Trace element needs in human pregnancy

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The importance of the trace metals zinc, copper and iron with respect to fetal growth in human pregnancy, with particular emphasis on their transfer to and uptake by the fetus, was discussed at a meeting of the Nutrition Society by Widdowson *et al.* (1974). The present paper examines the new information which is available in respect to the trace elements Zn, Cu, manganese, selenium and chromium.

When considering the needs of human pregnancy there are several possible points in the maternal–fetal handling of nutrients where limitation could occur: (a) the maternal diet (i.e. the provision of nutrients), (b) maternal absorption from the diet, (c) maternal utero-placental blood flow (i.e. delivery of the nutrient), (d) placental transfer, (e) fetal uptake.

Before looking at specific elements, there are some general considerations of maternal physiological adaptation to pregnancy which must be remembered. These include increased dietary absorption, of which there is some evidence for Fe (Heinrich *et al.* 1968; Apte & Iyengar, 1970; Svanberg, 1975); increased plasma volume which alters the concentrations of nutrients in the blood, e.g. folic acid (Hall *et al.* 1976); and increased urinary loss of nutrients because of increased renal blood flow and increased glomerular filtration rate such as occurs with amino acids (Hytten & Cheyne, 1972). In addition there are changes in the total number of erythrocytes and leucocytes with an alteration in the proportion of types of cells present (Letsky, 1980). There is also increase in maternal tissue protein (e.g. uterine muscle) and fetal tissue. Trace elements may be lost from the fetus into the amniotic fluid, but as gestation advances the fetal kidneys increasingly contribute to the volume of fluid, with consequent changes in the composition of the fluid (Lind *et al.* 1969). Some but not necessarily all nutrients thus 'lost' may be recycled by fetal swallowing.

Zn

While animal studies have continued to show that deficiency of Zn is coupled with abnormal pregnancies, the picture with respect to human pregnancy is much less clear. For example, with respect to retarded fetal growth some reports have shown an increased plasma Zn concentration (Jameson, 1976; Crosby *et al.* 1977; Patrick *et al.* 1982), some decreased plasma Zn concentration (McMichael *et al.* 1982; Abu-Assal & Craig, 1984; Mukkerjee *et al.* 1984) and some unchanged levels (Cherry *et al.* 1981; Hambidge *et al.* 1983; Hunt *et al.* 1984; Kulholma *et al.* 1984; Campbell-Brown *et al.* 1985; Ghosh *et al.* 1985; Tuttle *et al.* 1985).

Table 1 lists the recorded dietary intakes of energy, protein and Zn from populations in differing areas of the world. All the studies suggest that Zn intake is less than the previously recommended dietary allowance for pregnant women of 20 mg/d ((US) National Research Council, 1980), and show that Zn intake tends to parallel protein intake. In the majority of these studies the outcome of the pregnancy was entirely satisfactory, with normal healthy babies. Such findings of possible dietary Zn deficiency in human pregnancy, when coupled with the well-documented fall in plasma Zn concentration throughout human pregnancy (Fig. 1), led to the hypothesis that in human pregnancy there was a Zn deficiency state. Evidence is accumulating to the contrary.

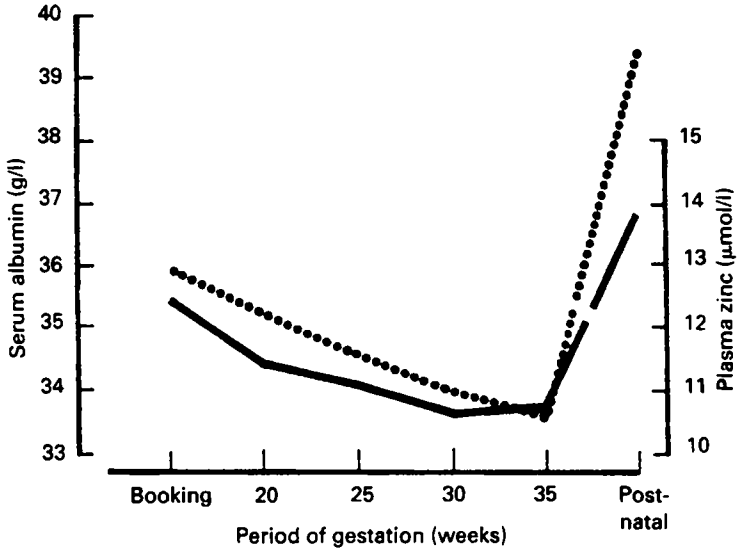

Fig. 1. Serum albumin (...) and plasma zinc (——) concentrations in thirty-three normal primigravidae.

First, the suggested dietary intake of Zn could only be achieved on natural diets at impossibly high protein intakes. Second, it is noted (Fig. 1) that the plasma Zn level decreases early in pregnancy (by 12 weeks gestation) and increases to normal non-pregnant values by 6 weeks post-partum in women receiving no mineral supplements. The expansion of plasma volume (Table 2) probably contributes to the decrease in plasma Zn concentration during human pregnancy. Multiplying both serum albumin and plasma Zn concentrations by plasma volume, we find that there is a significant increase in intravascular albumin mass, as has been previously reported by Campbell & MacGillivray (1977), and a small increase in Zn mass (Table 2).

Table 1. *Daily intakes of energy, protein and zinc in human pregnancy*

Population	Stage of pregnancy	Method	Energy (kJ)	Energy (kcal)	Protein (g)	Zn (mg)	Reference
Navajo	Mid	24 h recall	10240	2448	95	12	Butte *et al.* 1981
Middle-income, Denver		24 h recall or 3 d record	8490	2028	85	11·3	Hambidge *et al.* 1983
Private, USA	37 weeks	3 d duplicate diet	8460	2023	80	9·8	Moser & Reynolds, 1983
Middle income, vegetarian, USA	37 weeks	3 d recall				10·5	King *et al.* 1981
Aberdeen	30 weeks	7 d weighed intake	8390	2006	72·4	9·1	Tuttle *et al.* 1985
Hispanics	2nd trimester	24 h recall	6890	1646	68	9·73	Hunt *et al.* 1983
Gujarati:							
England		7 d weighed intake			61·8	8·4	Abraham, 1983
India		7 d weighed intake			39·6	5·2	Abraham, 1983

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Table 2. *Plasma volume, intravascular zinc mass and intravascular albumin mass in normal human pregnancy (from Tuttle* et al. *1985)*

(Mean values and standard deviations)

Period of gestation (weeks)	No. of subjects	Plasma volume (ml)		Zinc mass (μmol)		Albumin mass (g)	
		Mean	SD	Mean	SD	Mean	SD
14	29	2918	441	36·4	6·17	104·4	17·25
20	28	3202	377	37·2	8·01	112·9	13·45
25	32	3464	398	38·1	5·76	119·8	14·79
30	33	3642	328	39·4	5·71	123·5	12·94
35	31	3793	448	40·6	8·69	127·3	16·45

Third, Zn balance studies have attempted to check theoretical needs. These have been calculated from the increments in protein, both fetal and maternal, and estimate of Zn content (Table 3). This method assumes that both fetal and maternal protein have the same Zn concentrations but is likely to overestimate rather than underestimate the extra Zn added. Balance studies were carried out in seven normal women in their first pregnancy (Armstrong, 1985) at a late stage of pregnancy. Table 4 gives the results for Zn. The average net retention of 0·86 mg/d was very close to the theoretical requirement calculated in Table 3. In agreement with our work, Taper *et al.* (1985) found a Zn retention of about 1 mg/d in pregnancy from home metabolic balances, which are always slightly suspect. A Californian group (Schraer & Calloway, 1974; Swanson *et al.* 1983*b*) found higher Zn retention in pregnancy but at much higher dietary intakes (20 mg/d and above). Such intakes are well in excess of normal. The exaggerated Zn retention may reflect the response of the gut to a change to a very high dietary intake of Zn. In the non-pregnant women Zn retention was also higher than might have been expected. The mean difference of daily Zn retention between the pregnant women and the non-pregnant women was 1·3 mg.

Table 3. *Calculated zinc and copper requirements during human pregnancy*

(a) Cumulative theoretical increments

Period of gestation (weeks)	10	20	30	40
Protein (g)*	36	165	498	925
Zn (mg)†	4·6	21·1	63·7	118·4
Cu (mg)†	1·2	5·5	16·6	30·8

(b) Calculated need (mg/d)

Between weeks	1–10	11–20	21–30	31–40
Zn retention	0·066	0·236	0·609	0·780
Cu retention	0·017	0·061	0·158	0·283
Zn requirement‡	0·32	1·18	3·04	3·90
Cu requirement‡	0·06	0·20	0·53	0·68

*From Hytten & Leitch (1971).
†From Widdowson *et al.* (1951) assuming 128 μg Zn and 33·3 μg Cu/g protein.
‡Assuming 0·20 availability of Zn from the diet and 0·30 availability of Cu from the diet.

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Table 4. *Mean zinc, copper and manganese balance in late pregnancy (mg/d) for seven normal primigravidae receiving no trace element supplements (Armstrong, 1985)*

	Zn	Cu	Mn
Intake	9·11	1·1	2·37
Output: Urine	0·48	0·11	0·08
Faeces	7·77	0·91	2·52
Apparent absorption	1·34	0·19	–0·15
Retention	0·86	0·08	–0·23

Finally the placental transfer of Zn, as inferred from maternal and fetal concentrations of Zn, is similar in normal pregnancies, pregnancies with intrauterine growth retardation, and pre-eclamptic pregnancies (Table 5). Zn is transferred across the placenta to the fetus against a concentration gradient and is taken up thereafter by the fetus. Widdowson *et al.* (1974) have shown that the fetus normally accrues about 60 mg by birth, of which about one-quarter is present in the fetal liver. The exact mechanism of transfer is unknown but placental levels of Zn are reported to be higher than either maternal or fetal concentrations (Baglan, 1974). Thus, a similar situation is found for Zn as exists for some amino acids (Hytten, 1980). The regulatory mechanism of such transfer remains unknown but it seems likely that the decrease in plasma Zn concentration may be important.

Cu

Cu is the next-most-researched trace metal to Zn in human pregnancy. Animal studies have again suggested that dietary Cu deficiency is associated with specific abnormalities and growth retardation, but in human pregnancy the picture is clouded when considering pregnancy complications in relation to Cu status.

In sharp contrast to Zn, plasma Cu levels rise in pregnancy (Fig. 2) (Tuttle *et al.* 1985). Some 90% of Cu is incorporated in the plasma protein caeruloplasmin which increases in human pregnancy as a result of oestrogen stimulation. We have calculated the proportion of bound Cu and find that it remains unchanged in human pregnancy, as did Henkin *et al.* (1971).

Table 6 shows that the daily dietary intake of Cu is generally slightly lower than that recommended (2–3 mg/d) and tends, like Zn, to parallel protein intake. Table 3 shows the calculated theoretical pregnancy requirement for Cu. An extra 0·67 mg (approximately one-third of the total Cu intake) is required daily but this is probably an overestimate.

Table 5. *Maternal and fetal blood levels of zinc and copper in human pregnancy (μmol/l)*

	Zn		Cu	
	Maternal	Cord	Maternal	Cord
Normal pregnancies	10·8	20·2	32·9	6·6
Pregnancies complicated by IUGR	10·6	16·6	35·3	7·1
Pre-eclamptic pregnancies	10·2	19·5	36·5	8·0

IUGR, intrauterine growth retardation.

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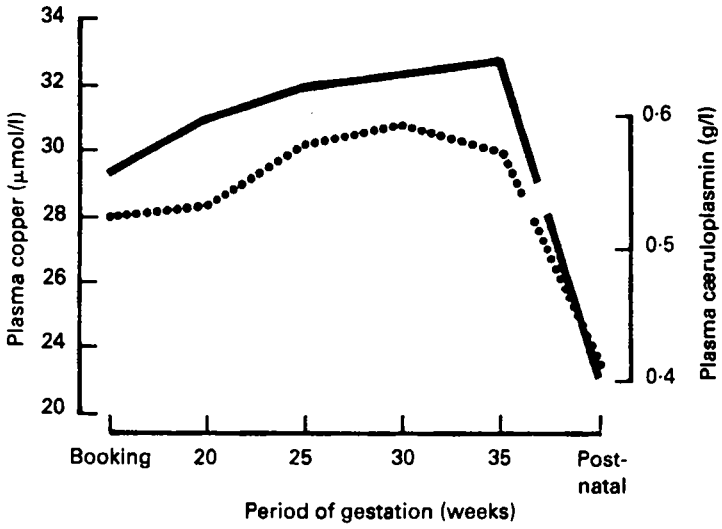

Fig. 2. Plasma copper (——) and caeruloplasmin (...) concentrations in thirty-three normal privigravidae.

From balance studies (Armstrong, 1985) seven healthy Aberdonian women eating to appetite (Table 4) on a low Cu intake with an apparent Cu absorption of 0·17 had an average Cu retention of 0·08 mg, much less than the calculated need. Turnlund *et al.* (1983) have studied Cu balance in pregnant women on two diets based on animal protein or vegetable protein. Cu intakes were higher than those in Aberdeen as was the apparent Cu absorption (0·22 on the animal-based diet, and 0·27–0·30 on the vegetable-based diet). They showed a high Cu retention in both pregnant and non-pregnant women. There was no difference in Cu retention between pregnant and non-pregnant women when the diet was animal-based, but on the vegetable-protein diet the mean difference was 0·09 mg/d, a similar value to that found in Aberdeen (Armstrong, 1985).

Table 6. *Daily intakes of energy, protein and copper in pregnancy*

	Energy		Protein	Cu	
	(kJ)	(kcal)	(g)	(mg)	Reference
Navajo women, USA	10 400	2488	95	1·57	Butte *et al.* 1981
Hispanics, USA	6890	1646	68	1·39	Hunt *et al.* 1983
Non-vegetarian, California	8380	2003	97	2·1	King *et al.* 1981
Vegetarian, California	10 230	2446	93	2·8	King *et al.* 1981
Hindu vegetarian, London	8250	1971	57·3	1·53	Campbell-Brown *et al.* 1985
Hindu meat-eater, London	9060	2165	75·1	1·80	
European, London	8500	2033	80·3	1·48	
Aberdeen:					
Normal pregnancies	8390	2006	72·4	1·5	Tuttle *et al.* 1985
At risk of IUGR	8170	1952	71·3	1·5	Tuttle *et al.* 1985
Twin pregnancies	8520	2036	70·3	1·42	Campbell *et al.* 1982

IUGR, intrauterine growth retardation.

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Turnlund *et al.* (1983) also studied Cu absorption using ^{65}Cu and found absorption from the gastrointestinal tract of about 0·40 as compared with 0·22–0·30 from their balance work. Their conclusion that Cu absorption increased during pregnancy, with slight Cu retention, is not fully justified. Although the same non-pregnant subjects were studied on both diets, two separate groups of pregnant women were used, and this may have influenced their findings. Also dietary Cu intakes were high and the relation of such intakes to absorption and retention must be considered.

Maternal and fetal Cu concentrations are given in Table 5. The very low concentrations in cord–fetal blood are well known, as is the fact that levels of Cu increase gradually after birth. There are no differences in maternal or fetal blood Cu concentrations associated with pregnancy complications. As caeruloplasmin is not transferred across the placenta, the fetus obtains its Cu in the free form. Although the proportion of bound relative to free Cu remains the same in human pregnancy, there is a higher total concentration of Cu in the mother relative to the fetus and a concentration gradient of free Cu is produced, favouring transfer to the fetus (Henkin *et al.* 1971). This is in keeping with the findings of Widdowson *et al.* (1974) who showed that the fetus accumulates Cu from early in gestation and that more than half is in the fetal liver as a store for use after birth.

Mn

Little or no information is available with respect to Mn requirements in human pregnancy. To date there is no information on dietary Mn intake and the total amount in the human fetus is not known (Shaw, 1980). Although there is some Mn in the fetal liver it is present in similar concentrations to that in the adult liver (Widdowson *et al.* 1972; Casey & Robinson, 1978).

In the non-pregnant woman, Mn status is controlled by biliary excretion into the gastrointestinal tract. Mn balance studies were carried out in the same women as mentioned earlier (Table 4). Intakes were found to approximate to those recommended, i.e. 2–3 mg/d. On average there was net negative balance, with mean faecal output of Mn being slightly higher than dietary intake. However, there was marked inter-patient variability. Faecal Mn was shown to vary with intake. Two of the seven women were in positive Mn balance, three were just in balance, and two were in negative balance, one of them with a particularly high negative value. It is difficult to know how to interpret such findings but it may be that a longer balance period is necessary. It is interesting to note that first we found a very slight net loss of Mn in pregnancy; second, there appears to be little or no Mn stored in the fetus; and third, there is a slight negative Mn balance in the newborn (Widdowson, 1969). This is clearly a difficult area that requires attention in the future.

Se

On the basis of changes in body mass and composition it has been possible to calculate that pregnant women should accumulate 3·5–5 μg Se/d. There are no reliable studies of dietary intake in pregnancy but various studies on non-pregnant subjects indicate intakes ranging from as low as 30 μg in New Zealand up to 100 μg/d in some parts of the United States (Thomson & Robinson, 1980). Are the lowest intakes adequate for pregnancy, and is there risk of toxicity at high Se intakes?

Se balance studies (Swanson *et al.* 1983*a*) have compared pregnant and non-pregnant groups on high Se intakes of 150 μg/d (Table 7). In human pregnancy there is a marked decrease in urinary Se excretion, which is the primary regulatory mechanism of Se status. Very high Se retentions were found both in the non-pregnant and pregnant groups. This

Table 7. *Selenium balance in pregnant and non-pregnant women (from Swanson et al. 1983a)*

	Non-pregnant	Late pregnancy
Se intake (μg/d)	150	158
Faecal Se (μg/d)	28	28
Urinary Se (μg/d)	111	96
Apparent absorption (μg Se/d)	122	130
Apparent retention (μg Se/d)	11	34

might be related to the unusually high dietary intake for particular individuals. The average difference in retention between pregnant and non-pregnant groups was 23 μg/d, four to five times the calculated required amount. In pregnancy the efficiency of absorption of Se was approximately 0·80 and this has been confirmed by the same group using ^{76}Se.

How to assess Se status in human pregnancy has not been clearly defined. Maternal plasma concentrations of Se are reported to be lower while the erythrocyte concentrations would appear to be unchanged (Rudolph & Wong, 1978; Behne & Walters, 1979). In the non-pregnant subject estimation of glutathione peroxidase (*EC* 1.11.1.9; GSHPx) has been suggested as being a good method of assessing Se status. In pregnancy GSHPx activity is reported to be lowered in the plasma but unchanged (Behne & Walters, 1979) or increased (Rudolph & Wong, 1978) in the erythrocytes. In human pregnancy, our own work (unpublished) has shown no relation between plasma Se and GSHPx levels. Further information on the relation between this enzyme and Se status is needed, particularly as it appears to change in pregnancy. Maternal and fetal concentrations (Table 8) indicate that there is a gradient favouring transfer from the mother to the fetus.

Cr

The interest in Cr in human pregnancy centres on the altered carbohydrate metabolism in human pregnancy and the possible role of Cr deficiency in this respect. We know nothing of dietary intakes of Cr. In pregnancy, fasting plasma Cr is reported to be lowered (Davidson & Burt, 1973) or unchanged (Hambidge & Droegemueller, 1974). Hair Cr concentration has also been reported to decrease in pregnancy, particularly in multiparous women (Hambidge & Rodgerson, 1969). Cr is present in the fetal liver and the Cr content of the fetus gradually declines after birth (Widdowson *et al.* 1972). Glinsmann *et al.* (1966) have reported a temporary increase in plasma Cr after a glucose load, in non-pregnant subjects. Davidson & Burt (1973), however, reported a substantial fall in plasma Cr after both oral and intravenous glucose loading, but also reported that

Table 8. *Maternal and fetal selenium status at delivery (from Rudolph & Wong, 1978)*

	Maternal	Fetal/cord	Non-pregnant
Plasma Se (μg/ml)	0·19	0·14	0·21
Erythrocyte Se (μg/ml)	0·52	0·39	0·52
Plasma GSHPx (units/ml)	0·140	0·103	0·195
Erythrocyte GSHPx (units/ml)	9·90	5·76	8·32

GSHPx, glutathione peroxidase (*EC* 1.11.1.9).

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this response was absent in pregnant subjects. Hambidge & Droegemeuller (1974) found an increase in plasma Cr after oral glucose administration in 33% of women in late pregnancy: both studies suggested the possibility of Cr deficiency. Since then, however, analytical problems have been reported for Cr and no further work has been done in this field.

Conclusion

(a) *Dietary intakes*. In most Western developed countries low intakes of trace elements are not a problem. Even in less-prosperous and less-well-developed societies, deficiencies of trace elements in the diet are unlikely, unless there is concomitant gross protein deficiency which at this stage has not been demonstrated in any pregnant population in the world.

(b) *Maternal absorption*. For all the elements considered so far it has been shown that there is an increased absorption from the gastrointestinal tract in human pregnancy, sufficient to meet the increased demand.

(c) *Fetal uptake*. Normal full-term infants have no difficulty in obtaining sufficient trace elements in their body, although those born preterm may not have time to accumulate sufficient nutrients for use after birth. Infants with congenital abnormalities may present, as yet unknown, problems.

(d) *Placental transfer*. Although the exact details and the regulatory mechanisms remain to be elucidated, it seems that the capacity of the placenta to transfer nutrients from mother to fetus is adequate. It is generally accepted that a small placenta is a result rather than a cause of a small baby.

(e) *Utero-placental blood flow*. This remaining limiting factor affecting the delivery of nutrients to the feto-placental unit is not specific to trace elements but applies equally to all nutrients. Factors directing blood flow away from the feto-placental unit, such as smoking or heavy exercise, resulting in problems of fetal growth and development may adversely affect trace element supply to the fetus.

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