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Relationship between pre-pregnancy BMI and plasma zinc concentrations in early pregnancy

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We previously reported that pregnant women whose plasma Zn concentrations were below the 50th percentile tended to have high pre-pregnancy BMI (kg/m^2) values. We therefore hypothesized that in pregnant women, plasma Zn concentrations are negatively correlated with BMI. We evaluated the association between BMI values and plasma Zn concentrations in 1474 women whose blood samples were obtained before 15 weeks of gestation. Their mean age was 22·7 years and mean gestational age at blood sampling was 10 weeks. The mean plasma Zn concentration and BMI were 11·6 μmol/l and 26·6 kg/m^2 respectively. Because plasma Zn concentrations decrease as gestational age increases, plasma Zn concentrations were standardized by Z-scores. Z-score distributions were compared among the quartiles of BMI. The highest BMI group had the lowest plasma Zn concentrations, whereas the lowest BMI group had the highest; the differences were significant between the BMI groups ($P<0·0001$). The interpretation of plasma Zn concentrations to assess Zn nutriture in pregnancy may be complicated not only by the well-established factor of gestational age at blood sampling, but also by a previously unrecognized factor, maternal BMI.

Plasma zinc: Body mass index: Pregnant women

Several groups of researchers have reported that plasma or serum Zn concentrations are significantly lower in overweight non-pregnant subjects than those in non-overweight control subjects (Atkinson *et al.* 1978; Chandra & Kutty, 1980; Chen *et al.* 1988; Di Martino *et al.* 1993; Marreiro *et al.* 2002). Lowy *et al.* (1986) showed that plasma and erythrocyte Zn concentrations as well as urinary and faecal Zn losses are increased during weight-reduction diets in obese men, and Serfass *et al.* (1983) reported similar findings in young obese women. Although these findings are not always consistent (Collipp, 1984; Tanaka *et al.* 1993; Marotta *et al.* 1995; Hashim *et al.* 1996), they suggest a possible association between the metabolism, transport and/or tissue distribution of Zn and overweight. None of these studies, however, involved pregnant women.

In a double-blind trial performed in indigent African-American women in Birmingham, AL, USA, we reported that prenatal Zn supplementation had a positive effect on fetal growth (Goldenberg *et al.* 1995). For that trial the subjects were selected on the basis of plasma Zn concentrations lower than the 50th percentile (Tamura *et al.* 2000). This resulted in our unintentionally selecting a group of women with high mean pre-pregnancy BMI of 28·0 kg/m^2 for the trial. Based on these findings and those of others reviewed earlier, we hypothesized that plasma Zn concentrations are negatively correlated with BMI in pregnant women. To test this hypothesis, we analysed the association between plasma Zn concentration in early pregnancy and pre-pregnancy BMI in 1474 women who were screened for the trial between 3 and 14 weeks of gestation.

Materials and methods

Subjects

The Institutional Review Board at the University of Alabama at Birmingham approved the study, and each subject gave signed informed consent. From 1991 to 1993, 1474 pregnant women between 3 and 14 weeks of gestation of all racial and ethnic groups using the Jefferson County Health Department for obstetric care were screened for plasma Zn concentrations for possible enrolment in a trial to evaluate the effect of Zn supplementation on pregnancy outcome (Goldenberg *et al.* 1995; Tamura *et al.* 2000). These subjects had plasma Zn concentrations measured, a recorded pre-pregnancy BMI and other pregnancy-related information. The mean maternal age was 22·7 (SD 5·4) years and the ages ranged from 11 to 44 years. The women were (%): African-American 85·4; white 13·4; other 1·2.

Clinical data and birth weight

The information on maternal age, pre-pregnancy anthropometric measurements and parity was obtained at the first

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prenatal visit at a mean of 10 weeks of gestation (ranging from 3 to 14 weeks). Maternal height was measured at the first prenatal visit, and BMI was calculated using the pre-pregnancy body weight reported by the subject at the first prenatal visit as reported previously (Goldenberg *et al.* 1995). Gestational age at the first visit was estimated based on the first day of the last menstrual period and ultrasound examination. When less than 2 weeks of discrepancy was found between the estimation by the two methods, the gestational age was defined based on the last menstrual period. However, when these two values differed by more than 2 weeks, the gestational age measured by ultrasound was used.

Blood sample collection

At the first prenatal visit between 3 and 14 weeks of gestation, non-fasting blood samples were obtained using a trace-mineral-free tube with sodium heparin (Vacutainer; Beckton Dickinson, Rutherford, NJ, USA). Samples were refrigerated immediately after drawing until plasma separation, and were then stored at $-70^{\circ}C$ until Zn analysis (Tamura *et al.* 1994).

Plasma zinc determination

Plasma Zn concentrations were measured by atomic absorption spectrophotometry. The CV of the analyses using pooled human plasma samples was about 4 % and the difference in the estimated Zn values of the standard reference material (no. 1598; National Institute of Standards and Technology, Gaithersburg, MD, USA) was about 6 % (Tamura *et al.* 1994).

Statistical analyses

Plasma Zn concentrations were standardized by Z-scores because values decreased as gestational age at blood drawing advanced (Tamura *et al.* 2000). The Z-score gives the number of standard deviations above or below the mean value on a standard normal curve centred on the mean for each gestational age at blood drawing. We divided the subjects into quartiles of BMI, and the Z-score distribution and other variables were compared using ANOVA. A multiple regression analysis was used to evaluate the factors associated with plasma Zn concentrations.

Results

Table 1 shows the characteristics of 1474 mothers divided by quartiles of pre-pregnancy BMI. The mean BMI of all subjects combined was 26·6 kg/m^2. Higher BMI was associated with greater maternal age ($P<0{\cdot}0001$). A higher percentage of African-Americans were found in the higher BMI quartiles ($P<0{\cdot}0001$), whereas the percentage of primiparous women was lower among the subjects with higher BMI ($P<0{\cdot}0001$). As expected, the mean birth weights of infants increased as maternal BMI increased ($P=0{\cdot}0007$).

The overall mean plasma Zn concentration was 11·6 μmol/l. Table 2 shows plasma Zn concentrations and

Table 1. Maternal characteristics by the quartiles of BMI*
(Mean values, standard deviations and ranges)

	Quartiles of BMI												
	Lowest (*n* 369)			Second (*n* 368)			Third (*n* 368)			Highest (*n* 369)			Statistical significance of effect: *P*
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	
BMI (kg/m^2)	20	1	15–21	23	1	22–25	27	2	25–30	36	5	30–57	$<0{\cdot}0001$
Age (years)	21	5	12–42	22	5	11–40	24	6	12–44	24	5	13–43	$<0{\cdot}0001$
Gestational age at blood drawing (weeks)	10	3	3–14	10	3	3–14	10	3	4–14	10	3	3–14	0·758
White (%)/African-American (%)		15/82			14/85			12/87			7/92		$<0{\cdot}0001$
Primiparous (%)		40			37			27			29		$<0{\cdot}0001$

*For details of study population, see pp. 773–774.

Table 2. Maternal plasma zinc concentrations and Z-scores by the quartiles of BMI*

	Quartiles of BMI												
	Lowest (*n* 369)			Second (*n* 368)			Third (*n* 368)			Highest (*n* 369)			Statistical significance of effect: *P*
	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	
Plasma Zn (μmol/l)	11·9	2·3	6·4–22·3	11·6	2·2	6·4–19·9	11·4	2·2	5·7–28·2	11·0	1·9	6·0–17·6	<0·0001
Plasma Zn Z-score	0·17	1·0	−2·3–5·1	−0·004	1·0	−2·2–4·3	−0·10	0·98	−2·7–6·7	−0·2	0·9	−2·5–2·9	<0·0001

*For details of the subjects, see Table 1 and pp. 773–774.

Table 3. Effect of maternal characteristics on plasma zinc concentrations using multiple regression analyses (*n* 1474)*

Maternal characteristics	Effect size (μmol/l)	Statistical significance of effect: *P*
Age (years)	−0·003	NS
BMI (kg/m^2)	−0·05	<0·0001
Gestational age at blood sampling (weeks)	−0·08	= 0·0004
Being African-American	−0·35	= 0·047
Being primiparous	0·18	NS

*For details of subjects and procedures, see Table 1 and pp. 773–774.

Z-scores of mothers divided by quartiles of BMI. The results indicate that the subjects with higher BMI had significantly lower plasma Zn concentrations than those with lower BMI ($P<0·0001$).

The regression analysis performed after adjusting for maternal age, gestational age at blood sampling, race and parity indicated that the increase of 1 unit of BMI (kg/m^2) was associated with a 0·05 μmol/l decrease in plasma Zn concentrations for all subjects combined ($P<0·0001$). Other factors associated with plasma Zn concentrations included gestational age at the time of blood drawing (1 week of increase was associated with a decrease of 0·08 μmol/l, $P<0·0004$) and being African-American (0·35 μmol/l lower than being white, $P=0·0049$), as shown in Table 3.

Discussion

In blood samples obtained at less than 15 weeks of gestation, we found that plasma Zn concentrations decreased as maternal pre-pregnancy BMI increased. Therefore, the interpretation of plasma Zn concentrations to assess Zn nutriture in pregnancy is also complicated by pre-pregnancy BMI in addition to gestational age at blood sampling (Hambidge & Droegemueller, 1974; Tuttle *et al.* 1985; Tamura & Goldenberg, 1996; Tamura *et al.* 2000). Our results are in agreement with others, who have suggested that Zn metabolism, transport and/or tissue distribution are related to the BMI through a yet-to-be-identified mechanism (Atkinson *et al.* 1978; Chandra & Kutty, 1980; Serfass *et al.* 1983; Lowy *et al.* 1986; Chen *et al.* 1988; Di Martino *et al.* 1993; Marreiro *et al.* 2002). In addition, our findings are consistent with the observations in animals indicating that tissue Zn distribution is different in overweight and lean mice and rats (Begin-Heick *et al.* 1985; Kennedy & Failla, 1986, 1987; Donaldson *et al.* 1987). The mechanisms causing such differences are unknown.

It is well established that plasma volume correlates significantly with BMI (Pearson *et al.* 1995). The lower plasma Zn concentrations in our subjects with higher BMI may be in part due to the increased plasma volume in these women. In fact, the decreasing plasma Zn concentrations observed during pregnancy may be due to the expansion of plasma volume seen in nearly all pregnant women. However, we do not know to what extent plasma volume expansion is responsible for decreasing Zn concentrations, because the relationship between micronutrient status and

plasma volume during pregnancy has not been extensively studied. There is evidence to suggest that foods rich in micronutrients are associated with greater birth weight and this relationship was attributed to greater expansion in plasma volume (Mardones-Santander *et al.* 1988). The decrease in plasma Zn associated with the increase in BMI observed in the present study may be related to our previous reports in which plasma concentrations of albumin and α_2-macroglobulin were lower in heavier pregnant women than in lighter subjects (Goldenberg *et al.* 1991; Maher *et al.* 1993). Because plasma albumin binds about 80 % total plasma Zn and α_2-macroglobulin binds about 20 % plasma Zn as a high-affinity Zn-binding protein (Giroux, 1975), low concentrations of these proteins in heavier pregnant women may account for the lower plasma Zn concentrations as compared with lighter women. In fact, Campbell & MacGillivray (1984) reported that there is a significantly positive relationship between intravascular albumin mass and Zn mass. In addition, low serum α_2-macroglobulin concentrations in non-pregnant obese subjects have also been reported in Thailand (Tungtromgchitr *et al.* 2003). However, at the present time we do not know why these protein concentrations are low in overweight subjects or whether the low protein concentrations are related to the metabolism, transport and/or tissue distribution of Zn. Furthermore, it is unlikely that Zn nutriture has any influence in regulating BMI.

Another possible reason for the low plasma Zn concentrations in women with high BMI is that they consume less Zn. However, it is worthwhile noting that in subjects who participated in the Zn supplementation trial (Goldenberg *et al.* 1995), there was no significant association between BMI values and dietary energy and Zn intakes assessed by a 24 h dietary record (T Tamura & RL Goldenberg, unpublished results). This finding strongly suggest that dietary energy and Zn intakes were independent of BMI values among the subjects evaluated in the study presented here, since they were of similar socio-economic backgrounds and dietary habits to those who participated in the trial. Therefore, it is likely that the different plasma Zn concentrations among different BMI groups found in the present study were not due to differences in dietary energy and Zn intakes.

Future studies are warranted to identify whether the differences in Zn concentrations among pregnant women with varying BMI are associated with pregnancy outcome. Low circulating Zn concentrations may in part contribute to physiological disadvantage during pregnancy among overweight women, since adverse pregnancy outcomes associated with obesity are well recognized (Cnattinguis *et al.* 1998). The population of obese individuals is increasing at an alarming rate (Yanovski & Yanovski, 2002); thus, it is important to identify the mechanism of altered Zn status in obese subjects. It would also be interesting to evaluate whether circulating levels of other nutrients also have an association with BMI in both non-pregnant and pregnant populations.

In summary, we found that the higher the pre-pregnancy BMI, the lower the plasma Zn concentrations in women whose blood samples were tested before 15 weeks of gestation. Although the changes due to BMI were relatively small, our results indicate that the interpretation of plasma Zn concentrations to assess Zn nutriture in pregnancy is complicated by the factor of BMI in addition to the well-established factor of gestational age at the time of blood drawing. It is important to take this association into account for the selection of pregnant subjects for future large-scale studies or the interpretation of plasma Zn data.

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