

Potential contribution of maternal zinc supplementation during pregnancy to maternal and child survival¹⁻³

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ABSTRACT Mild-to-moderate zinc deficiency may be relatively common worldwide, but the public health importance of this degree of zinc deficiency is not well defined. The purpose of this review was to provide a conceptual framework for evaluating the public health importance of maternal zinc deficiency as it relates to fetal growth and development, complications of pregnancy, labor and delivery, and maternal and infant health. The mechanisms through which zinc deficiency could influence health outcomes are well described. The results of experimental studies conducted in animal models have motivated concern about the potential health effects of mild-to-moderate maternal zinc deficiency. Observational studies in human populations have produced strong associations between poor maternal zinc status and various indicators of poor pregnancy outcome, but supplementation trials have not produced strong, or even consistent results. Supplementation trials are needed to define the public health importance of maternal zinc deficiency worldwide. *Am J Clin Nutr* 1998;68(suppl):499S–508S.

KEY WORDS Maternal zinc deficiency, pregnancy, child health, survival, supplementation, parturition, immunology, development

INTRODUCTION

In the past 20 y, much progress has been made in the area of child survival worldwide (1). Improvements in health care, water and sanitation, as well as socioeconomic development have substantially reduced the risks of childhood mortality. In many countries, a child's risk of dying during the first year of life remains high, but because efforts to prevent causes of infant death during the postneonatal period are becoming more and more successful, an ever-growing percentage of infant deaths occurs near the moment of birth. Therefore, efforts to further reduce mortality rates in developing countries will require public health planners and policymakers to place greater focus on understanding and addressing the causes of neonatal and perinatal mortality. Maternal nutritional status, with respect to both macro- and micronutrients, is known to be an important determinant of perinatal and neonatal survival and well-being (2), but maternal nutrition programs in developing countries have focused almost exclusively on the risks to the mother and infant from maternal iron deficiency anemia during pregnancy. Other micronutrients such as zinc may also be important for maternal

and infant survival during the critical period surrounding birth, but their importance is less well understood. The purpose of this paper is to provide a background and conceptual framework for evaluating the public health importance of maternal zinc deficiency as it relates to fetal growth and development; complications of pregnancy, labor and delivery; and maternal and infant health and well-being.

PREVALENCE OF MATERNAL ZINC DEFICIENCY

Although severe zinc deficiency is now considered rare, mild-to-moderate zinc deficiency may be relatively common throughout the world (3). In general, few data are available on the prevalence of mild to moderate zinc deficiency worldwide, in part because consensus has not yet been reached on appropriate indicators of zinc status for pregnant women or any other target group (4, 5).

Several reports have compiled estimates of dietary zinc intakes of women worldwide. Tamura and Goldenberg (6) compiled 27 studies reporting dietary zinc intakes of women of childbearing age worldwide. Of these, 2 studies from developing countries [Guatemala and Egypt (7, 8)] reported average usual intakes of 8–11 mg Zn/d and 2 studies of intakes of south Asians living in the United Kingdom (9, 10) reported usual intakes of 5–10 mg Zn/d. Most of the studies cited were conducted in the United States and United Kingdom, and average usual zinc intakes were reported to be in the range 8–14 mg/d across the studies. In addition to these studies, Lehti (11) reported intakes of 7.0 mg Zn/d among lactating Brazilian women, and Ferguson et al (12) reported intakes of 6.2–6.8 mg Zn/d among Malawian women. Parr et al (13) summarized data from 17 surveys in the literature between 1970 and 1991 and reported that pregnant and lactating

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women worldwide consume 9.6 ± 1.2 mg Zn/d ($\bar{x} \pm SD$). Zinc may also be ingested from drinking water, but intakes are typically increased by only 2% provided there was a usual water intake of 2 L/d (13).

The probability method can be applied to these data to derive an estimate of the prevalence of inadequate intakes of zinc (14). Using the estimated usual intakes of Parr et al (13) and an estimated distribution of the zinc required by women to meet their normative needs during pregnancy of 11.5 ± 1.75 mg/d [based on the US recommended dietary allowances (15)], it can be estimated that 82% of pregnant women worldwide likely have inadequate usual intakes of zinc. This estimate is gross for several reasons. First, the average requirement is overestimated to the degree to which the typical female body size on which it is based is greater than that of women in developing countries. Second, the requirement distribution is calculated with the assumption that the dietary zinc is highly bioavailable. This results in an underestimation of the zinc intake requirement distribution for women in developing countries whose diets consist mainly of cereal grains and legumes and is therefore of moderate-to-low bioavailability with respect to zinc (13). Third, most of the studies were from developed countries with higher usual intakes of zinc. Despite these considerations, this estimate indicates an alarming prevalence that should motivate concern that significant proportions of pregnant women worldwide have inadequate dietary zinc intakes and likely suffer health consequences attributable to zinc deficiency.

CONSEQUENCES OF MATERNAL ZINC DEFICIENCY

Severe maternal zinc deficiency has been associated with spontaneous abortion and congenital malformations (ie, anencephaly), whereas milder forms of zinc deficiency have been associated with low birth weight (LBW), intrauterine growth retardation, and preterm delivery (16). Importantly, milder forms of zinc deficiency have also been related to complications of labor and delivery, including prolonged or inefficient first-stage labor and protracted second-stage labor, premature rupture of membranes (PROM), and the need for assisted or operative delivery (16). These complications in turn impair maternal and perinatal health because they lead to increased risk of maternal lacerations, high blood loss, maternal infections, fetal distress, stillbirth, neonatal asphyxia (low Apgar scores), respiratory distress, and neonatal sepsis (16). These interrelations are shown in **Figure 1**. The evidence relating maternal zinc deficiency to fetal growth and development, birth outcomes, and maternal and perinatal health are considered in the following sections.

Fetal growth

Women are at increased risk of zinc deficiency during pregnancy [in part because of high fetal requirements for zinc (17)], and maternal zinc deficiency has been associated with poor fetal growth in both animal and human populations (17, 18). In humans, however, the research relating maternal zinc status and birth weight has not produced consistent results. Of 38 studies reporting associations between maternal plasma or serum zinc

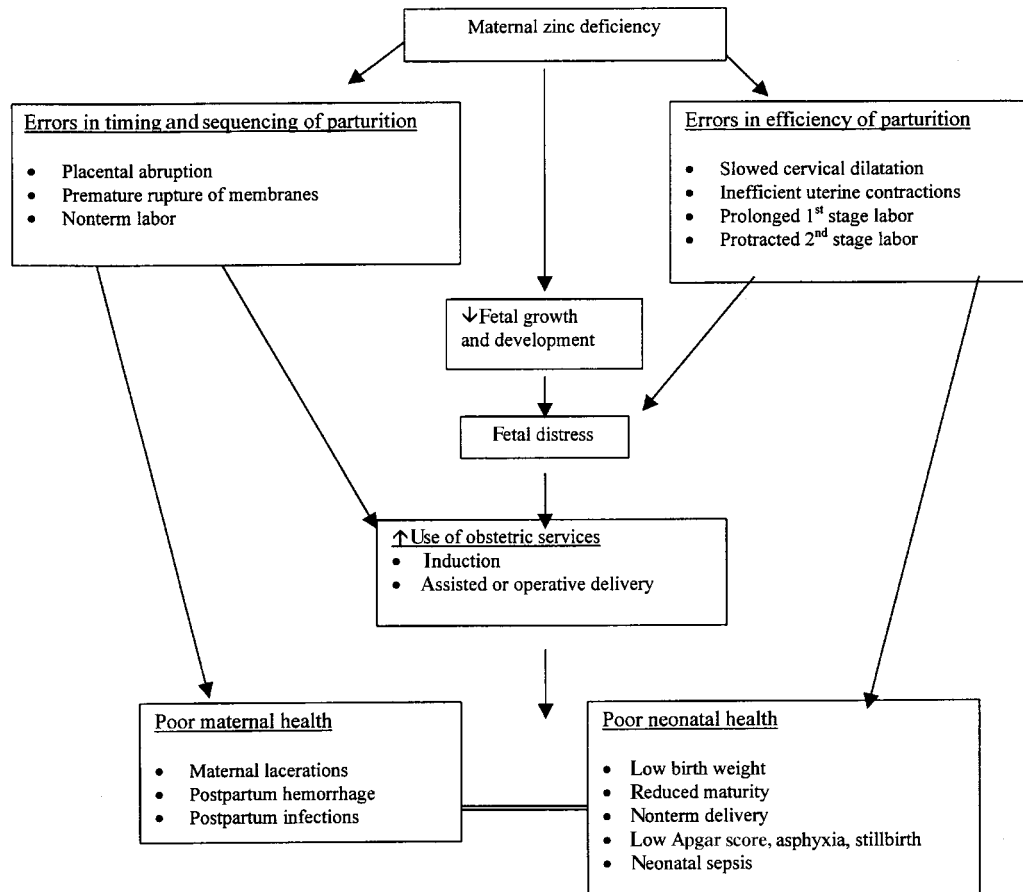


FIGURE 1. Consequences of maternal zinc deficiency on birth outcomes and maternal and perinatal health.

concentration and fetal growth (expressed either as birth weight or as some definition of adequacy, eg, birth weight >10th percentile), 18 studies (19–35) reported positive associations, whereas 20 studies (10, 36–54) reported negative associations. Of the 14 studies conducted in populations in developing countries, 9 reported positive associations (8, 20, 22, 26, 27, 28, 32–34) and 5 reported negative associations (37, 39, 40, 42, 48). Various reasons for these differences in associations can be postulated, including differences in 1) timing of the assessment (blood draw) during pregnancy and the effects of hemodilution, 2) laboratory methods and quality, 3) sample size and the potential for influential values to drive associations, and 4) the underlying zinc nutrition of the populations. It was also argued that the negative associations resulted because faster growing fetuses (with higher zinc requirements) drive down maternal serum concentrations (53).

The results of 10 zinc supplementation trials to improve birth weight in humans have also been mixed (55–65). The major problem with most of these trials is that they were conducted in well-nourished populations and thus are not addressing the central question of whether supplementing zinc-deficient women would improve fetal growth. Only 2 studies (57, 64) were conducted in poor women in developing countries. Ross et al (57) studied the pregnancy outcomes of 65 Zulu women in South Africa. Women receiving supplements containing between 4 and 13 mg Zn/d delivered babies weighing 80 g less at birth than those in the control group, but because mothers in the treatment group weighed considerably less than those in the control group at 20 wk gestation, the observed differences in birth weight may be explained. Garg et al (64) supplemented 106 Indian mothers with 45 mg Zn/d, and observed a 300–800 g difference in birth weight relative to a comparison group of 60 mothers. The differences between groups depended on the length of supplementation, with the greatest differences seen in those supplemented from the first trimester of pregnancy onward. Although these effects are remarkable, it is difficult to draw conclusions from this study because 1) the sample size was small, 2) the selection of the 60 mothers in the comparison group was not defined, 3) there was a high loss to follow-up, and 4) there was a lack of information on the comparability of the groups with respect to important confounding factors.

From an epidemiologic perspective, the trial with the greatest internal validity is that reported by Goldenberg et al (65), in which 580 low-income Alabamian women with low serum zinc concentrations at entry into prenatal care were randomly assigned to receive 25 mg Zn/d or placebo. Infants born to zinc-supplemented women weighed 126 g more at birth, were 0.6 cm longer, and had 0.4-cm larger head circumferences than infants born to mothers receiving the placebo. Further analyses revealed that the effects on fetal growth were limited to women who were not overweight when entering pregnancy. In this subgroup the results were much stronger, with a difference in birth weight between groups on the order of 250 g. How these findings can be generalized for women in developing countries is not clear, but the results should make clear the need for further research on this question to be conducted in developing country populations.

Despite the limitations of the trials discussed previously, except for the study by Ross et al (57), the birth weights of infants born to zinc-supplemented women in these trials were 14–800 g higher than those in the control groups, with 6 of the 10 trials reporting increases in mean birth weight of 40–170 g, and those conducted among high-risk subgroups of pregnant

women showing the largest effects on birth weight. A 40–170 g increase in the average birth weight may seem small, but it is similar in magnitude to the effects on birth weight observed with energy and protein supplementation (66).

Several zinc supplementation trials reported differences in other indicators of fetal growth. Two trials reported 26–90% reductions in the incidence of small-for-gestational age infants (61, 64), and Goldenberg et al (65) reported a 37% reduction in the overall incidence of very LBW (<1500 g) associated with zinc supplementation and a 62% reduction in very LBW among nonobese women. Two studies reported that babies born to zinc supplemented mothers were 0.5 cm longer (62, 65), whereas one study (60) observed babies in the zinc supplemented group to be 0.2 cm shorter than control infants at birth. Zinc-supplemented women in Alabama had infants with 0.2 cm greater arm and femur lengths, and 1–2 mm greater triceps and subscapular skinfold thicknesses (6).

Length of gestation

Part of the reason for observed increases in birth weights in babies born to zinc-supplemented mothers could be the effects of zinc supplementation on the duration of pregnancy rather than on fetal growth per se. The duration of pregnancy in most animal species is not subject to much variation, but experimental maternal zinc deficiency has been shown in several species to increase variability in the duration of pregnancy—in essence, to create in those species the well-recognized human problems of preterm and postterm delivery (18, 67, 68). As will be discussed later, these effects likely reflect the role of zinc in estrogen-dependent gene expression as it relates to the timing, coordination, and progression of parturition (69).

The effects of zinc supplementation on duration of pregnancy and preterm delivery were examined in some but not all of the zinc-supplementation trials described above. Of 5 trials providing results (57, 59, 62, 64, 65), maternal zinc supplementation lengthened the average duration of pregnancy by 0.3–1.0 wk, with 3 of the trials reporting a lengthening of 0.5 wk. Three studies reported reductions in the incidence of preterm delivery (<37 wk) of 18–36% and 2 reported reductions of 80–83%. In 2 studies (16, 65) 66–85% reductions in the incidence of delivery before 32 wk were also reported. These results indicate a consistent, albeit small, effect of zinc supplementation on the average duration of pregnancy that likely explains most or all of the improvements in size at birth described previously. Thus, it may be true that increases in average birth weight observed with zinc supplementation occur not from improvements in fetal growth rates, but rather from prolongation of time spent in utero. However, it is also clear that maternal zinc supplementation likely results in more sizable reductions in preterm delivery, particularly in those deliveries occurring before 32 wk gestation. Finally, Kynast and Saling (62) reported an 80% reduction in the variance of gestational age at delivery, suggesting that the incidence of nonterm delivery (delivery at <37 wk or >41 wk) diminished with maternal zinc supplementation.

Neurobehavioral development

Zinc is a critical nutrient for central nervous system (CNS) development, which occurs during pre- and postnatal life, for example: 1) zinc-dependent enzymes are involved in critical cell replication processes necessary for brain growth, 2) zinc-finger

proteins provide brain structure and are important for neurotransmission, and 3) zinc-dependent neurotransmitters in the mossy fiber system of the hippocampus are involved in brain memory function. In addition, zinc is involved in extra-CNS metabolic processes that ultimately affect CNS function, including hormone transport, receptor binding and metabolism, and neurotransmitter precursor production (70).

Because of the important role of zinc in CNS function, it is clear that maternal and early infant zinc deficiencies are likely to adversely affect fetal and infant neurologic and behavioral development (Figure 2). This is borne out in the work by Golub et al (70–74), who conducted a series of studies in rhesus monkeys investigating the effect of maternal and infant zinc deficiency on maternal and infant health outcomes, including fetal activity patterns, newborn motor development, and behavior patterns during infancy and pubescence. In these studies, the monkeys were exposed continually to marginally low concentrations of zinc (from the fetal period to adolescence) because this level of exposure would most greatly mimic zinc-deficiency in human populations. Using ultrasonographic techniques to quantify fetal movements, Golub et al (74) found that fetuses of zinc-deficient mothers had increased activity relative to their zinc-sufficient counterparts. However, newborns of zinc-deficient mothers were found to exhibit low postural muscle tone (hypotonia) but normal reflexes at birth (71). At 1 mo of age, the male infants were found to be less active, and lower activity levels associated with zinc deficiency were repeatedly observed in both sexes throughout childhood and into adolescence, despite a lack of differences in motor maturation between groups (72, 73). Finally, when cognitive performance tests were administered to the infants, the zinc-deficient infants exhibited reduced exploration and impaired visual discrimination learning performance, but improved spatial-delayed response performance—an expected finding in infants with lower activity levels. Taken together, the results of these studies overall suggest that maternal and infant zinc status influence in some way fetal and infant cognitive and behavioral development and highlight the need for studies in zinc-deficient human populations.

Case reports (75, 76) suggest that severe maternal zinc deficiency (associated with dietary deprivation or acrodermatitis enteropathica) increases the risk of neural tube defects in the offspring. As reported, maternal zinc supplementation allowed these women to produce healthy offspring in subsequent pregnancies. No experimental studies in humans have been conducted to evaluate the effect of mild-to-moderate maternal zinc deficiency on fetal and infant behavioral development. Two studies do provide evidence, however, of an important link between maternal zinc status and neonatal and infant behavior in humans. Kirksey et al (77) observed positive associations between maternal serum zinc concentrations during pregnancy and the developmental status of Egyptian newborns assessed by using the Brazelton Neonatal Behavioral Assessment Scale (78). Subsequently, Kirksey et al (8) reported that positive associations were still observed between maternal zinc status during pregnancy and infant developmental status when assessed at 6 mo of age by using the Bayley Scales of Infant Development (79).

Both the Brazelton (78) and the Bayley (79) tests are global assessments of developmental status, and therefore assess a variety of components of behavioral development and cognitive functioning. Importantly, the orientation and habituation components of both these tests were associated most strongly with

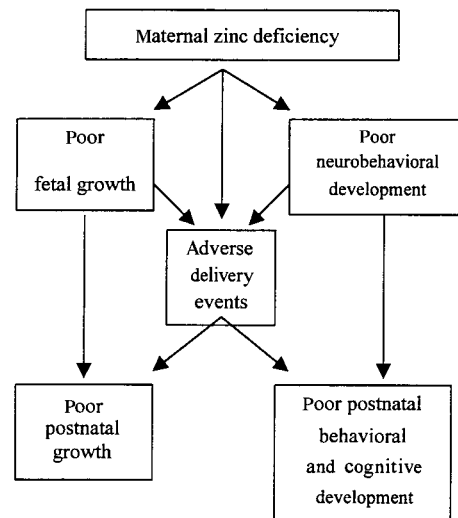


FIGURE 2. Interrelations between maternal zinc deficiency and pre- and postnatal growth and development.

maternal zinc status, and these are believed to relate directly to cognitive ability later in life (8). Orientation refers to the ability of the infant to respond appropriately to an environmental stimulus, whereas habituation refers to the ability of the infant to inhibit response to a repetitive or familiar environmental stimulus. More rapid habituation is generally interpreted as reflecting more focused attention and more efficient information processing by the infant. Speed of neonatal habituation has been related to measures of infant alertness, whereas measures of infant habituation have been shown to predict a variety of indexes of cognitive performance in the preschool years (80–82).

The associations were particularly strong between neonatal habituation measures and maternal zinc intakes and status during the second trimester (8). Given these results and knowledge that a phase of rapid neurogenesis and structural development occurs before the third trimester, it is reasonable to hypothesize that maternal zinc status during midpregnancy may be particularly important for ensuring optimal fetal CNS development and later cognitive functioning.

It should be added that dietary zinc insufficiency might not be necessary for adverse effects of zinc deficiency on CNS development to occur. The zinc pool in the mother's body that is transferred to the fetus is found in maternal plasma (83). Thus, factors known to influence maternal plasma zinc concentrations (other than chronically low dietary zinc intakes) may elicit the same CNS manifestations in the fetus seen in fetuses of mothers with low dietary intakes of zinc. Even transitory reductions in serum zinc may cause CNS malformations if they occur during organogenesis (84). Maternal plasma zinc concentrations are lowered as part of the acute-phase response of the body's immune system to disease, injury, or stress because zinc is sequestered away from the plasma and into maternal liver (85). Thus, it is hypothesized that frequent maternal morbidity or maternal stress may increase risk of poor neurologic development in the fetus by causing elicitation of acute-phase responses leading to sequestration of zinc from the plasma to the liver, where it is essentially unavailable for uptake by the fetus. Studies in animal models support the hypothesis that maternal injury and the associated acute-phase response result in preferential uptake of zinc by the maternal liver

[reviewed by Keen et al (85)]. If this is so, one would expect the benefits of maternal zinc supplementation on fetal and infant outcomes to differ depending on the morbidity burden experienced by the mother during pregnancy, and perhaps by the infant during postnatal life. To our knowledge, the importance of maternal zinc deficiency secondary to maternal morbidity has not been studied in human populations. Defining the importance of secondary zinc deficiency is likely critical for designing interventions in populations with high disease burdens in developing countries.

The work of Golub et al (70–74) also showed that differences in fetal neurologic development associated with maternal zinc deficiency persist to some degree postnatally. Other research in the developmental literature provides evidence for a relation between neurologic and motor development observed in utero with that observed during infancy, suggesting that developmental gains achieved during fetal life can be long lasting (86–88). Because research supports both the effect of variation in maternal nutritional status on fetal neurologic development as well as the postnatal permanence of neurologic development achieved in utero, it would be important to assess the effect of maternal zinc supplementation on fetal neurologic development and relate it to developmental status during infancy.

To summarize, despite both a clear biological role for zinc in CNS development and function and demonstration of behavioral effects from zinc deficiency in animal models, an assessment of the effects of mild-to-moderate maternal zinc deficiency on fetal and infant neurologic, behavioral, and cognitive development has never been undertaken.

Labor and delivery complications

Maternal mild-to-moderate zinc deficiency has been associated with increased risk of a variety of maternal and fetal complications of labor and delivery (26, 53, 54, 58–60). These can be categorized into 1) abnormalities in labor and delivery, 2) maternal morbidity during pregnancy and the puerperium, and 3) perinatal morbidity. These associations likely reflect the role of zinc in maintaining immunocompetence, cell membrane integrity, prostaglandin synthesis and function, and estrogen-dependent gene expression.

The relation between maternal zinc nutriture and parturition was first described by Apgar (89). Female rats fed 1- μ g Zn/g diet throughout pregnancy experienced difficult and prolonged labors as compared with control and pair-fed animals. Some zinc-deficient dams labored for 6 h or more and were exhausted or dead before delivering the entire litter. Hemorrhage, presumably due to uterine atony, placental abruption, or both, was also observed. The exhausted zinc-deficient females were less likely to eat the afterbirth and to clean up or care for their pups. Subsequently, Apgar (90) showed that zinc supplementation late in pregnancy could prevent difficulties in parturition in otherwise zinc-deficient dams. Since then, dystocia has been observed in zinc-deficient rats by other investigators as well as in zinc-deficient rhesus monkeys (91, 92). As described by Bunce et al (69), studies suggest that zinc deficiency results in normal estrogen concentrations late in gestation but decreased uterine estrogen receptors, uterine proteins, and the number of uterine gap junctions at delivery. These findings suggest that zinc deficiency impairs estrogen-dependent gene expression, not by interfering with estrogen production but rather by interfering with estrogen function via the estrogen receptor, which contains a zinc-finger protein. Thus, zinc is critical for the production of uterine proteins that convert

the uterus from its passive state to one capable of concerted contractions with sufficient force to expel a fetus. Zinc nutriture may influence other aspects of labor and delivery as well (69), including hormonal control of cervical ripening and dilatation (93) and the maintenance of fetal membrane and amniotic fluid integrity (93–95).

If what is observed in animal models is relevant to human pregnancy, we would expect maternal zinc deficiency to upset both the sequencing and efficiency of parturition (as shown in Figure 1). Sequencing refers to the optimal ordering of events during parturition at term, including cervical dilatation, labor, rupture of membranes, and expulsion of the fetus and placenta. Efficiency refers to the duration of each stage of labor and delivery and the strength of uterine contractions. Thus, errors in sequencing include nonterm delivery (as discussed previously), PROM, and placental abruption, whereas errors in efficiency include prolonged first-stage labor (both latent and active), protracted second-stage labor, and prolonged third-stage labor.

Observational studies in humans have associated low maternal serum zinc concentrations during pregnancy or at delivery with PROM, placental abruption, inefficient uterine contractions, and prolonged or nonprogressive labor, all of which can result in the need for assisted (eg, forceps) or cesarean delivery. Maternal zinc deficiency has been associated with a 3.5–7.0-fold increased risk for PROM (96, 97), a 2.8-fold increased risk of placental abruption (62), a 2–5-fold increased risk for a prolonged first-stage labor (both latent and active phases), a 9-fold increased risk for a protracted second-stage labor, and a 4-fold increased risk for having a labor lasting >20 h (98, 99). Lazebnik et al (98) also found nearly a 5-fold increased risk of third-degree lacerations associated with poor maternal zinc status.

Supplementation trials (16, 60–63), however, have not found such strong effects. Only the results of Simmer et al (61) suggest that supplementing pregnant women with zinc can lower the risk of such complications of labor and delivery; they found 60–80% reductions in the incidences of induction and cesarean delivery associated with zinc supplementation. Again, these studies had design flaws and were not conducted in zinc-deficient populations.

The question as to whether maternal zinc deficiency increases the likelihood of labor and delivery complications is critical for developing countries in which women have little access to essential obstetric services. Prolonged labor as well as other complications of labor and delivery increase risk to both the mother and baby (100). Fetal survival at birth is a function of the labor and delivery process as well as the ability of the fetus to survive that process (100, 101). Although not clear-cut, some preterm infants may have increased chances of survival if born by cesarean delivery (102). Babies with LBW or intrauterine growth retardation are less likely to survive a prolonged birth process, and if they do survive, are more likely to suffer morbidity directly resulting from that prolonged birth process, eg, asphyxia (low Apgar score) and respiratory distress from meconium aspiration, asphyxiation, or both (100, 103). Sepsis, either maternal or neonatal, is a likely consequence of PROM, and maternal lacerations and hemorrhage increase a woman's risk of dying from blood loss or infection.

Few studies have examined maternal and perinatal morbidity associated with zinc deficiency. Mukherjee et al (54) found that, overall, women with low serum zinc concentrations were 20–50% more likely to suffer from a variety of maternal and fetal compli-

cations of labor and delivery, including fetal distress and maternal infections. McMichael et al (53) reported a 1–2-fold increased risk of perinatal morbidities (low Apgar score, respiratory distress, fetal distress, or presence of meconium) associated with low maternal zinc status. In their quasi-experimental study, Kynast and Saling (62) found that zinc supplementation was associated with a 60% reduction in vaginal bleeding, placental abruption, and maternal hemorrhage. However, Mahomed et al (60), in a small supplementation trial, found no such effects.

In summary, problems with the current literature preclude drawing definitive conclusions regarding the importance of zinc supplementation during pregnancy as a public health intervention for preventing labor and delivery complications, and thereby ensuring maternal and neonatal health and well-being during the puerperium. The estimated effects from observational studies appear to be strong, but in many cases these effects are not significant because of small sample sizes. The results from supplementation trials are inconclusive because of major design flaws, which include sample sizes inadequate to detect differences in rare events. The implications of zinc deficiency for complications of labor and delivery are important for poor women living in developing countries, who are more likely to suffer negative consequences resulting from PROM, prolonged labor, maternal lacerations, and postpartum hemorrhage. These women are also more likely to have small or preterm babies who are less tolerant of a prolonged birth process, and both the mother and her baby will be less likely to either be treated for or recuperate from life-threatening maternal and perinatal morbidity.

Postnatal outcomes

Maternal zinc deficiency during pregnancy may result in problems for the infant during postnatal life. Effects from maternal zinc deficiency on growth and development in utero likely influence growth and development during neonatal life and beyond, as shown in Figure 2. Zinc is also important for the transfer of many substances to target tissues. Among these substances are 2 with recognized importance for child survival: immunologic factors and vitamin A. The interrelations between maternal zinc deficiency, infant vitamin A status, immunologic development, and postnatal health and survival are shown in **Figure 3**. These interrelations are dealt with in greater detail in other articles in this supplement (104, 105) and are discussed briefly below.

Immunologic development

A major determinant of postnatal survival is the ability of the infant to resist infection and respiratory and diarrheal disease. Because protective immunity develops as a result of exposure to pathogens, the newborn is at particularly high risk for infection during the first 6 mo of life when adaptive immunity is still not fully functional but exposure to invading pathogens is significant. Two factors, however, provide the infant with protection against pathogens. First, healthy infants develop natural immunity consisting of antibodies and T cells produced before infection that recognize common pathogens for respiratory and diarrheal disease. Second, the newborn has already received maternal antibodies in utero. These antibodies are not replenished after birth and their presence gradually decays to low values by 6 mo of age. In addition to providing protection, natural and maternal antibodies are believed to influence development of the emerging immune system in the child (106).

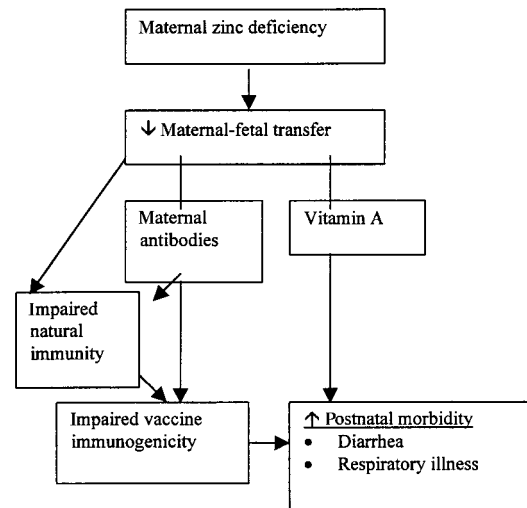


FIGURE 3. Potential links between maternal zinc deficiency and infant postnatal morbidity risk.

As discussed by Shankar and Prasad (104), perinatal zinc deficiency can result in poor development of natural immunity and decreased acquisition of maternal antibodies. Indeed, studies in mice and primates indicate that perinatal zinc deficiency can adversely affect the normal development of multiple tissues and organ systems of the fetus. One of the first sequelae of mild zinc deficiency is suppression of the immune response (107), indicating that the fetal immune system is particularly sensitive to suboptimal maternal zinc status. Perinatal zinc deficiency has been shown to result in decreased spleen and thymus size (108), impaired lymphocyte mitogenic responses and plaque forming activity (108), and depressed immunoglobulin concentrations, particularly for immunoglobulin M and immunoglobulin A (108, 109). Interestingly, the changes in immunoglobulin M and immunoglobulin A concentrations and some B cell responses persist into adulthood even after postnatal restoration of normal dietary zinc intake. In some cases they are passed on to subsequent generations (108–110). Because zinc is a necessary cofactor for the transport of immunoglobulins across the placental barrier, perinatal zinc deficiency may also diminish in utero acquisition of maternal antibodies by the fetus.

Given the central role of immunity in health and development, perinatal zinc deficiency may be a previously unrecognized cause of impaired disease resistance and decreased vaccine efficacy in infants. The ultimate effect of these sequelae on incidence, severity, and duration of diarrheal and respiratory disease is not known. Hence, research is needed on the influence of perinatal zinc deficiency on immunity and subsequent risk of morbidity as well as on the efficacy of prenatal maternal zinc supplementation and postnatal zinc-based therapies to boost protective immunity in neonates.

Vitamin A status

The relation between zinc and vitamin A status is well known (111). As reviewed by Christian and West (105), previous studies provide some indication that maternal zinc deficiency may influence newborn vitamin A status. Mild gestational zinc deficiency in pregnant rhesus monkeys was associated with lower maternal serum retinol and a lack of association between serum

retinol and retinol binding protein (112). In a related study, Peters et al (113) found reduced vitamin A concentrations in fetuses of mothers fed a diet throughout pregnancy that was marginal in zinc, but replete in vitamin A. Furthermore, vitamin A supplementation of these mothers did not overcome the deleterious effects of zinc deficiency on maternal transfer of vitamin A to the fetus. Given the well-documented, critical role of vitamin A for child survival (114), studies are needed to determine the public health importance of maternal zinc deficiency on vitamin A metabolism during pregnancy and lactation, and in particular, on delivery of vitamin A to the fetus and young infant.

Postnatal growth

The effect of zinc deficiency on growth has been well studied. Both animal and human studies provide evidence for the crucial role of zinc in supporting adequate growth, and results from supplementation trials in preschool and school-aged children support the public health importance of zinc deficiency in growth faltering during infancy and childhood (115). Research also suggests that the proportion of growth faltering attributable to zinc deficiency is likely greater in regions characterized by poor water and sanitation and hygiene practices that increase risk for diarrheal and respiratory infections, both of which increase the likelihood of zinc deficiency by increasing body losses or requirements (116).


The work of Golub et al (71) in rhesus monkeys suggests that growth faltering associated with maternal zinc deficiency during fetal life lasts throughout infancy. To our knowledge, no studies in human populations have been reported to determine whether improvements in birth weight and other anthropometric indexes associated with maternal zinc supplementation are long lasting. It may be true that improvements in birth weight achieved through maternal zinc supplementation in developing country settings are short-lived because the infants are born into environments characterized by high morbidity and diets of marginal quality and lose some or all of the gains achieved in utero. Alternatively, it is plausible that improvements in prenatal growth translate into even greater improvements in postnatal growth, with improvements in immune function and decreased risk of morbidity playing key roles in this process. Documenting the extent and duration of postnatal benefits to the infant from maternal zinc supplementation during pregnancy would be important for strengthening support for maternal nutrition programs and for understanding potential tradeoffs with infant-based supplementation programs when resources are scarce.

SUMMARY

Nutritionists have long been concerned that zinc deficiency affects large numbers of women and children worldwide. Little direct evidence of mild-to-moderate zinc deficiency is available, however, because the validity of biochemical indicators of zinc status are not established. There is considerable evidence that a high percentage of women worldwide consume diets inadequate in zinc; we estimated, albeit grossly, that 82% of pregnant women worldwide have usual intakes of zinc inadequate to meet the normative needs of pregnancy. In developing countries, the prevalence is likely to be near 100%. Therefore, program planners and policymakers should be concerned about maternal zinc deficiency in their populations, and the likely health burden for women and infants attributable to mild-to-moderate maternal zinc deficiency.

The purpose of this review was to define the range of poten-

tial health consequences for women and infants attributable to maternal zinc deficiency. As discussed above, the molecular roles of zinc in various biochemical processes relevant to maternal and infant health and survival are well established. Further, the results of experimental studies conducted in animal models including nonhuman primates suggest that maternal zinc deficiency does undermine several biological processes that ensure maternal and fetal well-being during pregnancy, parturition, and the puerperium, as well as infant health and survival in the first year of life and beyond. Observational studies conducted in human populations have found strong associations between various indicators of maternal zinc status and important health outcomes, including fetal growth and development, birth outcomes, and maternal and perinatal morbidity. However, outcomes such as infant immunologic development have not yet been investigated in human populations. For the most part, the results of the observational studies are provocative, but do not provide conclusive evidence about the role of maternal zinc deficiency in maternal and infant health because of methodologic flaws inherent in these studies. Further, because we are not sure what indicators of maternal zinc status mean, supplementation trials should be relied on more heavily to define maternal zinc deficiency, as well as the functional consequences of maternal zinc deficiency for women and infants. Unfortunately, the results of supplementation trials currently in the literature do not allow us to draw definitive conclusions.

It should be clear from the material presented that maternal zinc deficiency may be a triple threat to poor women in developing countries. These women are most likely to 1) be carrying a small fetus unable to withstand prolonged labor and delivery, 2) have the least access to assisted or operative delivery as treatment for prolonged labor and delivery, and 3) have the least access to health care for proper treatment of maternal and perinatal morbidity during the puerperium. However, the contribution of maternal zinc deficiency to maternal and infant morbidity and mortality rates in developing countries is not known. Supplementation trials are needed to define the health consequences for mothers and infants attributable to maternal zinc deficiency worldwide as well as the potential benefits to maternal and infant well-being and survival likely to result from maternal zinc supplementation programs. Currently, there are trials ongoing in several countries in Latin America and Asia to define the health consequences of maternal zinc deficiency. Thus, it is likely that within the next 2–5 y, nutrition policymakers will begin to have the data necessary to make decisions regarding the public health importance of maternal zinc deficiency and potential programmatic options for reducing the morbidity and mortality burden attributable to maternal zinc deficiency worldwide. 

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