and underlying zinc nutriture of the populations.

The results of 15 zinc supplementation trials (Table 2) have not shown a consistently significant improvement in weight, length, or head circumference at birth or a reduction in small-for-gestational age infants. Many of these subjects were from well-nourished populations in developed countries, and thus the studies did not address the basic issue of improvement in fetal growth in zinc-deficient populations. Six of the studies were conducted in poor women of developing countries. Ross et al. studied pregnancy outcomes in 65

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<tr>
<th>Study</th>
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<th>Indicator of Zinc Status</th>
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<tr>
<td>Cavdar et al., 1988&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Turkey</td>
<td>29/20</td>
<td>Mothers giving birth to child with NTDs&lt;sup&gt;*&lt;/sup&gt;</td>
<td>Maternal serum and hair zinc</td>
<td>Significantly ($P &lt; 0.05$) lower mean maternal serum and hair zinc concentrations in the NTD group compared with control mothers and non-pregnant women</td>
<td>In a subgroup of infants from the study, hair levels of zinc were found to be significantly ($P &lt; 0.05$) higher, whereas serum zinc levels were significantly ($P &lt; 0.01$) lower in cases; this presents a confusing picture about the role of zinc in NTDs</td>
</tr>
<tr>
<td>Bower et al., 1992&lt;sup&gt;32&lt;/sup&gt;</td>
<td>USA</td>
<td>54/128</td>
<td>Mothers of infants with NTDs</td>
<td>Maternal hair zinc</td>
<td>No evidence of an association between postpartum maternal hair zinc and offspring with NTDs</td>
<td>Role of other nutrients such as folic acid not controlled for</td>
</tr>
<tr>
<td>Hambidge et al., 1993&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Denver</td>
<td>27/108</td>
<td>Mothers of infants with NTDs</td>
<td>Serum zinc preconceptionally and at 12 weeks</td>
<td>No difference between serum zinc levels in cases and controls preconceptionally or in the first trimester of pregnancy</td>
<td>Prospective study using stored serum samples from women enrolled for a multivitamin supplementation study</td>
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<tr>
<td>McMichael et al., 1994&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Australia</td>
<td>69/592</td>
<td>Fetuses with NTDs</td>
<td>Maternal serum zinc</td>
<td>Higher ($P &lt; 0.05$) mean maternal serum zinc concentration in cases than controls</td>
<td>The study suggested an increased risk of NTDs in women with very high serum zinc levels, but no variation within the normal ranges; it remains unclear whether these high levels reflect deficient maternal-to-fetal transfer of zinc or better maternal zinc nutriture</td>
</tr>
<tr>
<td>Velie et al., 1999&lt;sup&gt;35&lt;/sup&gt;</td>
<td>USA</td>
<td>430/429</td>
<td>Mothers with NTD-affected infants</td>
<td>Maternal dietary zinc intake</td>
<td>Reduced risk for NTDs with increased total pre-conceptional zinc intake (quintile 5 vs. quintile 1; OR = 0.65; 95% CI 0.43–0.99)</td>
<td>Questionnaire-based study subject to reporting and recall biases; it remains unclear whether increased zinc intake or another nutrient or combination of nutrients highly correlated with zinc intake in the diet is causally associated with reduced NTD risk</td>
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Table 1. (Cont’d) Case-Control Studies of Maternal Zinc Nutriture and Congenital Malformations

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<th>Study</th>
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<tr>
<td>Srinivas et al., 2001³⁶</td>
<td>India</td>
<td>80/80</td>
<td>Newborns with NTDs and their mothers</td>
<td>Maternal and newborn serum and hair zinc</td>
<td>Significantly ($P &lt; 0.001$) lower hair zinc levels in the affected babies and their mothers; no differences observed in serum zinc levels</td>
<td>Discrepancy between serum and hair levels of zinc found in the study again suggests lack of availability of a valid indicator of zinc nutriture</td>
</tr>
<tr>
<td>Groenen et al., 2003³⁷</td>
<td>Netherlands</td>
<td>27/49</td>
<td>Pregnancies complicated by spina bifida</td>
<td>Amniotic fluid zinc</td>
<td>Significantly ($P &lt; 0.05$) higher mean amniotic fluid zinc concentrations in the cases at 15 weeks; no difference at 38 weeks</td>
<td>Derangement in zinc transfer to the fetus suggested as a mechanism for spina bifida; however, amniotic fluid level is a very crude marker of actual fetal conditions</td>
</tr>
<tr>
<td>Cengiz et al., 2003³⁸</td>
<td>Turkey</td>
<td>14/14</td>
<td>Women with second trimester termination due to fetal NTDs</td>
<td>Maternal serum zinc</td>
<td>Cases had significantly ($P &lt; 0.001$) lower serum zinc than controls (62.48 ± 15.9 vs. 102.6 ± 23.7)</td>
<td>Small sample size; cases also had low selenium and high copper levels, suggesting a complex interaction of micronutrients in causation of this defect</td>
</tr>
<tr>
<td>Krapels et al., 2004³⁹</td>
<td>Netherlands</td>
<td>84/102</td>
<td>Children with cleft lip with or without cleft palate and their mothers</td>
<td>Mother and children’s RBC zinc</td>
<td>Significantly lower RBC zinc concentrations in cases ($P = 0.003$) and their mothers ($P = 0.02$); low maternal RBC zinc concentration ($&lt;189$ μmol/L) increased the risk of CLP (OR = 2.0; 95% CI 0.8–4.8); children with low RBC zinc concentrations ($&lt;118$ μmol/L) were more likely to have CLP (OR = 3.3; 95% CI 1.3–8.0)</td>
<td>The other parameter studied (serum myo-inositol) had a stronger effect on risk of CLP; the contribution of other nutrients such as folic acid cannot be ruled out conclusively</td>
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*Mainly anencephaly.

CI = confidence interval; NTD = neural tube defect; OR = odds ratio; RBC = red blood cell
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<td>Hunt et al., 1984&lt;sup&gt;46&lt;/sup&gt;</td>
<td>USA</td>
<td>Randomized, double-blind, zinc and vitamin and mineral supplements vs. vitamin and mineral supplements alone</td>
<td>213 (107/106)</td>
<td>20 mg/d (variable from time of registration to antenatal clinic until delivery)</td>
<td>No difference in birth weight, low birth weight, or preterm birth</td>
<td>Double-blind with few exclusions after entry; sample size inadequate to confirm or reject an effect on any specific pregnancy outcome</td>
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<td>Hunt et al., 1985&lt;sup&gt;47&lt;/sup&gt;</td>
<td>USA</td>
<td>Randomized, double-blind, zinc and vitamin and mineral supplements vs. vitamin and mineral supplements alone</td>
<td>138 (70/68)</td>
<td>20 mg/d for the last two trimesters of pregnancy</td>
<td>No difference in birth weight</td>
<td>Conducted in setting of a developed country with very little risk of zinc deficiency; too many exclusions in the final analysis</td>
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<tr>
<td>Ross et al., 1985&lt;sup&gt;48&lt;/sup&gt;</td>
<td>South Africa</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>65 (32/33)</td>
<td>4.3–12.9 mg/d before 20 weeks of gestation until delivery</td>
<td>No difference in birth weight or duration of gestation</td>
<td>Intervention and control group were not comparable, as those in the treatment group weighed considerably less than those in the control group at 20 weeks of gestation</td>
</tr>
<tr>
<td>Kynast and Saling, 1986&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Germany</td>
<td>Randomized, unblinded, untreated women served as controls</td>
<td>524 (179/345)</td>
<td>20 mg/d (variable)</td>
<td>Increase of 82 g birth weight but not statistically significant; significant ($P &lt; 0.05$) difference in LGA, SGA, and preterm</td>
<td>Poorly controlled; conducted in setting of a developed country with very little risk of zinc deficiency</td>
</tr>
<tr>
<td>Cherry et al., 1989&lt;sup&gt;50&lt;/sup&gt;</td>
<td>USA</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>556 (268/288)</td>
<td>30 mg/d from before 25 weeks of gestation until delivery</td>
<td>No difference in birth weight; reduced rate of prematurity in zinc-supplemented compared with placebo</td>
<td>Reduced prematurity rates restricted to underweight multipara ($P = 0.008$) and normal weight primipara ($P = 0.05$); no benefit in underweight primipara, possibly because of other limiting factors</td>
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Table 2. (Cont’d) Summary of Zinc Supplementation Trials on Fetal Growth and Duration of Gestation

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<tr>
<td>Mahomed et al., 1989</td>
<td>UK</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>494 (246/248)</td>
<td>20 mg/d from before 20 weeks of gestation until delivery</td>
<td>No difference in birth weight or SGA</td>
<td>Double-blind with few exclusions after entry; sample size inadequate to confirm or reject an effect on any specific pregnancy outcome</td>
</tr>
<tr>
<td>Robertson et al., 1991</td>
<td>UK</td>
<td>Random formal-allocation, double-blind, placebo-controlled</td>
<td>134 (72/62)</td>
<td>62 mg/d from before 18 weeks of gestation until delivery</td>
<td>No difference in birth weight, low birth weight, high birth weight, LGA, or SGA</td>
<td>Conducted in the setting of a developed country with very little risk of zinc deficiency; small sample size</td>
</tr>
<tr>
<td>Simmer et al., 1991</td>
<td>UK</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>56 (30/26)</td>
<td>22.5 mg/d from the last two trimesters of pregnancy</td>
<td>Increase of 170 g in birth weight but not significant; significant decrease in SGA</td>
<td>Pregnant women at risk of delivering an SGA baby selected for the study; sample size inadequate to confirm or reject an effect on any specific pregnancy outcome</td>
</tr>
<tr>
<td>Garg et al., 1993</td>
<td>India</td>
<td>Randomized, unblinded, untreated women served as controls</td>
<td>168 (106/62)</td>
<td>45 mg/d (variable from the day of reporting until delivery)</td>
<td>Significant (300–800 g; ( P &lt; 0.001 )) difference in birth weight and duration of gestation (( P &lt; 0.01 )); effect related to duration of supplementation</td>
<td>Poorly controlled, small sample size, and high loss to follow-up</td>
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<td>Goldenberg et al., 199555</td>
<td>UK</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>580 (294/286)</td>
<td>25 mg/d from 19 weeks of gestation until delivery</td>
<td>Significant benefit in birth weight (126 g; ( P = 0.03 )), low birth weight, and head circumference (0.4 cm; ( P = 0.02 )); no difference in SGA or preterm</td>
<td>Low-income pregnant women with low serum zinc concentrations at entry into prenatal care included in the trial; effect occurred predominantly in women with low body mass index</td>
</tr>
<tr>
<td>Jonsson et al., 199656</td>
<td>Denmark</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>1206 (585/621)</td>
<td>44 mg/d from before 20 weeks of gestation until delivery</td>
<td>No difference in birth weight, LGA, SGA, or preterm</td>
<td>Excluded 40% of participants due to poor compliance</td>
</tr>
<tr>
<td>Caulfield et al., 199957</td>
<td>Peru</td>
<td>Randomized, double-blind zinc added to iron and folate vs. iron and folate alone</td>
<td>1016 (521/495)</td>
<td>15 mg/d from 10–24 weeks of gestation until delivery</td>
<td>No difference in duration of pregnancy, birth weight, preterm delivery, post-term delivery, low birth weight, high birth weight, head circumference, chest circumference, crown-heel length, mid-upper arm circumference, or skin-fold thickness</td>
<td>Well-controlled, conducted in setting of poor overall nutriture; maternal zinc concentrations remained lower than well-nourished populations even after zinc supplementation; higher doses might have been needed to improve outcome</td>
</tr>
<tr>
<td>Osendarp et al., 200058</td>
<td>Bangladesh</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>559 (269/290)</td>
<td>30 mg/d from 4 months (12–16 weeks) of gestation until delivery</td>
<td>No difference in birth weight, low birth weight, preterm, SGA, length, head, chest, or mid-arm circumference</td>
<td>Conducted in a malnourished population with low dietary intake of poorly bioavailable zinc; no effect demonstrated even with dosage almost twice the RDA; substantial dropout rate; more nulliparous women were lost to follow-up than women who had previously given birth, which may have resulted in a lower number of low-birth-weight infants</td>
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Zulu women in South Africa and reported no significant difference in birth weight between zinc-supplemented and control groups. However, in that study, the two populations were not identical in risk for low-birthweight babies, as the mothers in treatment group weighed considerably less than those in the control group at 20 weeks of gestation. Garg et al. observed a 300 to 800 g difference in birth weight in 106 Indian mothers who were supplemented with 45 mg/d elemental zinc compared with 60 unsupplemented controls. However, this was a poorly controlled study, the sample size was small, and there was high loss to follow-up at final analysis, making it difficult to draw conclusions. Caulfield et al. enrolled 1295 pregnant mothers with low zinc status in Lima, Peru in a placebo-controlled trial of supplementation with 15 mg of elemental zinc and found no differences in duration of pregnancy (39.4 ± 2.2 vs. 39.5 ± 2.0 weeks) or birth weight (3267 ± 461 vs. 3300 ± 498 g) between zinc-supplemented and control groups. In the same study population, it was found that although mothers receiving zinc supplementation had a higher serum zinc concentration than controls, the maternal zinc concentrations remained lower than values reported for well-nourished populations. It was concluded that higher doses of zinc may be needed to further improve the maternal zinc status of women in developing countries.

Osendarp et al. conducted a double-blind, placebo-controlled trial in 559 malnourished Bangladeshi women from the Dhaka slums, who were randomized to receive 30 mg/d of elemental zinc or placebo. Their results showed that although serum concentrations tended to be higher in the zinc-supplemented group than in the placebo group, there was no significant effect of treatment on infant birth weight, length, gestational age, or head, chest, and mid-upper arm circumferences. The study was conducted in a malnourished population in which the dietary zinc intake was low and poorly bioavailable and the dosage used was double the recommended dietary zinc intake for pregnant women.

In the Cochrane systematic review of five published methodologically sound randomized controlled trials, zinc supplementation had no significant effect on small-for-gestational age (relative risk [RR] = 0.9; 95% CI 0.64–1.28), low birth weight (RR = 0.74; 95% CI 0.56–1.06), or any other measure of growth. There was a small benefit (RR = 0.74; 95% CI 0.50–0.98) in terms of preventing preterm birth. Overall, there were some improvements in small-for-gestational age and low birth weight that suggested a benefit to zinc supplementation, but these did not reach statistical significance. It was suggested that trials of zinc supplementation should be conducted in regions of the world where an overall

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<td>Christian et al., 200359</td>
<td>Nepal</td>
<td>Double-blind, cluster-randomized; five different micronutrient regimens compared</td>
<td>4926 (982 in the zinc group)</td>
<td>25 mg/d from the day of detection of positive HCG urine pregnancy test until delivery</td>
<td>No additional advantage of adding zinc to iron and folic acid supplements in terms of birth weight, low birth weight, or prematurity</td>
<td>Small sample size meant only to pick up a large difference (250 g) in the birth weight between the two groups; 15% follow-up loss</td>
</tr>
<tr>
<td>Hafeez et al., 2005</td>
<td>Pakistan</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>241 (121/121)</td>
<td>20 mg/d from 10–16 weeks of gestation until delivery</td>
<td>No significant difference in birth weight or other data between the two groups</td>
<td></td>
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</tbody>
</table>

LGA = large-for-gestational age; SGA = small-for-gestational age

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deficiency of zinc is common. Since the date of the last significant update of this review, the results of at least four other trials from developing countries have been published, all of which have failed to show a significant or even marginal benefit of zinc supplementation in terms of fetal growth.\textsuperscript{57-60} Preliminary results from at least six other trials in at-risk populations (three from Indonesia, one from Equador, one from Chile, and one from Peru) are also not encouraging in terms of fetal growth and duration of gestation.\textsuperscript{40} In summary, the currently available evidence does not support a beneficial effect of maternal zinc supplementation on fetal growth and gestation.

**Postnatal Growth**

Experiments in rhesus monkeys suggest that growth faltering associated with maternal zinc deficiency during fetal life lasts throughout infancy.\textsuperscript{62} Follow-up data from the maternal zinc supplementation trial in Bangladesh detected no difference in infant growth until 6 months of age between treatment groups.\textsuperscript{63} The results of follow-up studies for other supplementation trials are forthcoming. It would be interesting to document the extent and duration of postnatal benefits (if any) to the infant in terms of growth independent of other factors such as reduced morbidity through enhanced immune function.

**Neurobehavioral Development**

The relationship between zinc deficiency and delayed development of brain function has been firmly established in animals.\textsuperscript{2,64} Zinc is a critical nutrient for central nervous system development because of zinc-dependent enzymes, zinc finger proteins required for neurotransmission, and zinc-dependent neurotransmitters in the mossy fibers of the hippocampus.\textsuperscript{65} Zinc also seems to be involved in the metabolism of thyroid hormones,\textsuperscript{66} hormone transport, receptor binding and metabolism, and neurotransmitting precursor production,\textsuperscript{67} all of which ultimately affect central nervous system function.

Because the intrauterine period is critical for brain growth in infants, maternal zinc deficiency could cause adverse effects on fetal and infant neurological and behavioral development. There are some animal data to support this hypothesis. Apgar\textsuperscript{13} reported apathy among zinc-deficient rat dams at parturition. In a series of experiments in rhesus monkeys, Golub et al.\textsuperscript{15,62,67-70} demonstrated that maternal and infant zinc deficiency had adverse outcomes on fetal activity pattern, newborn motor development, and behavior patterns during infancy and adolescence.

Observational data in humans linking the effect of prenatal zinc deficiency to neurodevelopmental changes in children are scarce. Kirskey et al.\textsuperscript{71} reported a significant positive association between maternal intake of dietary zinc and neonatal habituation behavior in a small village in Egypt. They subsequently documented in the same location the persistence of a positive association between maternal zinc status during pregnancy and infant developmental profile at 6 months of age.\textsuperscript{10}

There are few intervention studies that have attempted to evaluate neurobehavioral development as an outcome with maternal zinc supplementation (Table 3).\textsuperscript{72-75} Fetal heart rate and movement patterns were evaluated in 89 subjects as indices of neurobehavioral development\textsuperscript{72} in a subset of the Peruvian zinc supplementation trial. Fetuses of mothers who received zinc supplementation had fewer episodes of minimal fetal heart rate variability, an increased fetal heart rate variability range, an increased number of accelerations, an increased number of movement bouts, an increased number of time spent moving, and an increased number of large movements. Similar results were replicated in another trial of 195 women who were monitored starting from 20 weeks of gestation.\textsuperscript{75} The effect on fetal neurobehavior was more pronounced after 28 weeks. The authors concluded that improving maternal zinc status through prenatal supplementation might improve fetal neurobehavioral development. However, the surrogate measures employed to assess neurobehavioral development need validation. The results of postnatal follow-up studies should be interesting.

In a follow-up study of infants born to zinc- or placebo-supplemented mothers in Bangladesh, there was no benefit to the infants’ mental and psychomotor development with zinc supplementation in the mothers.\textsuperscript{73} Rather, the indices of development were slightly higher ($P = 0.04$) in the placebo group. The trial advised caution with antenatal zinc supplementation. In another recent study,\textsuperscript{74} the effect of prenatal zinc supplementation on the mental and psychomotor development of children who showed increased head circumference at birth with zinc supplementation compared with placebo was evaluated. There was no difference in the test scores of neurological development at 5 years of age between the two groups.

Overall, the available data do not suggest a role of maternal zinc status in neurobehavioral development of the infant. However, caution must be exercised before drawing definite conclusions because of the inherent problems of controlling for confounders in such studies. More well-controlled supplementation trials in zinc-deficient populations are needed to demonstrate any beneficial effect on motor and cognitive development.
Table 3. Summary of Trials Evaluating Effect of Maternal Zinc Supplementation on Fetal/Child Neurobehavior

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Design</th>
<th>N</th>
<th>Dose of Elemental Zinc and Timing of Supplementation</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merialdi et al., 1999(^2)</td>
<td>Peru</td>
<td>Randomized, double-blind; zinc added to iron and folate vs. iron and folate alone</td>
<td>55</td>
<td>15 mg/d from 10–24 weeks of gestation until delivery</td>
<td>Fetuses of mothers who received zinc supplementation showed fewer episodes of minimal fetal heart rate variability, increased fetal heart rate range, an increased number of accelerations, an increased number of movement bouts, an increased amount of time spent moving, and an increased number of large movements compared with the control group; all results were statistically significant ((P &lt; 0.05)) at 36 weeks of gestation</td>
<td>Surrogate markers of fetal neurobehavioral development; needs validation</td>
</tr>
<tr>
<td>Hamadani et al., 2002(^3)</td>
<td>Bangladesh</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>168</td>
<td>30 mg/d from 4 months (12–16 weeks) of gestation until delivery</td>
<td>No benefit of maternal zinc supplementation on mental development or neurobehavior at 13 months of age; infants in the placebo group had higher scores on mental development index ((\text{regression coefficient} = 3.3; \text{SE} = 1.6; 95% \text{ CI} 0.2–6.5; P = 0.04)) and psychomotor development index ((5.1, 2.4, 0.2–9.9, \text{respectively}; P = 0.04)) than those in the zinc-supplemented group</td>
<td>Only about 30% of the children born could be followed up for this outcome; most children had poor nutritional status, which could have negated any possible benefit; weight-for-age at testing was strongly related to developmental levels, which accounted for some of the treatment effect</td>
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</table>
Table 3. (Cont’d) Summary of Trials Evaluating Effect of Maternal Zinc Supplementation on Fetal/Child Neurobehavior

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Design</th>
<th>N</th>
<th>Dose of Elemental Zinc and Timing of Supplementation</th>
<th>Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamura et al., 2003&lt;sup&gt;74&lt;/sup&gt;</td>
<td>UK (African-American women of low socioeconomic status)</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>355</td>
<td>25 mg/d from 19 weeks of gestation until delivery</td>
<td>No differences in the test scores of neurologic development at 5 years of age between the two groups</td>
<td>The original trial resulted in a higher head circumference at birth with zinc supplementation; this increase did not result in an advantage in mental and psychomotor development in later life; however, there was 40% follow-up loss and study children had overall low scores; it is possible that any beneficial effect was obscured by poor environmental influences on this group of children</td>
</tr>
<tr>
<td>Merialdi et al., 2004&lt;sup&gt;75&lt;/sup&gt;</td>
<td>Peru</td>
<td>Randomized, double-blind Zinc added to iron and folate vs. iron &amp; folate alone</td>
<td>195</td>
<td>25 mg/d from 10–16 weeks of gestation until delivery</td>
<td>Zinc supplementation was associated with lower (as suggested by lowess curves) fetal heart rate, greater number of accelerations, and greater heart rate variability; the differences in average responses were not significant before 28 weeks: 0.10 beats/min (95% CI 0.26–0.46) for heart rate variability and 0.13 (95% CI 0.40–0.65) for accelerations, but were statistically significant ($P &lt; 0.05$) after 28 weeks of gestation: 0.40 beats/min (95% CI 0.04–0.76) for heart rate variability and 1.09 (95% CI 0.57–1.62) for accelerations; no differences in motor activity were observed</td>
<td>Surrogate markers of fetal neurobehavioral development; needs validation; the results regarding fetal motor activity are not consistent with the earlier investigation by the same group&lt;sup&gt;72&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

CI = confidence interval; SE = standard error of the mean.
Infection and Immunity

The immune system is particularly sensitive to perturbations in zinc status. Perinatal zinc deficiency in mice results in decreased spleen and thymus size, impaired lymphocyte mitogenic responses and plaque-forming activity, and depressed immunoglobulin concentrations. Decreased lymphocyte population with reduced functioning of helper T-lymphocytes and natural killer cells and an increase in $\beta$ cells have also been demonstrated. The adverse effect on the immune system might even be permanent, persisting after restoration of normal dietary zinc intake.

The effect of perinatal zinc deficiency on the immune status of infants has not been studied adequately in humans. In a supplementation trial designed to evaluate the effect of antenatal zinc supplementation on pregnancy outcome, no beneficial effect was observed in decreasing neonatal sepsis (1/294 in supplemental vs. 5/286 in controls; OR = 0.25; 95% CI 0.05–1.26). However, this trial was mainly designed to evaluate the effect on other important measures such as birth weight, so the sample size for evaluating the benefit in terms of neonatal sepsis was restricted.

The effect of maternal zinc supplementation in reducing the incidence of diarrheal and potential acute respiratory infection mortality in infants throughout the first year of life is under investigation. The results of one such trial have been published. The 6-month follow-up of infants from the Bangladesh trial documented that infants of mothers who received zinc during pregnancy had reduced risks for acute diarrhea (RR = 0.84; 95% CI 0.72–0.9), dysentery (RR = 0.36; CI 0.25–0.84), and impetigo (RR = 0.53; CI 0.34–0.82) compared with those in the placebo group. These reductions were seen in low-birth-weight infants but not in those with normal birth weight. Preliminary data from Peru also indicate a reduction in diarrheal and infectious morbidity incidence in infants throughout the first year of life with prenatal zinc supplements, which were not continued after birth. This benefit may be due to the impact of zinc supplementation on the ontogeny of immunologic development in the infant during the first year of life. Two other unpublished trials have documented a benefit in infant immune status in terms of acquisition of antibodies and response to vaccines with perinatal zinc supplementation.

Overall, there appears to be a benefit in infant immunity and decreased morbidity from infectious diseases with maternal zinc supplementation during pregnancy. However, more research is needed.

POTENTIAL ADVERSE EFFECTS

Before recommending routine supplementation with a micronutrient, it is essential to thoroughly address the safety issue, and this includes the consequences of interactions with other important micronutrients and vitamins. Fluctuation in the status of one micronutrient may alter the metabolism of the other, with functional consequences on the health of the individual. Seemingly minute changes in this context may assume practical significance in populations with borderline nutrition, as is the case in developing countries. Zinc is known to have interactions with iron, copper, and vitamin A. Unfortunately, the earlier supplementation trials were not designed to address this important aspect. Future research must give due importance to the safety issue, particularly on a subclinical scale.

CONCLUSIONS

The lack of a reliable indicator precludes a true estimate of zinc deficiency during pregnancy in various populations. However, it is possible that mild to moderate deficiency (as assessed by available indicators) may be common in the developing world. Animal experiments indicate that zinc deficiency can result in adverse fetal consequences. Human data, particularly from prenatal zinc supplementation trials, have failed to document a consistent benefit on evaluated outcome using measures such as fetal growth, duration of gestation, and immediate neonatal survival. With respect to neurobehavioral development, evidence is conflicting, with only one study reporting a positive outcome. Recent data and some preliminary findings indicate a beneficial effect of maternal zinc supplementation on neonatal immune status and infant morbidity from infectious diseases. There is preliminary evidence of possible prevention of congenital malformations (cleft lip/palate) with zinc supplementation. Future research should focus on these functional consequences and congenital malformations (with adequate sample sizes), and should also address the safety issue, particularly in relation to micronutrient interactions. In light of the currently available information, routine zinc supplementation cannot be advocated to improve pregnancy outcome.

ACKNOWLEDGEMENTS

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