Trace Elements and Human Pregnancy and Lactation

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This chapter considers the trace elements which have been studied most extensively in pregnancy and lactation (i.e., zinc, copper, selenium, and chromium) but excludes iron. The effects of pregnancy on the metabolism of these elements as well as the effects of an altered supply of these elements on pregnancy are considered. In contrast to the literature on animal models, there is remarkably little information on either of these aspects in human pregnancy and lactation.

ZINC

Acrodermatitis Enteropathica and Pregnancy

The interaction between zinc nutriture and metabolism and pregnancy is perhaps best illustrated by the reported pregnancies of women with acrodermatitis enteropathica. The manifestations of this rare autosomal recessive condition are caused by systemic zinc deficiency, which is probably secondary to an as yet uncharacterized defect in the intestinal absorption of zinc (1). Until the therapeutic efficacy of oral zinc supplements was discovered, this distressing condition was treated with variable success by a variety of antibiotics derived from 8-hydroxyquinoline, the most extensively used being 5,7-diido-8 hydroxyquinoline (DIH). There have been 14 reported pregnancies in women with acrodermatitis enteropathica who were not treated with zinc.

One patient who was not treated until DIH was introduced at the end of the first trimester gave birth to an achondroplastic dwarf; she remained on DIH, and her next three pregnancies were normal (2). Another woman who was treated with DIH needed an increased dosage because her symptoms were exacerbated during pregnancy. She gave birth to an infant weighing 2.52 kg; although this could be regarded as light, the mother herself weighed only 40 kg and was 1.51 m tall. The baby was delivered by cesarean section for cephalopelvic disproportion (3). A third woman being treated with DIH had a spontaneous abortion followed by a pregnancy which produced an anencephalic stillbirth (4). Four other pregnancies occurred in a woman who apparently had no specific treatment at all; her first two pregnancies and babies were normal, but during the subsequent pair of pregnancies her disease
deteriorated so much that therapeutic abortions were induced, with prompt clinical improvement ensuing (5). The remaining three pregnancies occurred in a woman with probable acrodermatitis enteropathica who was not diagnosed until the ninth month of her third pregnancy. During her first pregnancy this woman had had a severe exacerbation of the skin lesions which had plagued her intermittently since infancy. These resolved dramatically after she gave birth to a normal boy. Her next pregnancy was terminated during the first trimester, and during her third pregnancy her skin condition deteriorated considerably. In the last 10 days of this pregnancy her plasma zinc concentration was found to be 18 μg/dl (2.8 μmol/liter) and zinc supplements were introduced with immediate good effect. Despite the earlier possible zinc depletion, this woman gave birth to a normal male infant weighing 3.06 kg (6).

Possible Teratogenic Effects of Zinc Deficiency

This accumulated experience, albeit anecdotal, illustrates the possibilities that (a) zinc deficiency can be teratogenic in human pregnancy; (b) pregnancy may impose extra metabolic demands such that zinc deficiency can be induced with preexistent marginal zinc status; and (c) more speculatively, chronic zinc deficiency may impair maternal growth to such an extent that physical factors subsequently jeopardize the successful outcome of pregnancy and labor. Since these studies the successful outcome of two pregnancies in a woman with acrodermatitis enteropathica treated with zinc has been described (7), and there was similar success in one of Moynahan's original patients as well as that mentioned by Lombeck in this volume. In view of these reports of the protective effect of zinc, it seems unlikely that the occurrence of teratogenic defects in these women is due to a genetic trait linked to that for acrodermatitis enteropathica (8).

Other reports have advanced evidence that altered zinc metabolism is associated with congenital birth defects. It has been speculated that the prevalence of anencephaly in some areas of the Middle East may be related to that region's endemic zinc-responsive syndrome (9). Cavder and her colleagues (10) have described lower serum zinc concentrations at term [62.1 ± 2.5 (SD) μg/dl] in 10 women giving birth to anencephalic babies compared with 90 mothers having normal babies [73.4 ± 1.5 μg/dl]. The description by Bergman et al. (11) of increased hair zinc content in mothers delivering infants with spina bifida is equally intriguing. The reason for these associations remains to be established. There may be more than one, and because isolated zinc deficiency is rare it is possible that other nutritional insults may contribute as well. Additionally, it could be speculated that the neuroendocrine changes associated with anencephaly could modify zinc metabolism during pregnancy. Nevertheless, it is noteworthy that closure of the neural tube in the human embryo at about 7 weeks' gestation coincides with the time when the zinc content of the fetus is reported to increase some seven-fold (12). Further associations between apparently altered zinc metabolism and congenital birth defects have arisen from studies in Eire in which demonstrably lower plasma zinc concentrations were
found as long as 24 months after delivery in a group of mothers having infants with congenital defects (13). Other studies in Ireland have also shown high amniotic fluid zinc and copper concentrations in conceptuses with neural tube defects (14). Yet another study has shown elevated copper concentrations and depressed zinc content in the terminal 2 to 3 inches of hair of parents with children with achondroplasia (15). All of these studies are difficult to interpret, and they do not necessarily demonstrate a role for zinc deficiency in the etiology of the reported defects.

An extensive longitudinal and cross-sectional study from Sweden (16) reported that plasma zinc concentrations were reduced at midpregnancy in women who subsequently experienced obstetrical abnormalities such as prolonged labor, atonic bleeding, pica, dysgeusia, and cravings. It was also noted that women whose plasma zinc concentrations continued to fall after the 14th week of gestation had a greater incidence of abnormal labors than those in whom the plasma zinc concentrations increased between the 14th and 36th week of gestation. In this study a group of eight women with low plasma zinc levels had infants with congenital defects; these included hydrocele, undescended testes, hypospadias, ventricular septal defect, and multiple defects which occurred in the infant of a woman with diabetes mellitus. Furthermore, one of the women in Jameson's study who had a low plasma zinc (10.4 μmol/liter) in early pregnancy had an infant who developed zinc deficiency while being exclusively breast-fed (17).

Zinc Requirements During Pregnancy

Reports such as those above have been interpreted as providing evidence that dietary zinc requirements are increased during pregnancy. This, however, is not the natural corollary of the observation that zinc deficiency in women with acrodermatitis enteropathica may have an adverse effect on the outcome of gestation. In any event, the nature of the more serious defects suggests that the depredations of zinc deficiency are in effect before pregnancy would customarily be diagnosed. Nevertheless, a number of reports have recommended increased dietary zinc intakes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Total needed (mg)</th>
<th>Required intake (mg/day) assuming 10–40% bioavailability of zinc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10%</td>
</tr>
<tr>
<td>Nonpregnant</td>
<td>2.2</td>
<td>22</td>
</tr>
<tr>
<td>Pregnant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–20 weeks</td>
<td>2.55</td>
<td>25.5</td>
</tr>
<tr>
<td>20–30 weeks</td>
<td>2.9</td>
<td>29</td>
</tr>
<tr>
<td>30–40 weeks</td>
<td>3.0</td>
<td>30</td>
</tr>
<tr>
<td>Lactation</td>
<td>5.45</td>
<td>54.5</td>
</tr>
</tbody>
</table>

Data from World Health Organization Expert Committee (18).
for women during pregnancy (Tables 1 and 2). These recommendations vary considerably.

The additional requirements for zinc during pregnancy have been calculated as 0.75 mg/day over the last 20 weeks (20). The fetus accumulates zinc at an average approximate rate of 249 \( \mu g/kg \) body weight/day (21), and the total amount of zinc in the fetus and placenta at term (22) is thought to be in the order of 4.2\% of the amount present in the nonpregnant woman. As Widdowson pointed out, this demand for zinc is quite small relative to nonpregnant requirements. In the overall economy of zinc during pregnancy, one needs also to consider the amount no longer being lost with menstruation. This is estimated to be 0.23 ± 0.20 (SD) mg (23) or 0.48 ± 0.37 mg (24) per period.

**Dietary Zinc Intakes**

It is probable therefore that the requirements for zinc during pregnancy are overestimated. This appears to be indicated by the daily intakes of zinc reported in a number of studies on pregnant women. A selected sample is shown in Table 3. Whereas none of the these studies were designed to take into account the bioavailability of the metal from the diet, the intakes of zinc appear to be remarkably consistent among a range of social classes and geographical loci. It is also noteworthy that few of the intakes even approached the lowest national recommended intake (i.e., that of Canada).

Therefore if there is a need for increased zinc supply during pregnancy it is possible that it must be met by metabolic adaptation. A number of metabolic balance studies have been conducted on women during pregnancy; unfortunately, many have employed dietary zinc intakes which are in excess of those reported above and cannot therefore provide information on adaptations which may occur in women on customarily lower zinc intakes. Thus a study in pregnant teenagers fed 26, 29, and 32 mg of zinc in a randomized order showed that two patients had an apparently negative balance for zinc at the lower intakes (31). Such data may well represent a normal intestinal homeostatic response to the large intake. The

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<table>
<thead>
<tr>
<th>Country</th>
<th>Recommended intake (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonpregnant</td>
</tr>
<tr>
<td>Australia</td>
<td>14</td>
</tr>
<tr>
<td>Canada</td>
<td>10</td>
</tr>
<tr>
<td>Czechoslovakia</td>
<td>8</td>
</tr>
<tr>
<td>FRG</td>
<td>12</td>
</tr>
<tr>
<td>USA*</td>
<td>15</td>
</tr>
</tbody>
</table>
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*Recommendations followed in Italy, Spain, New Zealand, and Uruguay also.

Data from the International Union of Nutritional Sciences (19).
TABLE 3. Selected reported dietary intakes during pregnancy

<table>
<thead>
<tr>
<th>Population</th>
<th>Zinc (mg/day)</th>
<th>Copper (mg/day)</th>
<th>Protein (g/day)</th>
<th>Energy (kcal/day)</th>
<th>Methodology*</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navajo women (midpregnancy)</td>
<td>12 ± 6.9</td>
<td>1.57 ± 0.7</td>
<td>95 ± 41</td>
<td>2,448 ± 887</td>
<td>1b</td>
<td>25</td>
</tr>
<tr>
<td>Subsequent lactation</td>
<td>9.8 ± 0.6</td>
<td>—</td>
<td>80 ± 3</td>
<td>2,023 ± 70</td>
<td>3c</td>
<td>26</td>
</tr>
<tr>
<td>Nonlactation (at 37 weeks)</td>
<td>7.9 ± 0.5</td>
<td>—</td>
<td>63 ± 4</td>
<td>1,625 ± 100</td>
<td>3c</td>
<td>26</td>
</tr>
<tr>
<td>Hispanics (middle trimester)</td>
<td>9.73 ± 5.0</td>
<td>1.39 ± 1.7</td>
<td>68 ± 30</td>
<td>1,646 ± 589</td>
<td>1b</td>
<td>27</td>
</tr>
<tr>
<td>Aberdeen women (30 weeks) with subsequent birth weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;10 percentile</td>
<td>10.1 ± 3.1</td>
<td>1.55 ± 1.4</td>
<td>77.2 ± 19.3</td>
<td>2,055 ± 402</td>
<td>2b</td>
<td>28</td>
</tr>
<tr>
<td>&lt;10 percentile</td>
<td>9.9 ± 2.4</td>
<td>1.79 ± 0.8</td>
<td>70.4 ± 13.1</td>
<td>1,912 ± 34</td>
<td>2b</td>
<td>28</td>
</tr>
<tr>
<td>Middle income Denver (throughout pregnancy)</td>
<td>11.3 ± 4.1</td>
<td>—</td>
<td>85 ± 25</td>
<td>2,028 ± 500</td>
<td>1, 4b</td>
<td>29</td>
</tr>
<tr>
<td>Vegetarian (last trimester)</td>
<td>12.6 ± 0.9</td>
<td>2.8 ± 0.3</td>
<td>93 ± 7</td>
<td>2,446 ± 151</td>
<td>4c</td>
<td>30</td>
</tr>
<tr>
<td>Nonvegetarian (last trimester)</td>
<td>14.4 ± 0.6</td>
<td>2.1 ± 0.4</td>
<td>97 ± 5</td>
<td>2,003 ± 135</td>
<td>4c</td>
<td>30</td>
</tr>
<tr>
<td>Nonpregnant vegetarian</td>
<td>6.4</td>
<td>1.3 ± 0.2</td>
<td>51 ± 6</td>
<td>1,329 ± 138</td>
<td>4c</td>
<td>30</td>
</tr>
</tbody>
</table>

*Methodology: (1) 24-hour dietary recall; (2) seven-day weighed intake with analysis of duplicate diets; (3) 3-day duplicate diet with analysis; (4) 3-day record.

Standard deviation.

Standard error.

authors of this study were also concerned about the high dermal loss of zinc in these girls and believed that this route of zinc loss was possibly underestimated in general and in pregnancy in particular. Another study suggested, however, that this high sweat zinc content was also secondary to the high dietary intake of the element (32). In 15-day metabolic balance studies using a semisynthetic diet containing 20 mg of zinc, a lower fecal zinc loss was noted in 10 pregnant women compared with 5 nonpregnant women, and the net retentions in the two groups were marginally different at 2.4 ± 1.6 and 1.1 ± 1.3 mg zinc/day, respectively (33). Clearly these differences are not statistically significant, and in a subsequent study these same workers were unable to detect any difference in the absorption and retention of zinc in women studied at midterm who were consuming 16 mg of zinc/day derived from diets based on varying contents of animal and plant protein (34). Another study, reported in an abstract, has demonstrated mean zinc retentions of 1 mg/day in pregnant women consuming diets containing 7.1 mg of zinc/day (35). This is probably of most relevance in the context of zinc metabolism during pregnancy.
During early pregnancy other, as yet unidentified, physiological adaptations may occur to maintain the supply of zinc to the developing embryo. For example, whereas most workers agree that the urinary loss of zinc is increased, albeit marginally, during late pregnancy, Hambidge et al. (29) have noted that urinary zinc excretion may actually decrease during the first trimester.

**Serum and Plasma Zinc Concentrations During Pregnancy**

Although the unreliability of serum and plasma zinc levels as an indicator of zinc status has long been acknowledged, especially during pregnancy (36), many studies have sought relationships between these measurements and the progress of pregnancy, labor, and fetal well-being. With few exceptions (16,37) most studies agree that the serum or plasma zinc content declines progressively throughout pregnancy (8,29,36,38). This decline is not prevented by specific daily zinc supplementation that provides total intakes of 20 mg (29) and 30 mg (27) of elemental zinc. On the other hand, Jameson noted an increased serum zinc concentration in pregnant women receiving the large supplement of 90 mg of zinc daily during the latter half of pregnancy (16). This reported decline of plasma or serum zinc (average 0.07 μg/dl/day) has been detected as early as 6 weeks of pregnancy or between 21 and 40 days after ovulation (8,29). This phenomenon has been attributed to: (a) an estrogen effect, although Jameson could not confirm this (16); (b) the hypoalbuminemia of pregnancy and a reduced affinity of albumin for zinc (38); however, Swanson and King (39) found no alteration in the plasma distribution of zinc and its binding to albumin; and (c) the hemodilution effect of plasma volume expansion. The latter has been shown by Tuttle et al. (40), who measured simultaneously in primigravidas who were on no nutritional supplements the plasma volume and its zinc content from the end of the first trimester to the 35th week. The total quantity of zinc in the plasma compartment was constant throughout and did not correlate with the birth weight of the infants when corrected for maternal habitus. Although plasma volume increases early in pregnancy (i.e., at the 6th week), it remains to be seen if this is the only physiological factor influencing the zinc concentration.

Although some studies described a positive correlation between midpregnancy plasma and serum zinc content and birth weight (16,41), the populations studied comprised both primigravidas and multigravidas, and only one (41) allowed for this and for other maternal factors which could influence infant birth weight. This study reported a weak correlation between plasma zinc and infant birth weight in 103 women. On the other hand, other studies have detected a weak inverse correlation between birth weight and midpregnancy plasma zinc: that plasma zinc is higher in women having smaller babies (42-46). Thus one study reported mid-pregnancy (18 weeks) serum zinc concentrations of 11.2 ± 0.1 (SE) μmol/liter in normal pregnant women, 11.8 ± 0.3 μmol/liter in women with intrauterine growth retardation, and 13.3 ± 1.7 μmol/liter in women having stillbirths (42). Such data could be explained by the known changes of plasma volume which accompany some of these obstetrical problems. Other groups have also failed to find any association
between plasma or serum zinc and overall eventual birth weight of normal infants (27,29,43) or the duration of labor at term (25). Reduced plasma or serum zinc levels may accompany preeclamptic toxemia, intrapartum hemorrhage, and spontaneous abortions (42,43,46). An inverse relationship accounting for up to 5% of variance has also been noted between plasma zinc corrected for gestational age and infants’ Apgar scores (43).

The above discussion does not exclude the possibility that pathologically low levels of plasma zinc may occur during pregnancy, but it is difficult to detect these when there is a 20 to 25% fall in this value during the course of pregnancy. A regression equation for this decline, against which serum or plasma zinc content could be tested for “normality,” has been proposed by Hambidge and his colleagues (29) for evaluation in clinical practice. This is an alternative to an earlier submission that levels below 6.9 to 7.6 μmol/liter (45 to 50 μg/dl) may be indicative of suboptimal nutriture (36). This equation may not prove satisfactory, however, because it was derived from women on nutritional supplements (see below).

**Hair Zinc**

Early reports described a progressive fall in hair zinc concentration during pregnancy (summarized in ref. 36), and this has been observed in some (11,27,46) but not all (29) subsequent studies. In the absence of adequate understanding of the factors influencing hair growth and its zinc content during pregnancy, these data are difficult to evaluate and interpret (e.g., ref. 11).

**Leukocyte Zinc**

In an extensive appraisal of midpregnancy biochemical nutritional values as prognostic indicators of the outcome of pregnancy, plasma zinc content was thought to contribute up to 9% of the variance (41). However, in a subsequent reevaluation, assessments of the bioactivity of maternal mixed leukocytes were considered more effective. In this context it is noteworthy that mixed leukocyte zinc content may presage infant birth weight (47) as follows: Mothers with (a) normal birth weight infants: leukocyte zinc concentrations were 52.3 ± 0.67 (SE) ng/mg dry weight; (b) preterm infants: 49.0 ± 0.7 ng/mg; (c) prolonged intrauterine growth retardation: 38.0 ± 1.7 ng/mg; and (d) late-onset intrauterine growth retardation: 48.3 ± 0.7 ng/mg. A preliminary report (48) described a similar correlation between maternal leukocyte zinc content and the growth of the infant femur in utero as assessed by ultrasound and birth weight. However, there occurs during pregnancy a leukocytosis predominantly due to neutrophils, whereas eosinophils, although increasing in absolute numbers, are relatively less abundant (49). The neutrophilia is enhanced at labor. Because the zinc content of white blood cell (WBC) types differ, it would be of interest to know how the zinc content of WBC subsets correlate with fetal growth in order to exclude the possibilities that the total leukocyte zinc is not merely acting as a marker for the altered cell population, which may be influenced initially by endocrine changes, or for other single or multiple nutritional insults.
Nevertheless, the zinc content of cord blood mixed WBCs of babies with intra-uterine growth retardation is also reduced (50).

**Amniotic Fluid Zinc**

The zinc content of amniotic fluid is reduced in association with low birth weight (51,52). The inference of this depends on the source of the zinc; for example, after centrifugation, 60% of amniotic fluid zinc is associated with the pellet which contains particles of vernix, lanugo, and skin epidermis—which would relate to fetal size (53). The value of measuring amniotic fluid zinc is compromised also by meconium contamination, which even when it is detectable only by spectroscopy considerably elevates the zinc content of the liquor (53). All these fractions contribute to the increased amniotic fluid zinc concentration noted during the final trimester (52). In the supernatant 72% of zinc is bound to albumin, 7% is associated with IgG, and 8% is bound to a low-molecular-weight (<10,000) peptide (54). The latter may be the antimicrobial factor described by Schlievert and co-workers. The activity of this peptide is proportional to the amniotic fluid's ratio, by weight, of inorganic phosphate/zinc; at ratios of <100:1 the peptide is bactericidal against *Escherichia coli* type 06; at ratios between 100 and 200 it is bacteriostatic; and beyond this it is ineffective (55). This factor may have some clinical relevance to the incidence of postcesarean infections (56), but Gibbs et al (57), who excluded from their analysis all blood-stained samples of amniotic fluid, were unable to show any association of inorganic phosphate/zinc ratios with bacterial inhibitory activity in meconium-free samples of amniotic fluid.

The association of high amniotic fluid zinc and copper content in midtrimester amniocentesis samples from pregnancies with neural tube defects has been noted (14), but as yet too little is known for the zinc content of amniotic fluid to be used in any constructive way in the study of the interrelationship of zinc metabolism and pregnancy.

**Zinc Supplementation Studies**

Jameson reported that supplements of 90 and 45 mg elemental zinc have reduced the duration and incidence of abnormal labor as well as reducing blood loss at delivery (16,58). In a double-blind study zinc supplements had no effect on the incidence of altered perceptions of taste or smell (27), although it may increase the zinc content of hair and saliva (29). There was little alteration on the overall plasma zinc levels in one study, but supplementation did appear to reduce the number of women who had plasma zinc concentrations below approximately 8.5 μmol/liter (55 μg/dl) (27). Hambidge and his colleagues (29) used up to 15 mg elemental zinc supplementation and noted increased serum alkaline phosphatase activity. This was interpreted as a possible indication of suboptimal zinc nutrition, and the alkaline phosphatase activity correlated negatively with the use and dosage of antenatal iron supplements.
Interactions with Iron

The last observation highlights the difficulty of trying to assess the effects of pregnancy on the metabolism of zinc in women receiving nutritional supplements, particularly those of iron. Of the above studies, only those of Tuttle et al. (40) were conducted exclusively in women on no such supplements, and it is noteworthy that the decline in plasma zinc concentration in these women was less than that reported in studies on supplemented women. Simultaneous administration of inorganic iron to male adults impairs the plasma appearance of zinc after oral load (59), as does the more extended administration of a commercial combination of inorganic iron and folic acid (60). The use of such supplements in pregnant women is associated with depressed serum zinc concentrations and alkaline phosphatase activities (8,29) as well as impaired utilization of oral zinc supplements (8). Such interactions may therefore be of more than academic interest. In this context and in that of the susceptibility of the early stages of embryogenesis to teratogenic effects, it is interesting to recall that one study reported that during the first 56 days of pregnancy a higher proportion of mothers of infants with major abnormalities took iron supplements than in a reference group (61).

However, iron alone cannot be suspected of these effects on zinc utilization and the possible sequelae; for example, folic acid (400 μg on alternate days) increased significantly the fecal content of zinc in male volunteers consuming 3.7 and 8.5 mg of zinc/day, whereas at the same time urinary excretion of zinc was reduced (62). The clinical importance of this observation was implied by reference en passant to an increased incidence of fetal complications associated with women with low serum zinc and high serum folate concentrations. This further emphasizes the difficulty of trying to assess the interaction of zinc and pregnancy without reference to other nutritional factors.

Fetal Alcohol Syndrome

A small study noted an apparent correlation between the plasma zinc concentrations of alcoholic mothers at delivery and the number of birth defects in their babies (63). Because the stress of delivery itself may reduce plasma zinc content, this is probably an unreliable time to derive data implicating altered zinc metabolism in this syndrome. Nevertheless, studies in experimental animals have shown that, as with other nutrients, even a brief exposure to oral alcohol inhibits placental uptake and transfer in vivo to the fetus of radiolabeled zinc by about 40% and 30%, respectively (64); this abnormality is not overcome by zinc supplementation (65).

COPPER

The plasma or serum copper concentration and that of ceruloplasmin increase steadily throughout pregnancy to almost twice nonpregnant levels (36,66). This starts early in the first trimester and, like the changes in content of zinc, may be due to endocrine influences (36,67). These elevated copper and ceruloplasmin
concentrations return rapidly to normal after delivery. In fact, both are so sensitive to endocrine influences that their determinations have been proposed as indirect indicators of placental function, low levels being encountered with placental insufficiency (68), intrauterine death (69), and threatened abortion (70). In contrast, high concentrations are associated with toxemia (69,71). The physiological significance of these changes of plasma copper and ceruloplasmin are unknown. The copper may well be mobilized from the liver, and reduced hepatic copper content has been reported in pregnant women who die in road traffic accidents (72) and with late toxemia (73). Given that the former group of women are more physiological, the purpose of the mobilization of copper is obscure. It may be a manifestation of ceruloplasmin synthesis as part of an acute-phase reaction. Midpregnancy plasma or serum copper concentrations do not correlate with neonatal birth weight (66,69,70), although one study has found, perhaps fortuitously, a negative correlation between third-trimester serum copper and the head circumferences of the infants at birth (66). In their extensive study, Metcoff et al. (45) found that some copper–amino acid interactions contributed to the prediction equation for adjusted birth weight.

Serum copper concentrations are reduced significantly in women with premature rupture of the membranes and in the infants delivered (74). Additionally, the birth weights of the infants also were reduced. It seems more likely that these changes are secondary to other basic systemic influences rather than to any primary changes in copper metabolism, as was suspected; this appears to be substantiated by the fact that the copper content of the chorioamniotic membranes was the same as in a group of women with normal onset of labor.

Some studies have shown that hair copper content declines slightly during pregnancy (36,66), but even though this does not achieve statistical significance compared with nonpregnant data, hair copper in the third trimester may correlate positively with neonatal weight (66). Both hair copper and serum copper concentrations are said to be higher in primigravidae than in multiparous women. It has been proposed that this represents a progressive depletion of copper stores, but because neither parameter is a reliable indicator of copper status it seems equally reasonable to hypothesize that these changes represent the known altered endocrine responses to further pregnancies.

**Copper Requirements**

Copper requirements have not been adequately established, though it has been calculated that a pregnant woman would require 75 μg of elemental copper per day to meet the requirements of pregnancy (75). Shaw calculated that the daily copper accumulation by a fetus is 51 μg/kg body weight/day (76). The total amount in the fetus and placenta at term amounts to about 17% of that in the nonpregnant woman. Overall this represents an accumulation of approximately 45 mg of copper throughout pregnancy (22). Even though less than 3 mg is spared through the absence of menstruation, the increased requirement is relatively marginal, representing approximately 4% of the daily balance (75).
Recorded copper intakes by pregnant women are shown in Table 3; as yet there is no evidence to suggest that these are inadequate, and possibly fortunately there are no specific dietary requirements recommended for consumption during pregnancy. The intestinal absorption of copper in pregnant women has been studied using animal- and plant-based diets supplying 1.4 and 2.5 mg of copper daily, respectively. The absorption of copper was marginally higher in pregnant women compared with nonpregnant women for both diets; however, this only just achieved statistical significance with the diet based on plant proteins (75).

Although there is no clear description of the effect of maternal copper deficiency on fetal development in man, the effects of treatment with the “de-coppering” agent penicillamine on women with Wilson’s disease (hepatolenticular degeneration) or cystinuria are of interest. It is possible that the use of penicillamine may place the pregnant woman and her fetus at risk of copper deficiency; but the experience derived from patients with Wilson’s disease indicates that it is not associated with any undue adverse effect (77). There is, however, a single case report describing a neonate delivered of such a patient who had been treated with penicillamine (78). The child had an inguinal hernia, cutis laxa, and abnormalities of skin collagen and elastin. These features resolved rapidly and spontaneously. This outcome compares favorably with that of a child delivered to a woman with cystinuria who was also treated with penicillamine (79). This infant had cutis laxa, hypotonia, hyper-flexibility of the joints, venous fragility, and varicosities, and developed intestinal obstruction requiring an intestinal resection, following which the child died of a *Candida* septicemia and fungus encephalitis. The features of these two cases would be consistent with the neonate’s having an induced copper deficiency; this cannot be concluded confidently, however, because penicillamine can chelate many trace elements (e.g., zinc and iron) other than copper. Even so, it is possible that the second mother and child were more susceptible to copper depletion because of their relatively smaller copper burden compared to a woman with Wilson’s disease.

**Amniotic Fluid Copper**

In a cross-sectional study of amniocentesis samples, the mean copper content of the amniotic fluid declined throughout pregnancy. On the other hand, the ceruloplasmin oxidase activity was relatively constant (80). Because 95% of the copper in amniotic fluid is reported to be present as ceruloplasmin (54), the latter observations seem difficult to reconcile. As with zinc, meconium contamination of amniotic fluid increases the copper content (53); and, again, even though grossly elevated amniotic fluid copper concentrations have been reported in association with neural tube defects (14) and with Menkes’ disease (81), it seems unlikely in the foreseeable future that estimation of copper in amniotic fluid would be of any practical value.

**SELENIUM**

It has been calculated on the basis of lean body mass that the pregnant woman accumulates 3.5 to 5.0 μg of selenium a day (82). The precise fetal component is
not known. As yet there are no reports of any adverse effects which impaired selenium nutriture may have on pregnancy, and if any do occur it seems probable that they would do so in the areas of endemic selenium deficiency in the Peoples’ Republic of China.

There is some evidence of altered selenium metabolism during pregnancy (82). Metabolic balance studies on women with an intake of 150 μg/day noted a daily retention of 21 ± 4 μg and 34 ± 2 μg during early and late pregnancy, respectively. This seemed to be achieved by reduced urinary excretion of selenium, the net intestinal absorption of the element being estimated at about 80%. Retention in nonpregnant women was 11 ± 2 μg/day. The plasma content of selenium and glutathione peroxidase is reduced in later pregnancy (83,84), but whereas erythrocyte glutathione peroxidase activity is reduced the selenium content of the red blood cell (RBC) compartment is unaltered (84). Evidently some of the plasma changes could be attributed to hemodilution; but one report has described an increased RBC and plasma glutathione peroxidase activities in the presence of reduced plasma and whole blood selenium contents during pregnancy (85) yet another found no alteration in RBC and plasma selenium content accompanied by a reduced plasma and increased platelet glutathione peroxidase activities (82).

In essence, this confusion reflects our ignorance of the physiological regulation of selenium metabolism and glutathione peroxidase activity.

CHROMIUM

Interest in the metabolism of chromium during pregnancy centers on the role which this element may have in carbohydrate metabolism. Both these aspects have been extensively reviewed (86). The fasting plasma chromium in pregnant women (2.97 ± 0.11 ng/ml; 57 ± 2 nmol/liter) is reported to be less than that in normal nonpregnant women (4.7 ± 0.15 ng/ml; 90 ± 3 nmol/liter). Whereas in nonpregnant women both intravenous and oral glucose loads depress the plasma chromium, this was not observed in two similar studies in pregnant women (87,88). The cause of this altered metabolism has not been elucidated, but the presence of an inverse correlation between plasma glucose clearance and urinary excretion of chromium has been interpreted as indicative of chromium deficiency. This hypothesis awaits verification. As with other elements, the chromium content of the hair of pregnant women has been studied. It is lower in hair from multiparous women than in that from nulliparous women (89,90). This change is more marked in women with short birth intervals (91). These changes, however, have not been present in all studies (88).

LACTATION

Little is known about the metabolic adaptation of lactating women with respect to trace elements. Again, as in pregnancy, suppositions have been made about the ideal dietary requirements for lactating women; similarly the recorded intakes of
such women (Table 4) bear little relation to these recommendations. The trace
element composition of human breast milk is discussed elsewhere in this volume.
As yet in women there is little evidence that low trace element intakes alter the
content of these minerals in breast milk. This has been noted for zinc at intakes
of 11 and 28 mg/day (92) and women on a normal dietary range of zinc (93).
Similar conclusions have been drawn for copper (92,93), and even intravenous
copper does not appear to alter the breast milk content of the metal (94). These
studies were of limited duration, and it is possible that a more extended follow-up
of breast milk trace element content in relation to dietary intake and supplemen-
tation may show changes. Currently manganese is the only element for which a
correlation between dietary intake at 2.3 to 9.4 mg/day and its content in breast
milk has been noted (93). This could indicate impaired manganese status, or it
could equally well reflect the homeostatic mechanism for manganese secretion into
breast milk. A preliminary cross-sectional report from Brazil suggests that in some
communities zinc supplementation of lactating mothers may be beneficial (95).
Estimates of the daily body loss of elements during lactation vary. In early lactation
5 mg of zinc/day could be lost in breast milk. Because the elemental content of
milk declines with lactation, it is possible that at 3 months daily elemental losses
are in the order of 1 mg of zinc, 0.31 mg of copper, and 0.004 mg of manganese
per day (93).

The altered plasma contents of zinc and copper which are present during preg-
nancy return rapidly to nonpregnant levels after delivery. Similarly, the erythrocyte
zinc content, which increases steadily throughout pregnancy, declines equally in
nonlactating and lactating mothers (25). It is interesting that in some apparently
healthy lactating mothers plasma zinc does not return to the nonpregnant reference
range.

TABLE 4. Selected reported dietary intakes during lactation

<table>
<thead>
<tr>
<th>Population</th>
<th>Zinc (mg/day)</th>
<th>Copper (mg/day)</th>
<th>Protein (g/day)</th>
<th>Energy (kcal/day)</th>
<th>Methodology*</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finnish</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–8 days</td>
<td>13.7 ± 2.7</td>
<td>1.88 ± 0.6</td>
<td>—</td>
<td>2,429 ± 375</td>
<td>1b</td>
<td>93</td>
</tr>
<tr>
<td>17–32 days</td>
<td>12.8 ± 2.8</td>
<td>1.73 ± 0.6</td>
<td>—</td>
<td>2,125 ± 287</td>
<td>1b</td>
<td>93</td>
</tr>
<tr>
<td>Navajo, 1 month USA</td>
<td>12.2 ± 5.3</td>
<td>1.63 ± 0.9</td>
<td>87 ± 38</td>
<td>2,190 ± 990</td>
<td>2b</td>
<td>25</td>
</tr>
<tr>
<td>1 month</td>
<td>9.4 ± 0.5</td>
<td>—</td>
<td>78 ± 4</td>
<td>1,945 ± 121</td>
<td>3c</td>
<td>26</td>
</tr>
<tr>
<td>6 months</td>
<td>9.6 ± 0.7</td>
<td>—</td>
<td>76 ± 4</td>
<td>1,838 ± 106</td>
<td>3c</td>
<td>26</td>
</tr>
<tr>
<td>Nonlactating</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>4.7 ± 0.6</td>
<td>—</td>
<td>44 ± 4</td>
<td>1,133 ± 121</td>
<td>3c</td>
<td>26</td>
</tr>
<tr>
<td>6 months</td>
<td>5.6 ± 0.5</td>
<td>—</td>
<td>51 ± 5</td>
<td>1,357 ± 162</td>
<td>3c</td>
<td>26</td>
</tr>
</tbody>
</table>

*Methodology: (1) 7-day weighed intake with analysis; (2) 24-hour recall; (3) 3-day duplicate
diet with analysis.
^Standard deviation.
Standard error.
CONCLUSION

There are wide areas of ignorance relating to the metabolism of trace elements during pregnancy. Additionally, there is very little evidence in normal populations that trace element deficiencies occur to such an extent that they jeopardize the outcome of pregnancy. Much of the evidence on this subject is conjectural. If indeed trace element supply does affect the outcome of pregnancy, at the moment there is possibly as much evidence to suggest that the widespread use of supplementation is harmful as there is to say that intakes which are low relative to national recommended intakes are hazardous. This is not to suggest or impart an attitude of complacency; rather, the opposite is needed. There is continuing need to investigate effectively the metabolism of trace elements in pregnant and lactating women. Much of the available data are inconsistent. Some of these may reflect the heterogeneous groups studied as well as represent differing dietary intakes, but neither of these premises can be asserted without further study. It would be advantageous if studies could be done in women who were not receiving inorganic or organic nutritional supplements, as there is accruing evidence that this practice can perturb the metabolism of other nutrients. Furthermore, such studies would enable the reassessment of supplementation policies.

REFERENCES


HUMAN PREGNANCY AND LACTATION


DISCUSSION

Dr. Mertz: The recommended dietary allowance for zinc in pregnancy and lactation in the United States cannot be obtained from any normal diet; in other words, 20 to 25 mg
would call for supplementation. If you were responsible for setting a recommended dietary allowance, what would it be?

**Dr. Aggett:** I think that the recommended allowances in the United States for pregnancy and lactation are overestimated. Probably similar recommendations could apply to both. It is interesting that the WHO recommendations would be quite effective if one assumes a 20% bioavailability. Of course this begs the issue that probably the bioavailability of zinc from western diets is better than that from women subsisting on vegetable-based diets.

**Dr. Mertz:** You do not want to say what you consider to be a good recommended allowance for zinc in pregnancy.

**Dr. Aggett:** I think probably 15 mg if you want a wide margin of safety.

**Dr. Mertz:** Even 15 mg is very difficult to obtain from a typical American diet, so this would call for supplementation, at least in America; I do not know about the European diet.

**Dr. Golden:** We have been examining zinc in pregnant women in Jamaica and have followed 135 women throughout pregnancy. One thing we find is that pregnancy affects zinc metabolism much more than zinc affects pregnancy. The women who are putting on weight the fastest have the lowest plasma zinc levels; and the women who produce the heaviest babies have the lowest plasma zinc levels throughout pregnancy. It seems that the growth of the mother and of the fetus affect zinc metabolism much more than the other way around. We did not get any abnormalities in our studies; we had very few low-birth-weight infants despite very low plasma zinc levels throughout pregnancy. Which brings me to my point about supplementation and whether we should pay any attention to this type of information. I am concerned by the reports from Hyderabad of zinc supplementation of three women who subsequently aborted. Having gotten this result, the investigators stopped the trial of zinc supplementation in humans and went on to look at it in rats. The rats also had a higher prevalence of abortion. They therefore stopped zinc supplementation and said that within the Indian context zinc supplementation was dangerous. I would like you to comment on these reports because I think they are very important if we are to go around splashing zinc tablets into a population. We are in danger of repeating the iron splash that occurred 50 years ago.

**Dr. Aggett:** The Hyderabad experience in fact is very salutary, and I elected not to mention it when I said that the level of supplementation used, say in the Swedish study, of 90 mg of zinc was quite phenomenal. We do not have the data to consider reliably any ideal intakes. In Aberdeen, routine nutritional supplementation has not been used in any form in pregnancies for many years, and there is certainly no increase in the incidence of abnormalities, anemia, or anything like that.

**Dr. Van Caillie:** You let us see the work of Swanson with a dietary intake of selenium of 150 μg a day, which is a very high intake. This work is fascinating because if you look at the urinary excretion you may think there is a homeostatic mechanism which nobody knows about. In Antwerp we do not have a dietary intake of 150 μg; we have an average intake of 50 to 60 μg/day. We have been looking at the breast milk of 35 normal women with normal pregnancy, normal delivery, and normal infants, and we found very different values. According to our results, a child in Japan or in the United States receives much more selenium than Belgian infants. The question is: How much is enough? What is a normal intake?

**Dr. Aggett:** I think I can answer that in terms of Dr. Mertz's presentation, which provided some of the answers for an anionic element such as selenium. In some areas in the United States there is a selenium intake in excess of 150 μg, within the range of 200 μg. The
selenium intake in the United Kingdom is about 60 μg. Professor Diplock, do you have any experience on the outcome of pregnancies in the Keshan area?

Dr. Diplock: I do not think there is any information to indicate abnormalities in pregnancy. There is a parallel here with vitamin E, and because we should consider selenium and vitamin E together when examining oxygen stress in the neonate it is very interesting that the placenta transfers vitamin E very poorly and the vitamin E level of the neonate is very low. It may well be that the changes in selenium are due to an increased requirement of the fetus during pregnancy for selenium because the intake of vitamin E is low. It is interesting to see that the figure for selenium in colostrum is very high, as is the vitamin E level.

Dr. Hurley: My comments relate to the policy of supplementation with zinc. Dr. Golden mentioned the Hyderabad supplementation studies, but I find it impossible to evaluate them, as they were never published in detail. However, I do agree that blind supplementation is not a good idea and may be dangerous. On the other hand, the point to be emphasized is your last one, Dr. Aggett, that we really do not know what to look for yet. I still think that it is possible that zinc and/or other trace elements and/or other nutrients may, in combination with other factors, act together to precipitate some of these problems. Any time we get interactions of that kind it obviously becomes very difficult to unravel them.

Dr. Hambidge: One reason for performing supplementation studies, at least in the United States, is that most prenatal vitamin pills now contain zinc and most pregnant women do in fact get zinc supplements to a level of 15 mg/day. Hence I think there is good reason for trying to understand what this might do.