Peripheral blood leucocyte zinc depletion in babies with intrauterine growth retardation

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SUMMARY The zinc content of peripheral blood leucocytes from the cord blood of 63 normal and 20 preterm babies, and of 27 babies with evidence of idiopathic intrauterine growth retardation (IUGR) was measured. Leucocyte zinc depletion was present in babies with acute IUGR (IUGR babies compared with controls, mean 47.8 v 51.5 ng zinc/mg dry weight), but was especially severe in those with prolonged IUGR (mean 43.2 ng zinc/mg dry weight), while preterm babies were normal (mean 51.9 ng zinc/mg dry weight). We suggest that this fetal tissue zinc depletion is caused by maternal zinc depletion, and may reflect a reduction of whole body zinc status.

To estimate the whole body content of an element that is predominantly intracellular, it is necessary either to measure its intracellular content or some extracellular index that reflects accurately intracellular changes. We have shown that peripheral blood leucocytes represent a suitable nucleated tissue in which to measure zinc and predict the extrahepatic nucleated tissue status.¹

We reported that low values of zinc in maternal peripheral blood leucocytes are strongly associated with idiopathic intrauterine growth retardation (IUGR).² Small for gestational age infants have both an increased morbidity—minor neurological problems, learning disorders, and susceptibility to infections—and early mortality.³ Neonatal zinc deprivation is associated with thymic atrophy and defective cellular immunity and, in the more extreme forms, with skin rashes and diarrhoea. During the first 6 months after birth, small babies show increased growth velocity (or so called catch-up growth) and requirements for zinc, suggesting that intrauterine growth may have been limited by the supply of zinc.⁴ The bio-availability of zinc in breast milk is greater than that in formula feeds,⁵ but if maternal zinc depletion has already caused neonatal deprivation of this element, then it is unlikely that the mother's milk content will be adequate to correct the imbalance.

We have compared the results of maternal and fetal plasma and peripheral blood leucocyte zinc of normal, premature, and growth retarded babies and corresponding mothers to determine whether there is a relation between the values of maternal and fetal zinc and IUGR.

Patients and methods

We studied 110 mothers and babies: 63 mothers giving birth to normal babies; 20 to premature babies (gestational age assessed by Dubowitz score <37 weeks, and appropriate weight for age); 19 to acute onset idiopathic IUGR babies (gestational age >37 weeks and weight only below 10th centile); and 8 to chronic idiopathic IUGR babies (weight, length, and head circumference all below the 10th centile). All were assessed by the neonatal team.

Simultaneous samples (30 ml) of venous maternal and clamped, pulseless, umbilical cord blood were taken into heparinized syringes and the leucocytes separated.⁶ The isolated leucocytes were dried to constant weight, the zinc was extracted with 1.0 M hydrochloric acid and measured by atomic absorption flame spectrophotometry (AAS) (Instrumentation Laboratories Model 257). Details of our method have been published.¹ Five ml blood was separated, centrifuged at 300 g for 20 minutes, two 1.0 ml plasma samples were diluted 1:9 (vol/vol) with 80 mM nitric acid, and plasma zinc was measured by AAS.

The results are expressed as mean (SE) and were compared using the unpaired, 2-tailed Student's *t* test. The association between the variables, namely leucocyte or plasma zinc in the mother and fetus, were tested by regression of the second kind. The protocol for the study was approved by the hospital ethical committee and informed written consent obtained from each mother.

Results

The results of the maternal leucocyte zinc contents

Table Maternal and fetal peripheral blood leucocyte and plasma zinc (Zn) values; mean (SEM)

Group (No)	Maternal				Fetal			
	Leucocyte (ng Zn/mg dry weight)		Plasma (g/ml)		Leucocyte (ng Zn/mg dry weight)		Plasma (g/ml)	
Normal controls (63)	51.5	1.1	0.63	0.03	54.2	1.3	0.94	0.03§
Preterm (20)	51.9	2.1	0.60	0.03	53.9	2.1	0.89	0.10§
Prolonged IUGR (8)	43.2	3.6†	0.65	0.06	43.4	3.5†	0.86	0.09‡ (5)
Acute IUGR (19)	47.8	3.6*	0.63	0.04	50.7	1.6*	0.91	0.06§ (15)

*P = <0.05 } compared with controls
†P = <0.01 }
‡P = <0.05 } mother compared with fetus
§P = <0.01 }
IUGR = intrauterine growth retardation

are contained in previously published data.² The mean leucocyte zinc content of babies with prolonged IUGR was appreciably reduced compared with that of the normal babies (Table). The babies with acute onset IUGR also showed evidence of depletion, but this was less notable. Preterm babies were not leucocyte zinc depleted.

The plasma zinc values were unchanged in the leucocyte zinc depleted mothers and fetuses, but the values in the fetuses were significantly higher than in their mothers (Table). Furthermore, there was no significant relation between maternal and fetal plasma zinc (Fig. 1) ($r=0.01$, $P=NS$, $n=66$), nor was there a relation between maternal or fetal plasma and leucocyte zinc. A significant correlation was found, however, between maternal and fetal leucocyte zinc ($r=0.34$, $n=89$, $P<0.001$) (Fig. 2).

Fig. 1 Relation between maternal and fetal plasma zinc values.

Fig. 2 Relation between maternal and fetal leucocyte zinc values.

Discussion

Low tissue values of zinc, namely depletion, do not necessarily imply deficiency, or some disorder of cellular function caused by a shortage of zinc. We have shown previously, however, that maternal leucocyte zinc depletion is strongly associated with IUGR, while the mothers of preterm babies had normal values.² We have now shown that their own leucocyte zinc was also reduced in small for gestational age babies, but particularly in those with clinical evidence of prolonged IUGR, while preterm babies had normal leucocyte zinc tissue values. We have, in addition, shown a positive correlation between maternal and fetal leucocyte zinc values; however, no correlation was found between maternal and fetal plasma zinc values.

We have no explanation for the relatively high fetal plasma values, but they may reflect an increased amount or affinity of zinc binding proteins in fetal

plasma. The fetal values again confirm, however, the lack of association between values of zinc in plasma and tissues.

The mechanism whereby maternal zinc depletion causes depletion of leucocyte zinc in the fetus is unknown. The zinc deprived mothers may be unable to provide sufficient zinc, particularly since the fetus may derive its supply chiefly from the more rapidly turning over zinc pools in plasma—the larger pools in muscle and bone being relatively inaccessible.⁷ Even in normal mothers the plasma and leucocyte zinc pools fall throughout pregnancy,² while zinc deprived mothers may even remove zinc from the fetus.⁸

Alternatively, the placenta from deprived mothers may be unable to transfer zinc to the fetus. The placentae of fetuses showing IUGR are small, with signs of ischaemia. In man the synthesis of the powerful vasodilatory prostaglandin prostacyclin (PGI₂) is reduced in umbilical arteries from fetuses with IUGR,⁹ while in the rat, chronic zinc deprivation increases the formation in the placenta of the vasoconstricting metabolites of prostaglandins.¹⁰ So maternal zinc depletion may cause placental ischaemia that limits the transfer of zinc to the fetus.

Zinc is a component of enzymes such as DNA and RNA polymerases⁷ that are fundamental for growth, so although fetal zinc depletion may slow growth,⁷ this will in turn reduce the zinc requirements of the fetus. After birth, small babies grow faster than normal.⁴ Zinc deprived mothers may, however, be unable to provide the increased zinc for this growth, even though the zinc in breast milk is more available than that in formula feeds. There are many mothers from lower socioeconomic groups in our health district and they are more likely to formula feed than other mothers, and to have large families in which the average zinc intake per person is particularly low.¹¹

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