

Determinants of maternal zinc status during pregnancy¹⁻³

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ABSTRACT Zinc deficiency in pregnant experimental animals limits fetal growth and, if severe, causes teratogenic anomalies. Although the data from human studies are not consistent, similar outcomes have been observed and were associated with poor maternal zinc status. This paper reviews human studies of zinc status and pregnancy outcome, describes the physiologic adjustments in zinc utilization during pregnancy to meet fetal needs while maintaining maternal status, and identifies dietary and environmental conditions that may override those physiologic adjustments and put the health of the mother and fetus at risk. Adjustments in intestinal zinc absorption appear to be the primary means by which zinc retention is increased to meet fetal demands. However, transfer of sufficient zinc to the fetus is dependent on maintenance of normal maternal serum zinc concentrations. Conditions that could interfere with zinc absorption include intake of cereal-based diets that are high in phytate, high intakes of supplemental iron, or any gastrointestinal disease. Conditions that may alter maternal plasma zinc concentrations and the transport of zinc to the fetus include smoking, alcohol abuse, and an acute stress response to infection or trauma. Supplemental zinc may be prudent for women with poor gastrointestinal function or with any of these conditions during pregnancy. *Am J Clin Nutr* 2000;71(suppl):1334S-43S.

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INTRODUCTION

Severe maternal zinc deficiency has a devastating effect on pregnancy outcome. Studies of experimental animals and humans show that maternal zinc deficiency can cause infertility, prolonged labor, intrauterine growth retardation, teratogenesis, or embryonic or fetal death. Although the teratogenic effects of zinc deficiency in the developing fetus are well documented, much less attention has been given to the impact on maternal function and health.

The purpose of this review was to 1) compare the maternal response to varying degrees of zinc deficiency during pregnancy, 2) describe the physiologic adjustments that occur in zinc metabolism to support maternal and fetal needs, and 3) describe conditions that may override these physiologic adjustments and put the health of the mother and fetus at risk.

VARYING DEGREES OF ZINC DEFICIENCY AND PREGNANCY OUTCOME IN EXPERIMENTAL ANIMALS

The teratogenic effects of severe zinc deficiency were first observed in chicks hatched from hens fed zinc-deficient diets (1).

The offspring had numerous skeletal defects and abnormalities of the brain (2), and many were weak and died within 4 d. Subsequent studies soon showed that severe zinc deficiency was also teratogenic in mammals. Hurley and Swenerton (3) reported that rats fed a zinc-deficient diet throughout pregnancy had fewer offspring and that they were growth retarded with multiple anomalies. Every organ system displayed abnormalities of development; malformations of the heart, lungs, brain, and urogenital system were common. External defects included misshaped heads and fused or missing digits of the feet. Similar defects were reported later in zinc-deficient mice, sows, and ewes.

Acrodermatitis enteropathica produces severe zinc deficiency in humans. This is an autosomal genetic recessive defect in zinc metabolism and causes a marked inhibition of zinc absorption. The advent of treatment with diiodohydroxyquin in 1953, a drug that improved zinc absorption but did not normalize plasma zinc concentrations, allowed the survival of patients with the disorder. The outcomes of 7 pregnancies in 3 acrodermatitis enteropathica patients showed the devastating effect of acrodermatitis enteropathica on fetal development (4). Of the 7 pregnancies, 5 resulted in poor outcomes—1 spontaneous abortion, 1 ancephalic fetus, 1 achondroplastic dwarf, and 2 low-birth-weight infants. Later, acrodermatitis enteropathica patients were treated with large oral doses of zinc. When these patients were given sufficient zinc to maintain normal plasma zinc concentrations throughout gestation, pregnancy outcomes were normal (5). Thus, plasma zinc concentration is an important determinant of pregnancy outcome.

The underlying mechanism whereby severe zinc deficiency causes developmental defects is not known with certainty; however, it is likely to be the result of the impairment of several metabolic functions. Abnormal synthesis of nucleic acids and protein, impaired cellular growth and morphogenesis, abnormal tubulin polymerization with resultant reductions in cellular motility and development, chromosomal defects, excessive cell death, and excessive lipid peroxidation of cellular membranes may all occur in severe zinc deficiency and contribute to teratogenic effects.

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Very little zinc is required to prevent congenital anomalies. In rats, the addition of only 1 mg Zn/L drinking water, to provide a total dietary zinc intake of ≈ 2.5 $\mu\text{g/g}$, eliminated all overt signs of developmental defects (6). The characteristic cyclic pattern of food intake throughout gestation, as seen with severe deficiency, was also eliminated. Apparently, the demand for zinc in early gestation to support normal embryogenesis is very small and is provided by extremely low-zinc diets. However, a sharp decline in food intake occurred on day 18 and continued for the last 3 d of gestation. An intake of 11 mg Zn/L drinking water was required to eliminate this anorexia. There is little transfer of zinc to the fetus before day 18. Anorexia corresponds with the sharp increase in permeability of the placenta to zinc and transfer to the fetus. Perhaps the fetal demand precipitated a more severe maternal deficiency, a drop in plasma zinc concentrations, and the anorexia and weight loss.

Using ^{65}Zn as a tracer, Masters et al (7) showed that the primary source of zinc for the developing rat fetus during the last 3 d of gestation in dams fed marginal diets is maternal muscle zinc. Dietary zinc is the primary source for the offspring of control dams who do not display anorexia. Masters et al estimated that about twice as much zinc than what is needed by the total conceptus is released from maternal tissues in conjunction with the onset of anorexia and rapid weight loss. Fairweather-Tait et al (8) also found that the uptake of an oral dose of ^{65}Zn into maternal bone was lower in marginally deficient pregnant dams than in controls. This implies that a higher proportion of the zinc absorbed from a marginal diet is directed to the developing offspring in comparison with controls.

Examination of pup and maternal weights showed that the response varies with the extent of zinc deprivation (6). At very low intakes (2–5 mg Zn/L drinking water), the dam's weight, as a percentage of the control dam's weight, was lower than was the pup's weight as a percentage of the controls. This suggests that the fetus has a high priority for the available zinc, and fetal growth was supported at the expense of maternal weight gain. At a more mild deficiency (11 mg Zn/L in drinking water), the dam's weight was equivalent to that of the controls fed 25 mg Zn/L in drinking water, but the pup's weight was still low. The fetal and maternal response to zinc deprivation may differ in humans, in whom there is only one offspring. It is apparent, however, that there is a threshold for dietary zinc that must be met to support fetal growth.

Most of the studies of zinc and pregnancy outcome have been done in rodents in which the demand for zinc is high because of multiple births. Studies in pregnant rhesus monkeys are especially useful because there is only one offspring and the outcome is likely to be more similar to that of humans. In general, the findings in monkeys mimic those in rats. When pregnant monkeys were fed 4 μg Zn/g diet, no overt signs of zinc deficiency occurred in the first half of gestation and the young were born without any developmental defects. Plasma zinc concentrations dropped in all animals after mid gestation. The fall in plasma zinc was related to the degree of anorexia, ie, when plasma zinc concentrations were low, the more mild the anorexia (9). Pregnancy loss was about 3 times higher in zinc-deficient animals than in controls (10). Symmetrical growth retardation occurred in 7 of the 8 male infants in the zinc-deficient group and in 2 of the 8 females. Birth weight was negatively correlated with plasma zinc concentrations. This suggests that in zinc-deficient animals, the decline in food intake led to maternal weight loss

and transfer of zinc from tissues to the plasma for uptake by the placenta and transfer to the fetus.

In most animal studies of zinc and pregnancy, low-zinc diets are started at conception. In practice, women eating low-zinc diets have probably done so for years before conception. Lowe et al (11) tried to reproduce the human situation more closely by adapting rats to a low-zinc diet (6 $\mu\text{g/g}$) 6 wk before conception. No congenital anomalies occurred and the weight of individual pups was not low. However, there was an insignificant decrease in the number of pups, and the total weight of the conceptus was slightly lower in the low-zinc group. In these animals, as in other studies of marginal zinc intakes, maternal food intake dropped abruptly on day 17, leading to a cessation of maternal weight gain. ^{65}Zn was infused on day 21 of gestation and the plasma disappearance of the tracer was modeled by using a 2-h zinc kinetics model. Two rapidly exchangeable zinc pools, which probably represent the plasma and part of the liver zinc concentration, were identified in the model. The turnover rates and zinc losses from these rapidly exchangeable zinc pools were higher in marginally deficient dams than in controls. Thus, during late pregnancy when the fetal demand for zinc is high and the dietary supply is low, the plasma turns over more frequently and transfers more zinc out of the circulation, probably to the fetus to support growth and development.

In summary, these studies in experimental animals showed that the only source of maternal tissue zinc available for the developing fetus is that released from catabolized tissue during anorexia. With diets totally devoid of zinc, cyclic periods of anorexia occur throughout gestation. However, this does not prevent multiple anomalies. Very little zinc is required to prevent these anomalies; as little as 4 $\mu\text{g/g}$ diet was sufficient for normal development in rhesus monkeys. This is comparable with 2 mg/d in human diets. With marginal intakes in the rat ranging from 2.5 to 9 $\mu\text{g/g}$ diet, the onset of anorexia coincides with the sharp increase in placental zinc transfer. Birth weights of monkeys with marginal zinc intakes were higher in those animals with lower plasma zinc concentrations and a higher degree of anorexia. To what extent catabolism of maternal tissue and subsequent zinc release offset insufficient intakes in humans is unclear. However, taken together, the data from animal studies support the need for information on maternal energy and zinc intakes along with measures of plasma zinc concentrations to clarify the relation between maternal zinc status and pregnancy outcome.

HUMAN STUDIES OF MATERNAL ZINC STATUS AND PREGNANCY OUTCOME

The poor pregnancy outcomes in women with acrodermatitis enteropathica and low plasma zinc concentrations document the important role of zinc in human pregnancy, and the effects observed in those mothers were similar to those in zinc-deficient pregnant animals—congenital anomalies and fetal growth retardation. Acrodermatitis enteropathica is quite rare, however. The effect of marginal maternal zinc status on pregnancy outcome is a more pertinent issue.

The first comprehensive evaluation of maternal zinc status and pregnancy outcome was reported by Jameson in 1976 (12). He studied 316 pregnant women and found that 60% of the women who gave birth to infants with congenital anomalies had low serum zinc concentrations in the first trimester. Also, women who

TABLE 1Surveys of the association between maternal zinc status and birth weight¹

Investigator	Year	Location	Number of subjects	Finding
Crosby et al (14)	1977	US	182	Mid pregnancy plasma zinc correlated with birth weight
Atinmo et al (15)	1980	Nigeria	50	Plasma zinc correlated with birth weight
Meadows et al (16)	1981	UK	238	Leukocyte zinc lower in mothers with SGA infants
Meadows et al (17)	1983	UK	90	Leukocyte zinc lower in mothers with IUGR infants
Patrick et al (18)	1982	Canada	13	Leukocyte zinc correlated with birth weight
Ghosh et al (19)	1985	Hong Kong	437	Birth weight positively correlated with serum zinc and negatively correlated with hair zinc
Simmer and Thompson (20)	1985	UK	79	Leukocyte zinc lower in mothers with SGA infants
Mameesh et al (21)	1985	Iran	57	Serum zinc correlated with birth weight, length, and head circumference
Wells et al (22)	1987	UK	70	Leukocyte zinc concentrations predicted low birth weights
Singh et al (23)	1987	India	92	Low serum zinc correlated with reduced birth weight and number of low-birth-weight infants
Higashi et al (24)	1988	Japan	228	Low serum zinc in third trimester associated with more low-birth-weight infants
Mbofung and Subbarau (25)	1990	Nigeria	22	Placental zinc content correlated with birth weight
Neggers et al (26)	1990	US	476	Serum zinc associated with adjusted birth weights
Yasodhara et al (27)	1991	India	176	Low serum zinc and higher cord blood zinc associated with larger birth weights
Jeswani and Vani (28)	1991	India	60	Lower cord blood zinc in SGA and preterm infants
Speich et al (29)	1992	France	66	Erythrocyte and plasma zinc predicted birth weight
Kirksey et al (30)	1994	Egypt	29	Serum zinc in second trimester accounted for 20% of variance in birth weight

¹US, United States; UK, United Kingdom; SGA, small-for-gestational age; IUGR, intrauterine growth retardation.

delivered either before or after normal term had low serum zinc concentrations in the third trimester. Thereafter, several studies of maternal zinc status and pregnancy outcome were done worldwide. Although the results of those studies were mixed, several adverse outcomes have been associated with maternal zinc status. Adverse fetal outcomes include congenital anomalies, reduced birth weight for gestational age, and preterm delivery. Maternal complications include pregnancy-induced hypertension, preeclampsia, intrapartum hemorrhage, infections, and prolonged labor.

There have been more studies of the relation between maternal zinc status and resulting birth weight than of any other pregnancy outcome. Because birth weight is a continuous variable, it can be studied in smaller sample sizes than can the incidence of congenital anomalies, maternal hemorrhaging, or maternal hypertension. A total of 41 studies of maternal zinc status and birth weight were published between 1977 and 1994 and were reviewed by Tamura and Goldenberg (13). I could not locate any other papers published since 1994. Seventeen of the 41 studies reported a significant relation between an indicator of maternal zinc status and birth weight or the incidence of fetal growth retardation (**Table 1**). The 17 studies were conducted throughout the world; 7 were performed in developing countries (India, Nigeria, Iran, and Egypt), whereas the other 10 were conducted in the United States, the United Kingdom, Canada, Hong Kong, Japan, and France. No geographic pattern was apparent. Studies that reported no association between maternal zinc status and pregnancy outcome were from the same countries.

The lack of consistency across studies may be due in part to 2 problems associated with data interpretation: an incorrect assessment of the predictor variable, maternal zinc status, and a failure to determine the independent effect of zinc on fetal growth after other factors that influence birth weight were controlled for. Although plasma zinc concentration is commonly used as an indicator of zinc status, interpretation of the measure-

ment is difficult because plasma zinc concentrations decrease with infection, vigorous exercise, and food intake. Assessment is more difficult during pregnancy because plasma zinc concentrations decline in proportion to the increase in plasma volume (31). Because plasma volume expansion is not consistent across all pregnancies, the fall in plasma zinc concentration is quite variable. Failure to document the stage of pregnancy at the time of the blood drawing and to use gestational-appropriate standards for evaluating the plasma zinc concentrations lead to erroneous conclusions about maternal zinc status.

Most of the studies used nonfasting blood samples drawn from women in clinics. A few studies attempted to control for the effect of food intake on plasma zinc concentrations by collecting blood within a specified time period, eg, 1000–1200 (26, 30). This reduced the variation in plasma zinc concentrations due to food consumption if all women in the study ate at approximately the same time before the blood was drawn.

The primary outcome variable, birth weight, is dependent on many factors besides maternal zinc status, eg, sex of the infant, maternal age, race, weight, gestational weight gain, smoking, and alcohol consumption. If a significant correlation between birth weight and serum zinc concentration is found, a follow-up stepwise multiple regression analysis should be performed to assess whether the association was due to confounding factors that may or may not influence birth weight. Most of the studies merely reported the correlation and did not perform the follow-up stepwise multiple regression analysis. The studies done by Neggers et al (26) and Kirksey et al (30) are exceptions.

A total of 12 randomized, controlled intervention trials of supplemental zinc and pregnancy outcome have been reported (**Table 2**). Of the 12 trials, 6 found no effect of the zinc intervention on pregnancy outcome. Two studies reported that supplemental zinc significantly improved fetal growth (40, 41). Both studies were done in populations in whom maternal zinc

TABLE 2
Randomized controlled trials of zinc supplementation and pregnancy outcome¹

Investigator	Year	Population	Number of subjects		Zinc supplementation mg/d	Effect of supplement
			Zinc	Placebo		
Jameson (32)	1976	Swedish women	64	248	45	Reduced delivery complications
Hunt et al (33)	1984	Hispanic Californian women	107	106	20	Reduced incidence of PIH
Hunt et al (34)	1985	Hispanic Californian teens aged <17 y	70	68	20	No effect
Ross et al (35)	1985	South African women, <20 wk gestation	32	33	4.6–12.9	No effect
Kynast and Saling (36)	1986	German women	170	345	20	No effect
Mahomed et al (37)	1989	UK women, <20 wk gestation	246	248	20	No effect
Cherry et al (38)	1989	US teens, primarily black	268	288	30	Reduced preterm delivery in normal-weight women
Simmer et al (39)	1991	UK women at risk for IUGR	30	26	22.5	Reduced IUGR in 29 compliers
Garg et al (40)	1993	Poor, urban Indian women	106	62	45	Increased birth weight and gestational age; reduced number of preterm and SGA infants
Goldenberg et al (41)	1995	Medically indigent, primarily black US women	294	286	25	Increased birth weight and head circumference; effect only in women with a BMI (in kg/m ²) <26
Jonsson et al (42)	1996	Danish women, <20 wk gestation	585	621	44	No effect
Osendarp et al (43)	2000	Poor, urban Bangladeshi women	269	290	30	No effect

¹US, United States; UK, United Kingdom; PIH, pregnancy-induced hypertension; IUGR, intrauterine growth retardation; SGA, small-for-gestational age.

depletion was likely. In the study conducted in India (40), the birth weights of infants born to women in the placebo group averaged only 2.6 kg. Infants born to zinc-supplemented mothers were 0.3–0.8 kg heavier, depending on the length of time supplemental zinc was provided. If the zinc supplement was initiated in the first trimester, the effect on birth weight was greater than if it was initiated in the third trimester. Goldenberg et al (41) studied the effect of supplemental zinc on birth weight in a group of medically indigent African American women. Only women with plasma zinc concentrations below the median for their population at 20 wk gestation were included in the study. Thus, women at risk of poor zinc nutriture were targeted for the intervention study. In the group as a whole, supplemental zinc increased birth weight by 126 g and increased infant head circumference by 0.4 cm. The significant effect of supplemental zinc was limited to nonobese women [ie, those with a body mass index (in kg/m²) of <26]. The lack of an effect of supplemental zinc on birth weight in obese women may be because obese women tend to have large babies. The influence of high maternal weight on birth weight may obscure any beneficial effect of zinc supplementation in that population.

Simmer et al (39) studied mothers at risk of delivering infants with intrauterine growth retardation. Risk was defined as having had a small-for-gestational-age infant previously, being maternally underweight, or being a smoker. Unfortunately, only 29 of the 56 women recruited were compliant. Thirteen of the 29 women took supplemental zinc; the remaining women took placebos. No women taking zinc had infants with intrauterine growth retardation, whereas 4 members, or 25%, of the placebo group delivered small infants.

Three of the studies reported a significant reduction in preterm deliveries in the zinc-supplemented groups (38, 40, 41); the effect was only observed among normal-weight women in the group studied by Cherry et al (38). Among Indian women (40), gestational age of the infant increased more with longer

periods of supplementation; the infants of those women supplemented from the first trimester had an average gestational age of 39.4 wk, whereas the infants of those supplemented from only the third trimester had a gestational age of 38.8 wk. The average gestational age among the placebo group was 38.3 wk. The reported increase in birth weight in this study is probably confounded by the increase in gestational age. Goldenberg et al (41) reported a tendency toward an increase in gestational age ($P < 0.08$) among women with BMIs <26.

Two groups reported that supplemental zinc reduced the incidence of maternal complications (32, 33). In a study of Swedish women, no statistical analysis of the data was performed, so the significance of the finding cannot be determined (32). Hunt et al (33, 34) found that 20 mg supplemental Zn reduced the incidence of pregnancy-induced hypertension among adult Hispanic women but not among adolescent Hispanic women.

Many of these randomized, controlled trials of zinc supplementation and pregnancy outcome lacked a sample size sufficient to detect differences. Several studies reported higher birth weights in the supplemented groups, but did not have sufficient power to achieve statistical significance (36, 39). The largest study completed enrolled 2000 volunteers, but only 1208 of these subjects took the zinc supplements as prescribed (42). Possibly, results from some of the other studies are flawed because of poor compliance. The major challenge in conducting zinc supplementation trials is the lack of a reliable index of zinc status to identify populations at risk and, therefore to assess responsiveness to zinc therapy. The study by Goldenberg et al (41) probably detected a significant effect because they targeted women at risk by selecting only those who had plasma zinc concentrations below the median for study.

The outcomes of these 12 studies on zinc supplementation and pregnancy outcome indicate the need for several important features in a randomized clinical trial: 1) a sample size sufficient to detect the effect of zinc supplementation after all other variables

influencing fetal growth are controlled for; 2) procedures to ensure compliance with the intervention; 3) inclusion of women at risk of zinc deficiency, such as those with low plasma zinc concentrations at entry because this increases the probability of a detectable effect; and 4) consideration of maternal body weight in the data evaluation. Several studies showed that overweight women (41) and underweight women (38, 41) are less responsive to zinc intervention than are normal-weight women.

PHYSIOLOGIC ADJUSTMENTS IN ZINC METABOLISM DURING PREGNANCY

On the basis of the total weight of the pregnancy tissues gained during gestation and the zinc concentration of those tissues, it is estimated that the additional need for zinc in a human pregnancy is $\approx 1540 \mu\text{mol}$, or $\approx 100 \text{ mg}$ (44). This represents $\approx 5\text{--}7\%$ of the whole-body zinc concentration in a nonpregnant woman. Most of the zinc gained is deposited in the fetus (57%), and in the uterine muscle (24%).

This additional need for zinc during pregnancy can be met by an increase in zinc intake or by adjustments in zinc homeostasis. Surveys show that pregnant women consume an average of 10 mg Zn/d (31). In 27 reported studies, dietary zinc intakes of nonvegetarians ranged from 5.7 to 22 mg/d ; the intakes of vegetarians ranged from 5 to 12.6 mg/d with a mean of $\approx 8 \text{ mg/d}$. There is no evidence that pregnant women increase their intake of zinc. The methods available for assessing zinc intakes may be too imprecise to detect small changes in intake, however. Because there is no evidence of a marked increase in dietary zinc intakes during gestation, homeostatic adjustments in zinc utilization must be the primary mechanism for meeting the additional zinc demands for reproduction. The homeostatic adjustments are likely to be greater in women consuming diets low in zinc.

Studies in experimental animals suggest that changes in intestinal zinc absorption may be the primary homeostatic adjustment in zinc metabolism to meet the needs for pregnancy. Davies and Williams (45) found that zinc absorption from ligated segments of the duodenum in rats increased 2-fold by late pregnancy and continued to increase during lactation. However, the results of studies of zinc absorption in pregnant women are not as straightforward. Swanson and King (46) found that apparent zinc absorption calculated from metabolic balance studies was higher in pregnant women than in nonpregnant women fed the same diet, resulting in a net gain of 1.0 mg Zn/d in the pregnant group. The difference was not significant, however. In a follow-up to that study, zinc absorption was measured by using a stable isotope in pregnant and nonpregnant women consuming plant- or animal-based diets (47). Both pregnant and nonpregnant women absorbed $\approx 25\%$ of the zinc from each of the diets; there was no difference due to gestation. The cross-sectional design of the study combined with the small sample size may have prevented detection of any differences. Fung (48) completed a longitudinal study of zinc absorption and metabolism in women during pregnancy and lactation. Thirteen women were followed from before conception to early lactation (8–12 wk postpartum). Fractional zinc absorption from a standardized breakfast meal increased by 30% during gestation, from a mean ($\pm \text{SEM}$) $14.6 \pm 1.3\%$ before conception to $19.4 \pm 2.6\%$ in the third trimester. This increase was not significant. However, during lactation when the additional need for zinc is greater, zinc absorption increased by 75%, to $25.3 \pm 3.9\%$ ($P < 0.05$). Moser-Veillon et al (49) also found that zinc absorp-

tion of lactating women was $\approx 80\%$ higher than that of nonlactating-postpartum or never-pregnant women. These data suggest that intestinal zinc absorption is a site of regulation of zinc metabolism during pregnancy and lactation, and that the change during lactation is greater than that during pregnancy probably because of the increased need.

Other potential mechanisms for adjustment of zinc metabolism include reduced endogenous gastrointestinal zinc excretion, renal conservation, and release of maternal tissue zinc. Fung (48) found no changes in endogenous fecal zinc losses in her longitudinal study; however, because the women were not consuming constant diets, this possibility cannot be ruled out. Jackson et al (50) measured endogenous fecal zinc excretion in a group of slum-dwelling lactating women in the Amazon. They found that the increased need for zinc during lactation was met in part by a decrease in endogenous fecal zinc losses.

The concentration of urinary zinc increases during gestation, reaching a value nearly twice that preconception (48). Urinary zinc concentrations decline during lactation but are still higher than prepregnant concentrations. Others have observed marked increases in urinary zinc excretion during pregnancy, possibly because of an increase in the glomerular filtration rate (46, 51). Renal conservation does not appear to be a mechanism for retaining zinc during pregnancy and lactation.

The demand for zinc to support fetal growth may also be met by the release of maternal tissue zinc, as is observed in experimental animals fed low-zinc diets that induce anorexia (7). There are no reports that pregnant women experience anorexia near term leading to muscle catabolism. Approximately 30% of whole-body zinc is found in bone. Measurements of bone mineral content before conception and immediately after delivery failed to find any changes in bone mineral (52). It appears, therefore, that adjustments in zinc absorption are the primary means by which additional zinc needs are met during pregnancy. A model depicting the quantitative adjustments in zinc metabolism to meet the daily needs in late pregnancy is shown in Figure 1.

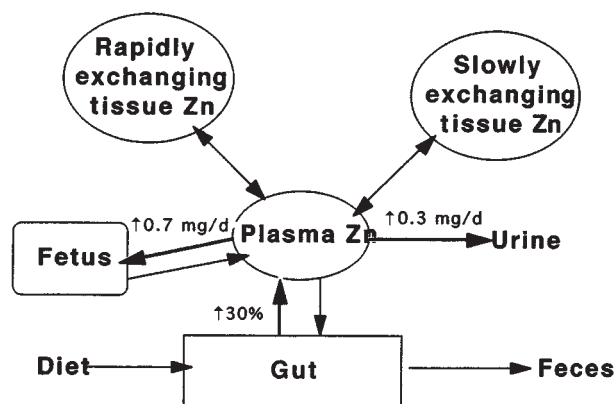


FIGURE 1. Model of zinc metabolism in late pregnancy. Zinc absorption increases on average $\approx 30\%$ in late pregnancy, or by $\approx 1 \text{ mg/d}$; $\approx 0.7 \text{ mg}$ of the absorbed zinc is transferred to the fetus. Urinary zinc excretion increases by $\approx 0.3 \text{ mg/d}$. Anorexia occurs if the dietary supply of zinc is limited in experimental animals, leading to an increased turnover of zinc from rapidly exchanging tissue (ie, liver) or a release of zinc from tissue more slowly turning over (ie, muscle).

TABLE 3
Conditions that may induce a secondary zinc deficiency during pregnancy

Factors that may limit the net absorption of zinc
High intake of dietary inhibitors of zinc absorption, such as phytate, fiber, and calcium
High doses of supplemental iron
Gastrointestinal diseases that limit zinc absorption, such as intestinal bypass, Crohn disease, bacterial overload, and viral or bacterial infections
Factors that may interfere with placental transport of zinc
Cigarette smoking
Alcohol abuse
Acute maternal infections
Strenuous exercise
Therapy with certain drugs

SECONDARY ZINC DEFICIENCY DURING PREGNANCY

A net increase in zinc absorption seems critical in meeting the fetal demands for zinc. Dietary factors that inhibit zinc absorption, or any gastrointestinal disease that interferes with the capacity to absorb zinc, would put the mother and fetus at risk. Zinc is transferred to the fetal-placental unit via the plasma. Thus, any factor that alters that transport function could also put the pregnancy at risk. Conditions that could interfere with adjustments in zinc absorption or plasma transport and, therefore, cause a secondary zinc deficiency are listed in **Table 3**.

Dietary phytate

The nutritional adequacy of dietary zinc depends on both the amount in the diet and its bioavailability. Of the factors known to affect zinc bioavailability, phytate is one of the greatest inhibitory factors. The degree to which phytate inhibits zinc absorption has been defined by the ratio of phytate to zinc in the diet (53). There is some disagreement about the magnitude of the ratio of phytate to zinc above which zinc status may be compromised (54); some have used 15 as the cutoff and others have used 20. The World Health Organization (53) recommends an algorithm for estimating zinc bioavailability that is based on zinc intake and an availability factor. The availability factor, ie, the percentage available dietary zinc, is estimated to range from 10% to 50% depending on the phytate-zinc molar ratio in the diet. Zinc availability is projected to be 10% if the phytate-zinc ratio is >30, 15% if the ratio is 15–30, 30% if the ratio is 5–15, and >50% if the ratio is <5. Diets with a phytate-zinc ratio >15 are high in unrefined, unfermented, and ungerminated cereal grain, especially when fortified with inorganic calcium salts and when intake of animal protein is negligible. Such diets are consumed by many poor women living in developing countries.

Intake of a high-phytate diet during pregnancy may interfere with maternal zinc absorption and lead to a secondary zinc deficiency. Kirksey et al (30) studied the relation between maternal zinc nutriture and pregnancy outcome in a group of women living in an Egyptian village. The zinc intakes of these women were not particularly low, ≈ 9.7 mg/d. However, the dietary phytate-zinc ratio was 14.8 and the estimated availability of dietary zinc was 21%, with the use of an algorithm published by Murphy et al (55). Thus, only 2.0 mg dietary Zn was available for absorption. If fetal demands are ≈ 0.7 mg/d during the last quarter of pregnancy, only 1.3 mg of dietary Zn is left to replace maternal losses. The amount of bioavailable zinc was not related to birth

weight, but it was part of a profile of micronutrient intakes that related to neonatal habituation behavior, a measure of early information processing. Additionally, performance on the Bayley motor test at 6 mo of age was negatively related to maternal intakes of plant zinc, phytate, and fiber, suggesting that the amount of available zinc consumed during pregnancy influences infant cognitive development during the first 6 mo of life (56).

A recent study in Malawi showed that high intakes of phytate, along with frequent pregnancies and malarial infections, reduced the zinc status of pregnant women (57). The median phytate-zinc ratio in this population was 17. Plasma zinc concentrations at 24 wk gestation in women with a phytate-zinc ratio below the median did not differ from those women with a ratio above the median; the median plasma zinc value was 7.9 $\mu\text{mol/L}$. 37% of women had values below the cutoff value specific for stage of gestation. Women with phytate-zinc molar ratios above the median were significantly older, had more pregnancies, and had significantly lower hair zinc concentrations than did their counterparts, 1.6 compared with 1.4 $\mu\text{mol/g}$ ($P < 0.027$). Hair zinc reflects chronic zinc status over the period of hair growth and is a more stable indicator than is plasma zinc. Plasma zinc is an acute index of zinc status that is difficult to interpret during pregnancy because during this time period there is a decline in plasma zinc concentration that begins in the first trimester and continues throughout gestation (57). These data show that chronic intake of diets with high molar ratios of phytate to zinc limits zinc absorption and reduces maternal zinc status. It is interesting that there was no relation between dietary phytate-zinc ratios and plasma zinc concentrations in these women. Possibly, other compensatory adjustments in zinc metabolism occurred to maintain plasma zinc concentrations in the presence of poor zinc absorption. Additionally, the relation between plasma zinc concentration and phytate intake may be more difficult to detect because of the many factors besides zinc status that influence plasma zinc, including disease states, diurnal variation, fasting, length of time before separating the plasma from cells, and sample refrigeration conditions.

High calcium intakes in the presence of high phytate may further reduce the availability of zinc (54). In a group of Guatemalan women, zinc intake was comparable with that of healthy North American populations consuming omnivorous diets. However, the Guatemalan diet is largely plant-based and contains high amounts of phytate, calcium, and fiber. Tortillas contain a relatively high concentration of calcium derived from lime used to soak the maize before making the tortillas. The critical ratio of calcium \times phytate to zinc that inhibits zinc bioavailability has not been defined. It has been suggested that values >22/MJ, to account for differences in the amount of food consumed, may induce marginal zinc deficiency. The ratios of periurban Guatemalan women during the third trimester of pregnancy averaged 40/MJ. It is likely that the zinc nutriture of these women is compromised. Further studies of maternal zinc status, physiologic adjustments in zinc metabolism, and pregnancy outcome in populations consuming diets with low zinc availability are necessary to define thresholds for supporting good pregnancy outcomes.

Iron supplementation

Practically all pregnant women around the world receiving prenatal care are given supplemental iron. In the United States, most pregnant women take prenatal vitamin-mineral supplements.

Although the Institute of Medicine (58) and the American College of Obstetrics and Gynecology recommend 30 mg Fe/d for all pregnant women, commercial prenatal vitamin-mineral supplements listed in the 1997 *Physician's Desk Reference* (59) contain an average of 54 mg Fe; the amount of iron in the supplements ranges from 36 to 65 mg.

Additionally, many physicians in the United States prescribe therapeutic doses ≥ 100 mg Fe/d as a prophylactic measure to prevent iron deficiency. The frequency of that practice is not documented. Furthermore, the World Health Organization recommends 60–120 mg Zn/d for women in developing countries (60). Supplemental folic acid is also recommended, but supplemental zinc is not. Thus, women in developing countries typically receive ≈ 100 mg supplemental Fe throughout their pregnancies without any additional zinc. As mentioned above, the dietary zinc intakes of these women are typically low and the zinc is poorly available. The typical iron-zinc ratio in their diets is estimated to be 24:1, ≈ 120 mg Fe:5 mg Zn. This imbalanced intake of iron and zinc may put their zinc status at risk during pregnancy.

Interactions between iron and zinc occur during gastrointestinal absorption. The deleterious effect of supplemental iron on zinc absorption and a depression in plasma zinc concentrations were shown in studies of experimental animals and humans (61–70). The mechanisms for this iron-zinc interaction probably involved a combination of intraluminal and intracellular effects (66). Iron and zinc may compete in the absorption process by: 1) displacing one another on the molecule necessary for their uptake from the lumen into the intestinal cell, 2) competing for pathways through the mucosal cell into the blood stream, or 3) interacting with one another and a third substance to form an insoluble complex, impairing the absorption of both minerals.

Studies evaluating the effect of iron fortification in infant formulas (71) or weaning foods (72) fail to show an effect on zinc absorption. Possibly, the difference between the effects of food fortified with iron compared with supplemental iron are because of differences in the dose and form of iron given. The amount of iron provided by supplements is greater than that in one serving of fortified cereal or formula and is in a highly soluble form, i.e., ferrous sulfate, enabling the iron to readily bind with ligands in the intestine.

Using ^{65}Zn , Lonnerdal et al (73) attempted to delineate the mechanism by which iron interferes with zinc status in pregnant rhesus monkeys. Supplemental iron ($4 \text{ mg FeSO}_4 \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$) decreased the intestinal uptake of zinc, but whole-body zinc turnover also decreased by 25%, compensating in part for the decrease in absorption. Tissue zinc concentrations were conserved and plasma zinc concentrations did not change. Studies in pregnant women in which stable isotopes and kinetic models of zinc metabolism are used to determine the effects of varying concentrations of supplemental iron on intestinal zinc absorption and maternal zinc status are needed.

Smoking

After all factors influencing birth weight were controlled for, infants born to mothers who smoked consistently weighed less than did infants who were born to nonsmoking mothers (74). The adverse effects of smoking on fetal growth are proportional to the frequency of smoking. Besides reducing fetal growth, exposure to cigarette smoke in utero increases the risk of preterm delivery, perinatal mortality, and, possibly, spontaneous abortion (74). Cigarette smoke contains >2000 different compounds. The mechanism by

which exposure to cigarette smoke reduces uterine growth is not known, but intrauterine hypoxia and reduced uteroplacental blood flow are 2 widely quoted mechanisms (74). A secondary zinc deficiency may also contribute to the reduction in fetal growth.

Several studies have shown that zinc is trapped in the placentas of smokers leading to a reduced transfer of zinc to the fetus and impaired growth (75–79). Additionally, the zinc status of infants born to smokers is lower than that of infants born to nonsmokers. The infants of smokers had significantly lower concentrations of plasma zinc, alkaline phosphatase, and cord vein erythrocyte zinc. Possibly, cadmium from tobacco smoke induces the synthesis of metallothionein, a cadmium binding protein that also binds zinc, causing zinc to be sequestered in the placenta and less available to the fetus. Cadmium may also induce higher concentrations of metallothionein in maternal tissues, such as the liver, and reduce the availability of zinc to the fetus. These theories are supported by data from Kuhnert et al (80), who showed that birth weight was negatively related to placental cadmium and placental zinc.

The synthesis of α_2 -macroglobulin is induced by tobacco smoke, and the plasma concentrations of α_2 -macroglobulin are higher in smokers (81). Although the exact biological function of α_2 -macroglobulin is unclear, one of its functions is to bind a wide variety of compounds, including proteolytic enzymes, lymphokines, lectins, and ions such as zinc and nickel. In a study of 289 women who had serum samples drawn at 18 and 30 wk gestation (81), a high α_2 -macroglobulin concentration as early as 18 wk gestation was associated with a significant increase in fetal growth retardation. The effect was greater in women who smoked. In smokers, each 1.0-g/L increase in serum α_2 -macroglobulin was associated with a 227-g decrease in birth weight after gestational age at delivery, maternal race, infant sex, maternal body mass index, and history of a previous low-birth-weight infant were controlled for. α_2 -Macroglobulin is 1 of 2 major zinc binding proteins in the plasma; the second is albumin. α_2 -Macroglobulin has a higher binding constant for zinc, making zinc bound to that protein less available than that of albumin-bound zinc. Plasma zinc concentrations did not differ among the smokers and nonsmokers in the above study. However, the tissue availability of zinc in the smokers may have been reduced because a higher proportion of the serum zinc was bound to α_2 -macroglobulin.

Although tobacco smoke may alter zinc metabolism and reduce its availability to the fetus, sufficient dietary zinc intakes may overcome these effects. However, most studies show that the quality of the diet and the quantity of nutrients consumed are lower in smokers than in nonsmokers (82–86). For example, the zinc intake of a group of pregnant women in London who smoked was 20% lower than that of nonsmokers, and their diets only supplied 51% of the amount recommended for pregnancy (85). Given the potential effects of tobacco smoke on zinc metabolism, it is likely that pregnant women who smoke can have a secondary zinc deficiency, particularly if their zinc intake is poor.

Alcohol abuse

Alcohol is a potent teratogen. The exact mechanism by which alcohol intake adversely affects fetal growth and morphogenesis is not known. Because zinc deficiency is also a potent teratogen and because urinary zinc losses increase with alcohol use, it has been hypothesized that zinc deficiency is a coteratogen with alcohol (74).

Studies in rats show that zinc deficiency in addition to alcohol intake had more severe effects on fetal development than did

either alcohol or low zinc intakes alone (85). Fetal weights were lower in the groups fed the zinc-deficient diet with either 15% or 20% of energy from alcohol. Also, the combination of alcohol with a zinc-deficient diet increased the amount of resorption and external malformations more than with did a zinc-deficient or ethanol-containing diet alone. The results suggest that zinc deficiency potentiates the teratogenic effects of alcohol. Alcohol reduces the placental transport of zinc (88), and a reduction in intestinal absorption may also occur (89).

There are few studies of the effect of alcohol on maternal zinc status. One study compared the zinc status of 25 alcoholic and 25 nonalcoholic, pregnant women (90). Maternal and umbilical cord blood zinc concentrations were significantly lower in the alcoholic than in the nonalcoholic women: 0.51 compared with 0.72 mg/L and 0.66 compared with 0.81 mg/L, respectively. The incidence of birth defects was correlated with maternal plasma zinc concentrations but not with cord blood concentrations.

Zinc supplementation has been suggested as a way to prevent or lessen adverse alcohol-related effects. However, a study in rats failed to show that supplemental zinc increased the placental transport of zinc in the presence of a high-ethanol diet (91). A marked increase in plasma zinc concentrations may be necessary to overcome the hyperzincuria associated with alcohol as well as impaired placental transport.


Acute maternal stress

Keen et al (92) proposed that an acute phase reaction due to a number of diverse drugs and environmental challenges induces a secondary zinc deficiency in pregnant animals by stimulating the synthesis of metallothionein. Metallothionein is a small, cysteine-rich, intracellular protein that binds zinc and copper with high affinity. Although the divalent cations are classic inducers of metallothionein, many organic compounds, endogenous hormones (adrenocorticosteroids), and cytokines can also stimulate its synthesis. An enhanced synthesis of metallothionein is a component of the acute phase response. As a consequence of its synthesis, zinc is sequestered in the liver and plasma zinc concentrations decline. This reduction in plasma zinc concentrations reduces the availability of zinc to the fetus and could represent a developmental risk.

Many developmental toxins given to experimental animals in mid gestation elevated maternal liver metallothionein and zinc concentrations and decreased maternal plasma zinc concentrations and embryonic zinc uptake (92). Examples of developmental toxins with this effect include 6-mercaptopurine, valproic acid, urethane, α -hederin, ethanol, and cytokines. For example, administration of tumor necrosis factor α to a group of pregnant rats on day 8 of gestation increased maternal liver ^{65}Zn uptake by 8% and reduced the plasma and embryonic content by 38% and 57%, respectively. These studies suggest that any condition that increases the release of cytokines for a chronic period of time could reduce the availability of zinc to the fetus and cause developmental defects. Chronic, strenuous physical activity throughout gestation is associated with a reduction in birth weight. Strenuous exercise also leads to an increase in cytokine release. Possibly, the reduction in birth weight is due, in part, to hepatic sequestering of zinc and a fall in plasma zinc concentrations.

SUMMARY

Studies in experimental animals show that maternal zinc deficiency impairs fetal growth and increases the risk of complica-

tions at delivery. The degree of fetal growth retardation is related to the degree of zinc depletion. In humans, an association between maternal zinc status and birth weight has been reported. It is likely, however, that poor maternal zinc status is due to the presence of a condition or factor that alters zinc utilization rather than to the intake of a zinc-poor diet. Conditions that could reduce maternal zinc status include subsistence on a cereal-based diet that is high in phytate, ingestion of high amounts of supplemental iron, smoking, alcohol abuse, and an acute stress response to infection or trauma. All of these conditions could lower plasma zinc concentrations and reduce the amount of zinc available to the fetus. Women with these conditions could be given a supplement providing ≈ 25 mg Zn during pregnancy to decrease the risk of complications associated with zinc deficiency. 

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