# Maternal plasma zinc concentrations and pregnancy outcome[1–3]

*Tsunenobu Tamura, Robert L Goldenberg, Kelley E Johnston, and Mary DuBard*

**ABSTRACT**
**Background:** There is no consensus in the literature as to whether maternal zinc nutriture is associated with pregnancy outcome or fetal growth.
**Objective:** We evaluated the associations between plasma zinc concentrations during pregnancy and various measures of pregnancy outcome and neonatal conditions at birth.
**Design:** We measured zinc concentrations in plasma samples obtained at a mean of 16 wk of gestation (range: 6–34 wk) from 3448 women who were screened for a trial designed to evaluate the effect of zinc supplementation on fetal growth. Subjects were from low socioeconomic backgrounds and attended a public health clinic for their prenatal care. Plasma zinc concentrations were compared with pregnancy outcome, including complications during pregnancy and delivery, and anthropometric measures and Apgar scores of neonates.
**Results:** Plasma zinc concentrations declined as gestation progressed. After plasma zinc concentrations were adjusted for gestational age, they were not significantly associated with any measure of pregnancy outcome or neonatal condition.
**Conclusion:** We conclude that plasma zinc concentrations during the late first trimester to the early third trimester do not predict pregnancy outcomes in women of a low socioeconomic background. *Am J Clin Nutr* 2000;71:109–13.

**KEY WORDS** Zinc, pregnancy outcome, fetal-growth retardation, preterm delivery, hypertension, amnionitis, postpartum infection, birth weight, Apgar score, infants, women

## INTRODUCTION

During the past few decades, many investigators have evaluated the relation between maternal zinc nutriture and pregnancy outcome in humans and animals (1–3). It is well known that zinc deficiency during pregnancy in experimental animals causes fetal-growth retardation and malformations (4, 5). In humans, however, a firm consensus has never been reached as to whether there is a positive association between maternal zinc nutriture and pregnancy outcome, including birth weight of infants and complications during pregnancy and delivery. This lack of agreement may be largely because the methods used to assess zinc nutriture are not sufficiently sensitive and specific (3). Zinc nutriture of pregnant women has been assessed by measuring maternal zinc concentrations in plasma or serum, leukocytes, erythrocytes, and amniotic fluid as well as by other indexes including dietary zinc intake (1–3, 6–9).

To resolve this issue, the effect of zinc supplementation on various measures of pregnancy outcome was evaluated by several groups of investigators (10–17). If zinc supplementation was proven to be effective in improving pregnancy outcome in a certain population, this would provide conclusive evidence that this population had inadequate zinc nutriture and that zinc is important in human pregnancy. However, the results of these studies were also equivocal (3). Although many studies showed no favorable effect of zinc supplementation, our trial in a group of women in the Birmingham area indicated that zinc supplementation improves pregnancy outcome. This double-blind study was conducted in low-income African American women with plasma zinc concentrations below the 50th percentile of the entire population screened at ≈16 wk of gestation (17). When subjects were screened for this trial, plasma zinc concentrations were measured in a total of 3448 plasma samples obtained from pregnant African American and white women (17). In the study reported here, we used the data from these 3448 women to evaluate the relations between plasma zinc concentrations and pregnancy outcome, including birth weight and Apgar scores of infants and various complications during pregnancy and delivery.

## SUBJECTS AND METHODS

### Subjects

The plasma zinc concentrations of 3742 pregnant women at <34 wk of gestation were measured when the women were screened for enrollment in a double-blind trial to evaluate the effect of zinc supplementation on pregnancy outcome (17). Nearly all women were of a low socioeconomic background and received their prenatal care at 4 clinics of the Jefferson (Alabama) County Public Health Department between March 1991 and August 1993. The trial was reviewed annually and approved by the Institutional Review Board at the University of Alabama at Birmingham, and each subject or guardian provided signed, informed consent.

[1] From the Departments of Nutrition Sciences and Obstetrics and Gynecology, University of Alabama at Birmingham.

[2] Supported in part by the National Institutes of Health (HD27289 and HD28119) and the Agency for Health Care Policy and Research (290-92-0055).

[3] Address reprint requests to T Tamura, Department of Nutrition Sciences, 218 Webb Building, University of Alabama at Birmingham, UAB Station, Birmingham, AL 35294-3360. E-mail: tamurat@uab.edu.

Received March 11, 1999.
Accepted for publication June 24, 1999.

Of the total number of women screened, 580 pregnant African American women were selected to participate in the zinc supplementation trial. These women had plasma zinc concentrations below the 50th percentile of the population screened after adjustment for gestational age. Of these 580 participants in the trial, 294 women were supplemented with zinc and the remaining 286 were given placebo (17). The 3448 women screened who did not receive supplemental zinc throughout pregnancy were the subjects of the study presented here. All women, including zinc-supplemented subjects, were offered a daily prenatal multivitamin and mineral tablet (Mission Pharmacal, San Antonio, TX) to be taken from the time of the first prenatal visit until delivery. The tablet contained a daily dose of 30 mg Fe as ferrous gluconate, 50 mg Ca, 400 μg folic acid, and other vitamins, but not zinc. Because this was a general obstetric population, neither compliance with taking the supplement nor dietary intake data were evaluated. However, mean compliance in the subjects who participated in the zinc supplementation trial was 78% by pill counting (17).

### Clinical data and anthropometric measurements

Information on the mothers' medical conditions and their habits during pregnancy was obtained at each prenatal visit throughout pregnancy; delivery information was also collected. Information on maternal age, prepregnancy weight, and parity was obtained at the first prenatal visit at an average of 16 wk of gestation (range: 3–33 wk). Gestational age (wk) at the first visit was estimated based on the first day of the last menstrual period. Gestational age at birth was also determined from the first day of the last menstrual period when a difference of <2 wk was found between this estimation and gestational age determined by ultrasound examination. When a discrepancy of >2 wk was found between these 2 values, or the subject was not sure of the time of her last menstrual period, the gestational age measured by ultrasound was used. Blood pressure was measured with a sphygmomanometer at each visit. Hypertension was defined as a systolic pressure >140 mm Hg or a diastolic pressure >90 mm Hg at any time during prenatal care or as any type of hypertension at the time of delivery. Under this definition, pregnancy-induced hypertension, preeclampsia, eclampsia, and chronic hypertension were included. The clinical data were stored in a computer system at the Department of Obstetrics and Gynecology.

Anthropometric measures of infants, including birth weight, were made within 1 h of birth, and the Apgar score was measured by an experienced nurse in the delivery room. All subjects delivered their babies (49% girls and 51% boys) at an average of 38.3 ± 3.2 wk of gestation at the university or county hospital. The infants' mean (±SD) birth weight was 3121 ± 672 g. Fetal-growth restriction was defined as a birth weight less than the 10th percentile for gestational age at birth as established previously (18).

### Zinc measurement

Nonfasting blood samples were collected at the first prenatal visit in trace element–free tubes containing sodium heparin (Vacutainer; Becton Dickinson, Rutherford, NJ). Blood samples were refrigerated immediately and plasma was then separated by centrifugation at 900 × *g* for 10 min at 22°C. Plasma samples were stored at –70°C until zinc concentrations were measured by atomic absorption spectrophotometry; a detailed description of the procedures followed was reported previously (19). The CV of repeated zinc analyses of pooled plasma samples was ≈4% in our laboratory.

### Statistical analyses

Basic statistical analyses were performed by using Student's *t* test, analysis of variance, chi-square, and Pearson correlation tests. Because zinc concentrations declined as pregnancy progressed, they were adjusted for gestational age by using *z* scores. In the analysis of maternal complications, we compared the prevalence of each condition in women in the lowest quartile of plasma zinc concentration with that in women in the upper 3 quartiles. The maternal complications analyzed included the prevalence of fetal-growth restriction, preterm delivery, hypertension, amnionitis, and postpartum infection. The relations between plasma zinc concentrations and birth weight, head circumference, crown-heel length, Apgar scores at 1 and 5 min, and gestational age at birth were evaluated by Pearson correlation coefficients. All analyses were performed with SAS (version 7, TS T1; SAS Institute Inc, Cary, NC). *P* values <0.05 were considered significant.

## RESULTS

Of 3448 subjects, 85% were African American and 15% were white; 33% were primiparous. The subjects' mean age was 22.4 y (range: 11–44 y). The characteristics of the subjects are presented in **Table 1**. The mean gestational age at screening was 1 wk later in African Americans than in whites. The mean body mass index (BMI) and weight of the African American subjects were significantly larger than those of whites, although there were no significant differences in mean height and age between groups. Significantly more whites smoked cigarettes or used alcoholic beverages or drugs. The mean plasma zinc concentration of whites was significantly higher than that of African Americans because of both the earlier gestational age of the whites when blood was drawn and racial differences (20).

To investigate the characteristics of women who enrolled for care at different times in their pregnancy, comparisons were made among 3 groups divided according to the timing of the first prenatal visit (**Table 2**). Most subject characteristics were not significantly different among these groups, with the exception of maternal age, for which differences were minimal. Nevertheless, plasma zinc concentrations were lower in the subjects who had their first prenatal visit later in pregnancy. This is consistent with the finding of a steady decline in plasma

**TABLE 1**
Comparison of characteristics between African American and white women

| | African Americans (*n* = 2943) | Whites (*n* = 505) | $P^2$ |
|---|---|---|---|
| Age (y) | 22.3 ± 5.4[1] | 22.9 ± 5.2 | NS |
| Gestational age at screening (wk) | 15.4 ± 7.3 | 14.4 ± 6.8 | 0.002 |
| BMI (kg/m²) | 26.6 ± 6.5 | 25.0 ± 5.9 | 0.0001 |
| Weight (kg) | 71.4 ± 18.7 | 67.2 ± 18.0 | 0.0001 |
| Height (cm) | 163 ± 6 | 163 ± 7 | NS |
| Primiparous (%) | 33 | 31 | NS |
| Smoking (%) | 13 | 53 | 0.001 |
| Alcohol or drug use (%) | 17 | 26 | 0.001 |
| Plasma zinc at screening (μmol/L) | 10.9 ± 2.4 | 11.3 ± 2.4 | 0.002 |

[1] $\bar{x}$ ± SD.
[2] Student's *t* test.

**TABLE 2**
Characteristics of subjects by gestational age at the first prenatal visit[1]

| | <12 wk (*n* = 1341) | 12–19 wk (*n* = 1140) | ≥20 wk (*n* = 976) | $P^2$ |
|---|---|---|---|---|
| African American (%) | 83 | 85 | 88 | NS |
| Age (y) | 22.7 ± 5.3[a,3] | 22.3 ± 5.4[b] | 22.1 ± 5.4[b] | 0.03 |
| BMI (kg/m$^2$) | 26.3 ± 6.7 | 26.5 ± 6.7 | 26.2 ± 5.4 | NS |
| Weight (kg) | 70.7 ± 19.4 | 70.5 ± 19.1 | 71.2 ± 17.0 | NS |
| Height (cm) | 162 ± 6 | 163 ± 6 | 163 ± 6 | NS |
| Primiparous (%) | 34 | 33 | 28 | NS |
| Smoking (%) | 17 | 20 | 21 | NS |
| Alcohol or drug use (%) | 19 | 17 | 18 | NS |
| Plasma zinc at screening (μmol/L) | 12.0 ± 2.2[a] | 10.9 ± 2.4[b] | 9.7 ± 2.2[c] | 0.0001 |
| Female infants (%) | 51 | 49 | 48 | NS |

[1] Means within a row with different superscript letters are significantly different.
[2] ANOVA with Duncan's new multiple-range test for post hoc comparison.
[3] $\bar{x}$ ± SD.

zinc concentrations between 8 and 22 wk of gestation at a rate of ≈0.2 $\mu mol \cdot L^{-1} \cdot wk^{-1}$ in all subjects combined, after which concentrations plateaued (**Figure 1**).

The prevalence of maternal complications in our total population as well as in subjects in the lowest and upper 3 quartiles of plasma zinc concentrations is shown in **Table 3**. There were no significant differences in the prevalences of fetal-growth restriction, preterm delivery (<37 wk gestation), early preterm delivery (<32 wk gestation), hypertension, amnionitis, and postpartum infections between these 2 groups. Similar comparisons were made between women in the lowest and highest quartiles of plasma zinc concentrations; there were also no significant differences between these 2 groups in the prevalences of all complications.

There were also no significant correlations between plasma zinc *z* scores and various neonatal anthropometric measures, including birth weight, head circumference, crown-heel length, Apgar scores at 1 and 5 min, and gestational age at birth (**Table 4**). Regression analyses adjusted for maternal age, maternal weight, race, gestational age at birth, and plasma zinc *z* score confirmed that there was no significant relation between plasma zinc concentrations and any of the pregnancy outcomes studied.

## DISCUSSION

Mean plasma zinc concentrations in the study population declined as pregnancy progressed until ≈22 wk of gestation, and then plateaued thereafter (Figure 1). This finding is consistent with other investigations (21–24). The decline in plasma and serum zinc concentrations during pregnancy has been well documented, whereas the mechanisms of this phenomenon have yet

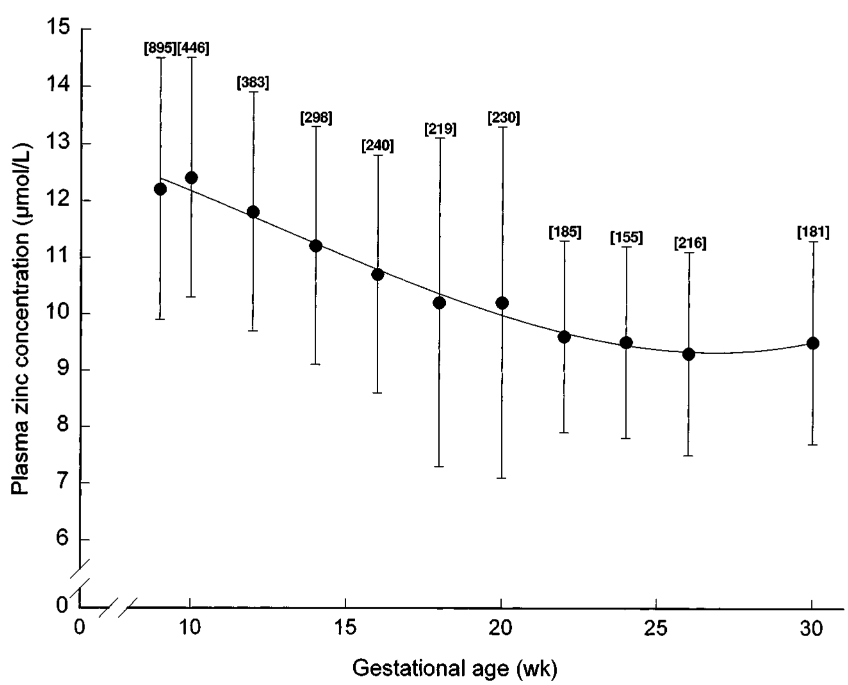


**FIGURE 1.** Mean (±SD) plasma zinc concentrations during pregnancy. *n* for each point in brackets.

**TABLE 3**
Prevalence of maternal complications[1]

| | All women ($n$ = 3448) | Women in the lowest plasma zinc quartile ($n$ = 826) | Women in the upper 3 plasma zinc quartiles ($n$ = 2586) |
|---|---|---|---|
| | | *n (%)* | |
| Fetal-growth restriction | 139 (4.5) | 36 (4.8) | 103 (4.4) |
| Preterm delivery (<37 wk gestation) | 505 (14.7) | 132 (15.3) | 373 (14.5) |
| Early preterm delivery (<32 wk gestation) | 136 (4.0) | 29 (3.4) | 107 (4.2) |
| Hypertension | 271 (7.9) | 66 (7.7) | 205 (7.9) |
| Amnionitis | 146 (4.2) | 33 (3.8) | 113 (4.4) |
| Postpartum infection | 213 (6.2) | 52 (6.1) | 161 (6.2) |

[1] There were no significant differences between women in the lowest quartile and women in the upper 3 quartiles of plasma zinc concentrations.

to be identified. These may include a normal physiologic adjustment to pregnancy, a response to hormonal changes, hemodilution, or a combination of these (22–24). The deterioration of zinc nutriture during pregnancy has also been proposed. However, none of these possibilities appear to sufficiently explain this apparently complex event (3).

As reviewed by Tamura and Goldenberg (3), >40 studies have been carried out to date to evaluate the association between maternal zinc nutriture and pregnancy outcome. About half of these investigations indicated some positive association; however, the other half found no such relation. All the investigations had different study designs and different sample sizes, with a maximum of 878 subjects. In the present study of 3448 pregnant women, we found no significant association between plasma zinc concentrations and various measures of pregnancy outcome and neonatal condition. These measures included the incidence of fetal-growth restriction, preterm delivery, hypertension, and postpartum infection as well as Apgar scores and anthropometric measures of neonates (Tables 3 and 4).

Our findings do not agree with those of several groups of investigators who found a positive association between maternal zinc nutriture and fetal growth, but agree with others (6, 25–27). Furthermore, McMichael et al (25) reported that maternal serum zinc concentrations correlated negatively with gestational age at delivery; however, Lao et al (28) found no such association. The association between maternal zinc nutriture and pregnancy-induced hypertension or preeclampsia is also controversial. Some investigators reported that maternal plasma zinc concentrations are significantly lower in women with preeclampsia than in those without (29–31), whereas others showed no such association (25, 28). In our study, we found no significant association between plasma zinc concentrations and several different types of hypertension. Additionally, we found no significant relation between quartiles of plasma zinc concentrations and anthropometric measurements and Apgar scores of neonates. These findings contrast with those of Mukherjee et al (32); however, the reason for this discrepancy is unknown.

**TABLE 4**
Correlation between neonatal anthropometric measurements and plasma zinc $z$ scores[1]

| | Anthropometric measurement ($n$ = 3448) | Correlation coefficient between measure and $z$ score |
|---|---|---|
| Birth weight (g) | 3117 ± 680[2] | −0.013 |
| Head circumference (cm) | 33.8 ± 2.5 | 0.005 |
| Crown-heel length (cm) | 40.6 ± 14.2 | −0.005 |
| Apgar score at 1 min (median) | 8 | 0.016 |
| Apgar score at 5 min (median) | 9 | 0.010 |
| Gestational age at birth (wk) | 38.3 ± 3.2 | 0.009 |

[1] Plasma zinc concentrations were adjusted for gestational age for Pearson correlation analysis. None of the correlations were significant.
[2] $\bar{x}$ ± SD.

In a clinical trial conducted to evaluate the effect of zinc on pregnancy outcome, we found a positive effect of supplementation on birth weight and other anthropometric measures of neonates born to 580 women (16). These positive findings indicate that zinc nutriture was inadequate in these subjects. Subjects were selected for the clinical trial because they had plasma zinc concentrations below the 50th percentile of all the women described in the study presented here. Thus, it may be reasonable to speculate that at least one-half of the present study population had suboptimal zinc nutriture. Because zinc nutriture is important for pregnancy outcome, if plasma zinc concentrations are a reliable indicator of zinc nutriture in pregnant women, we should have found a positive correlation between plasma zinc concentrations and the various pregnancy outcome measures in this study. However, we observed no such positive associations, suggesting that a one-time measurement of plasma zinc concentrations at a mean gestational age of 16 wk is not suitable for predicting pregnancy outcome.

In summary, plasma zinc concentrations during the late first trimester to the early third trimester did not predict pregnancy outcome in 3448 subjects from a low socioeconomic background. To our knowledge, our study population was the largest number of subjects studied in an investigation of this nature to date.

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