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Vitamin A and related essential nutrients in cord blood: relationships with anthropometric measurements at birth

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Abstract

Following the advice given by the Department of Health to women who are, or may become pregnant, not to eat liver and liver products because of the risk of vitamin A toxicity, the concentrations of vitamins A and E, and copper, magnesium and zinc in cord blood were investigated. The study was conducted in Hackney, an inner city area of London. Esters of vitamin A were not detected in any of the samples, indicating that there was no biochemical evidence of a risk of toxicity. Indeed, vitamin A correlated significantly with birthweight, head circumference, length, and gestation period. There was also a significant positive relationship between zinc and birthweight. In contrast, copper showed a negative correlation with birthweight and head circumference. Vitamin E and magnesium were not associated with any of the anthropometric measurements, although magnesium showed an increasing trend with birthweight. The data suggest that most of the mothers of the subjects studied may have been marginal with respect to vitamins A and E and zinc. In those with low birthweight babies, a higher intake would have improved their nutritional status and possibly the outcome of their pregnancy. For these low-income mothers, liver and liver products are the cheapest and the best source of vitamins A and E, haem iron, B vitamins and several other essential nutrients; hence the advice of the Department of Health may have been misplaced.

Keywords: Vitamin A; Vitamin E; Copper; Magnesium; Zinc; Cord blood; Fetal development

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1. Introduction

Low birthweight is associated with neonatal mortality, morbidity and disability [30]. The incidences of severe neuro-visual developmental disorders such as mental retardation, blindness, deafness, cerebral palsy, autism and some forms of epilepsy increase with decreasing birthweight. Malformations associated with low birthweight, however, may reflect extreme clinical manifestations of a wider problem. It may be that a significant number of low birthweight babies are born with subtle anomalies that may be manifested in physical and/or mental impairments later in life. Villar et al. [52] reported that damage in intrauterine growth retarded (IUGR) infants can remain latent and subsequently be exposed under adverse conditions. Low birthweight babies, primarily those with type II IUGR, are known to exhibit a catch-up growth. However, 3–8-year follow-up studies show a significant proportion of them have poor cognitive function, academic achievement, neuro-motor competence, and other disabilities of varying severity [20,33,34,52]. Recent epidemiological findings [4] suggest that non-insulin-dependent diabetes and cardiovascular disease in adult life may have their origins in poor embryonic and fetal development.

Low birthweight has a multifactorial causality, with smoking, gestational nutrition and low prepregnancy weight being the primary factors in developed countries [26]. Impaired placental functions and abnormal haemodynamic changes are also known to have a strong negative influence on birthweight [18]. The association between maternal nutrition and birthweight is now clearly established [25]. In developing countries maternal malnutrition explains the greatest proportion of low birthweight with caloric malnutrition accounting for two-thirds of the intrauterine growth retardation [18]. An insufficiency and/or an imbalance of certain essential nutrients rather than gross malnutrition is thought to be the primary cause of gestational malnutrition in the developed countries. However, Doyle et al. [14] in a study of 513 pregnancies in Hackney reported that mothers who subsequently gave birth to low birthweight babies had low intakes of 43 out of the 44 nutrients measured including copper, magnesium, zinc and vitamins A and E.

As an extension of our earlier study in Hackney [14], an inner city area of London which has one of the highest low birthweight babies in the UK, we have investigated the levels of vitamins A and E, and Cu, Mg and Zn in cord blood. The study was particularly pertinent because women who are, or intending to become, pregnant have been advised, by the Department of Health, not to eat liver or liver products because of a risk of vitamin A toxicity.

2. Materials and methods

2.1. Subjects

Babies born at the Homerton Hospital, Hackney, London, UK, in February and March 1993 were studied. None of the babies had congenital malformations or any other disorder that would have had an influence on the levels of the parameters investigated. The babies were born to Afro-Caribbean, Asian or Caucasian parents.

Gestational age, birthweight, head circumference, length and clinical details of the babies pertinent to the study were recorded at birth. Birthweight was measured using electronic scales accurate to 5 g, length by a Holtain Infantometer, and head circumference with a non-stretch plastic tape measure around the head at level of occipital protuberance. Measurements were carried out by the midwives and the inter-observer variability was less than 2.5%. In addition, obstetric history and other relevant maternal and family information were collected by the use of a short standard questionnaire designed for the study.

Immediately after birth, about 3 ml of cord blood was taken into heparinised tubes. Plasma was separated by cold centrifugation at 1000 *g* for 15 min, flushed with nitrogen and stored at −70°C until required for analysis.

2.2. Analytical methods

Vitamins A and E were determined by Varian high performance liquid chromatograph (HPLC) equipped with a variable wavelength UV-9050 and a fluorometer (Fluorichrom II) detectors (Varian Ltd., Palo Alto, CA) in series. Absorption area was integrated by a Varian 4290 integrator. The eluting solvents and column conditions employed have been described by Ghebremeskel and Williams [16].

Copper, magnesium and zinc were analysed by inductively coupled plasma optical emission spectrometry (ICPOES) using a JY24 Inductively Coupled Plasma Optical Emission Spectrometer (Instruments SA, Longjumeau, France). Each sample was transferred to plastic tubes which had been washed overnight in 3.0 M nitric acid (Analar grade) and rinsed with deionised water. Analyses were carried out on samples diluted 1:10 with 0.110 M nitric acid, prepared using double deionised water and ultra pure nitric acid. Analytical lines for Cu, Mg and Zn were 324.754, 279.553 and 213.856 nm, respectively. Dilution, spiking, and recovery experiments were performed [41] and linear response and full recoveries were obtained.

2.3. Data analysis

Data are expressed as means and standard deviations (S.D.). Regression analysis was used to test for any relationship between the parameters investigated and birth dimensions. The parameters were also sorted by weight and divided into quartiles. Differences between the quartiles were tested by the analysis of variance (ANOVA). All the statistical analyses were performed by the use of the Minitab statistical package (PC Version Release 8.2)

3. Results

Seventy-nine samples were analysed for vitamins A and E, and 42 for the metallic elements. Thirty-seven samples were not analysed for the metals because of an insufficient volume for duplicate analysis. Of the 79, 73 were term babies, four had a gestational age of 36 weeks, and two were born at 35 weeks. A summary of the anthropometric measurements, and concentrations of copper, magnesium, zinc and vitamins A and E are presented in Table 1.

Table 1
Anthropometric measurements and concentrations of copper, magnesium, zinc and vitamins A and E in cord plasma of babies at birth

	Minimum	Maximum	Mean ± S.D.
Gestational age (weeks)	35	42	39.4 ± 1.4
Birthweight (g)	2235.0	4750	3244.2 ± 455.8
Head circumference (cm)	30.0	38.0	33.87 ± 1.42
Length (cm)	43.0	62.0	50.91 ± 3.16
Copper (μmol/l)[b]	2.66	25.18	6.17 ± 3.37
Magnesium (mmol/l)	0.50	0.95	0.67 ± 0.09
Zinc (μmol/l)[c]	7.55	18.38	13.19 ± 2.59
Vitamin A (μmol/l)[a]	0.55	2.60	1.25 ± 0.39
Vitamin E (μmol/l)	1.65	14.88	8.71 ± 2.44

[a]Vitamin A correlated with birthweight ($r = 0.420$, $P = 0.0001$), head circumference ($r = 0.322$, $P = 0.004$), length ($r = 0.320$, $P = 0.004$), gestation age ($r = 0.252$, $P = 0.024$) and vitamin E ($r = 0.338$, $P = 0.002$).
[b]Copper correlated with birthweight ($r = -0.350$, $P = 0.023$) and head circumference ($r = -0.512$, $P = 0.001$).
[c]Zinc correlated with magnesium ($r = 0.472$, $P = 0.001$), vitamin A ($r = 0.32$, $P = 0.001$) and had a low association with birthweight ($r = 0.12$, $P = 0.025$).

3.1. Vitamins A and E

Concentrations of vitamin A in cord blood correlated significantly with birthweight, head circumference, length and gestation age (Table 1). Mean vitamin A levels of the babies categorised by birthweight are shown in Table 2. The bottom birthweight quartile babies had significantly lower concentration of vitamin A than those of quartiles two, three, two and three, and four. Parity, maternal age or smoking habit (Tables 3 and 4) and gender did not have significant effect. The preterm

Table 2
Mean (± S.D.) concentrations of vitamin A and E in cord blood of the babies of different birthweight quartiles ($n = 79$)

	1st quartile	2nd quartile	3rd quartile	4th quartile
Birthweight (g)	<2960	2960–3200	3201–3540	>3540
Vitamin A (μmol/l)	0.97 ± 0.22[d]	1.34 ± 0.45[a]	1.26 ± 0.28[b]	1.46 ± 0.41[c]
Vitamin E (μmol/l)	9.06 ± 2.09	8.59 ± 2.79	8.13 ± 2.32	8.82 ± 2.55

[a]Significantly higher than the 1st quartile ($P = 0.002$).
[b]Significantly higher than the 1st quartile ($P = 0.0009$).
[c]Significantly higher than the 1st quartile ($P = 0.0001$).
[d]Significantly lower than the mean of quartiles 2 and 3 ($P = 0.0007$).

Table 3
Mean (± S.D.) concentrations of vitamin A and E in cord blood of the babies grouped by parity

	Parity 1	Parity 2–3	Parity > 3
Vitamin A (μmol/l)	1.22 ± 0.42	1.32 ± 0.45	1.25 ± 0.29
Vitamin E (μmol/l)	9.10 ± 0.26	8.73 ± 2.09	8.98 ± 2.65
Copper (μmol/l)	6.00 ± 1.17	6.16 ± 1.51	5.36 ± 2.48
Magnesium (mmol/l)	0.66 ± 0.07	0.69 ± 0.08	0.63 ± 0.08
Zinc (μmol/l)	13.62 ± 3.45	13.33 ± 2.37	12.55 ± 2.46

Parity did not have significant effect on the concentrations of the vitamins or the metalic elements ($P > 0.05$).

babies had lower vitamin A levels than had the term babies but the difference did not reach a level of significance (Table 5).

Because of the insufficiency of sample volume the concentration of lipid was not determined and consequently vitamin E/lipid ratios have not been assessed. There was no significant correlation between the levels of vitamin E and any of the anthropometric measurements, nor was there a difference in the mean levels between the different birthweight quartiles. Parity, maternal age or smoking habit, or the gender of the babies did not influence the concentration of vitamin E. However, there was a significant relationship between the concentrations of vitamins E and A (Table 1). The preterm babies had a lower mean vitamin E concentration than had the term babies but the difference was not statistically significant.

3.2. Copper, magnesium and zinc

Copper concentrations showed a significant negative correlation with birthweight and with head circumference (Table 1). Mean copper level decreased with an increase in birthweight but the difference was only significant between the bottom and the top quartiles (Table 6).

Table 4
Mean (± S.D.) concentrations of vitamin A and E in cord blood of the babies categorised by maternal age

	<20 years	20–30 years	>30 years
Vitamin A (μmol/l)	1.19 ± 0.24	1.28 ± 0.40	1.27 ± 0.43
Vitamin E (μmol/l)	7.94 ± 2.21	9.03 ± 2.21	9.15 ± 3.27
Copper (μmol/l)	6.18 ± 1.66	5.95 ± 2.21	5.36 ± 1.04
Magnesium (mmol/l)	0.69 ± 0.08	0.65 ± 0.07	0.68 ± 0.09
Zinc (μmol/l)	13.21 ± 3.14	13.21 ± 2.58	12.87 ± 2.54

Concentrations of the vitamins or the metalic elements were not influenced significantly by maternal age ($P > 0.05$).

Table 5
Mean (± S.D.) anthropometric measurements and concentrations of vitamin A and E in cord blood of term and preterm babies

	Preterm ($n = 6$)	Term ($n = 73$)
Gestational age (week)	35.7 ± 0.5	39.6 ± 1.0
Birthweight (g)	2809 ± 717	3274 ± 422
Head circumference (cm)	32.75 ± 1.73	33.95 ± 1.37
Length (cm)	48.9 ± 3.65	51.03 ± 3.11
Vitamin A (μmol/l)	1.01 ± 0.19	1.29 ± 0.39[a]
Vitamin E (μmol/l)	8.66 ± 2.88	8.99 ± 2.44[a]

[a]Not significantly different from the corresponding values in preterm babies ($P > 0.05$).

Magnesium did not have significant relationship with head circumference, length or gestation age, but there was an increasing trend in the concentrations of magnesium with an increase in birthweight (Table 6). Significant association was observed between magnesium and zinc (Table 1).

Concentrations of zinc correlated with vitamin A but not with gestational period, head circumference or length. It had a low but significant association with birthweight (Table 1). Parity, maternal age or smoking habit did not seem to influence the concentration of zinc.

4. Discussion

Mean vitamin A concentration was comparable with some of the published data [2,21,24,53]. Other studies [3,8,36,45], however, have reported lower cord blood vitamin A values. The type of population studied, the method of analysis — including the use of an internal standard — and, more significantly, the year in which the study was undertaken may explain the discrepancy. Vitamin A values from studies of the

Table 6
Mean (± S.D.) concentrations of metals in cord blood of the babies of different birthweight quartiles ($n = 42$)

	1st quartile	2nd quartile	3rd quartile	4th quartile
Birthweight (g)	<3025	3025–3240	3241–3610	>3610
Copper (μmol/l)	7.00 ± 2.67	5.72 ± 1.62	5.38 ± 0.89	5.06 ± 1.33[a]
Magnesium (mmol/l)	0.66 ± 0.07	0.66 ± 0.07	0.67 ± 0.11	0.70 ± 0.11
Zinc (μmol/l)	13.11 ± 2.51	12.39 ± 2.48	13.34 ± 2.08	14.15 ± 3.21

[a]Significantly different compared to the 1st quartile ($P = 0.05$).

late 1980s, and 1990s would be expected to be higher than those from earlier investigations because of a rise in intakes of vitamin A by some sectors of the population in the developed countries. This is primarily due to the increase in the vitamin A content of liver and liver products [15,38] as the result of incorporation of vitamin A into animal foodstuffs. There has also been a widespread use of vitamin supplements [48].

Birthweight, head circumference, length and gestation period correlated with the levels of vitamin A. The observations suggest that the growth and development of these babies were impaired by an insufficiency of utilizable vitamin A. This may have been due to inadequate maternal and fetal liver vitamin A stores, restricted mobilization because of impaired synthesis of retinol binding protein, or both. All the anthropometric measurements were significantly associated with vitamin A concentrations; therefore, it is likely that a low maternal status, and hence an insufficient supply to the fetus, was the main limiting factor. A positive relationship between vitamin A and birthweight have also been reported in previous studies [36,43].

Maternal vitamin A status was not determined in this study, consequently the relationship between maternal and cord plasma vitamin A concentrations was not assessed. Several investigations [2,9,21,24,53] have observed higher concentrations of vitamin A in maternal blood but the relationship with cord levels were inconsistent. Since the fetus ultimately depends on the mother for vitamin A, the reported inconsistent relationship between maternal and cord blood may be primarily a reflection of maternal vitamin A status.

Under conditions of maternal–fetal vitamin A deficiency the requirement of the fetus would take precedence and the concentration of cord blood approximates, and in some cases exceeds, that of the mother. A higher vitamin A level in cord than in maternal blood was reported by Lund and Kimble [28]. A similar pattern was also evident in the low birthweight group in the study of Baker et al. [3] and in a mother with a very low circulating vitamin A [21]. Night blindness manifested during the third trimester and which was reversed after delivery or by vitamin A therapy [12] may be indicative of the pre-eminence of fetal requirement with respect to vitamin A.

It is generally acknowledged that the biochemical criterion of risk for vitamin A is less than 1.05 μmol/l. Twenty-eight babies, 35% of those investigated, had values within the risk range. Low vitamin A status at birth would be particularly critical in preterm babies as the level is reported to fall during intensive-care [54] and to remain low, in many, for $\geq$4 months [39]. Low vitamin A status is associated with bronchopulmonary dysplasia in babies [22] and with mortality and morbidity in infants [10]. Supplementation with vitamin A lowers morbidity from bronchopulmonary dysplasia [46] and morbidity and mortality from infectious diseases [17,47], and reverses abnormalities in T-cell subsets in vitamin A deficient children [42].

Mean vitamin E concentration was analogous to some of the published studies [29,35,53]. Vitamin E status was not influenced significantly by maternal age, parity or gender. Parity and gender were also reported not to have a significant effect in other studies [27,53]. Smoking is thought to depress vitamin E but the levels of the nutrient in the babies born to the smoking and the non-smoking mothers were similar. This observation may not reflect reality since only 13 mothers, 17.6% of the subjects, conceded to smoking before or during their pregnancy, a figure which is much lower than the national average.

Based on multiple measures of vitamin E status of premature and low birthweight infants during the first 21 days of life and mathematical and statistical modelling of these measures, Gutcher et al. [19] have established that the ex utero vitamin E protective cover is best achieved at total tocopherol or α-tocopherol concentration >14.86 and >11.61 μmol/l, respectively. Phelps [40] reported that infants with plasma total tocopherol levels of <11.61 to 18.57 μmol/l should be suspected of vitamin E deficiency, particularly if they have fat malabsorption. Sixty-nine of the babies (87.3%) had vitamin E (α-tocopherol) concentration <11.61 μmol/l, 52 (65.8%), <9.29 μmol/l and 17, <6.97 μmol/l. It appears that the majority of the babies in the study were marginal to deficient in vitamin E status and hence at risk of oxygen radical mediated injury. Neonatal disorders in which reactive oxygen species are implicated include bronchopulmonary dysplasia, subependymal and intraventricular haemorrhage, necrotising enterocolitis, anaemia of prematurity and retinopathy of prematurity [40,49]. These disorders affect mainly, but not exclusively, preterm and low birthweight babies.

Concentrations of vitamins A and E in the preterm babies were lower than those of the term babies by 21.8% and 3.6%, respectively, indicating that the babies with gestational ages of 35 and 36 weeks had relative deficits of both nutrients. It may be that the transfer of vitamin A from the mother to the fetus accelerates or mostly occurs during the later stages of gestation. Also, the mobilisation mechanism of both nutrients from the fetal liver may not fully develop until term as is the case with the antioxidant enzymes.

Mean plasma zinc concentration was comparable with the values reported by Atinmo et al. [1] and Butte and Calloway [9]. They were, however, lower than the corresponding values published by Bogden et al. [6] and Meadows et al. [31]. There was a low but significant correlation between zinc and birthweight and the mean zinc concentration of the top birthweight quartile was 7.9% higher than that of the bottom quartile. The strong correlation between vitamin A and zinc indicates that the influence of zinc on birthweight was mediated through the synthesis of retinol binding protein and thus vitamin A. Atinmo et al. [1] found a significant association between plasma zinc level and birthweight. In contrast, Meadows et al. [31] and Butte and Calloway [9] did not find a significant association between cord plasma zinc and birthweight. Incongruities have also been reported between maternal plasma zinc level and birthweight. As has been outlined by Neggers et al. [37], the discrepancy may be attributed to the homogeneity of subjects studied and their zinc status. There may be a cut-off point (a saturation state) above which birthweight becomes insensitive to any increase in zinc status. If a homogeneous population with zinc status above the cut-off point, or a heterogenous group with a range of concentrations which would overlap with the cut-off point is studied, then the association may not be apparent. This is consistent with the data from Doyle et al. [14] who described a dose response relationship between several nutrients and birthweight up to, but not above, 3270 g.

The mean magnesium concentration was consistent with those published by Vobecky et al. [53] and Bogden et al. [6] but lower than the subsequent result of Bogden et al. [7]. Magnesium did not correlate with birthweight but the mean value of the babies of the top birthweight quartile was higher than those of the first, second and third quartiles by 5.5%, 5.7% and 5.1%, respectively. In an earlier study in Hackney, Doyle et al. [13] found a significant correlation between maternal magnesium intake, and birthweight, length and head circumference.

The reason for the significant association between magnesium and zinc is not obvious. Magnesium and zinc decrease during normal pregnancy [44,50], and there seems to be an independent correlation between maternal and cord concentrations of both elements [1,7,53]. Hence, the observed association between the two elements may be a reflection of this trend rather than functional association.

Both birthweight and head circumference showed significant negative correlation with copper. The mean copper level was also higher in the bottom birthweight quartile than in the top birthweight quartile. No relationship was observed between copper and zinc; therefore, the findings could not be explained by the competitive inhibition of zinc by copper. A higher level of copper in low-birthweight than in normal birthweight babies was also evident in other investigations [1,7]. Metcoff et al. [32] found a higher plasma copper concentration in women who gave birth to small babies. Whereas, Tuttle et al. [51] did not find any association between maternal plasma copper and centile birthweight distribution. In a study of Asian pregnancies in Britain [11], the Hindus had significantly shorter gestation period and delivered lighter babies than the Caucasians. More significantly, the Hindus also had higher copper and lower zinc plasma levels [11]. The authors did not report any association between copper or zinc and birthweight; a conclusion that was also queried by Jameson [23].

The levels of both vitamin A and zinc were associated with birth dimensions. Babies of the top birthweight quartile had higher levels of both nutrients than those in the bottom birthweight quartile. Also, most of the babies had a borderline vitamin E status. These suggest that the mothers of the low birthweight babies may have been marginal with respect to some of the micronutrient and a higher intake would have improved their status and possibly the outcome of their pregnancy.

Esters of vitamin A were not detected in any of the samples, indicating that there was no biochemical evidence of a risk of toxicity. For the population studied, the guidance given by the Department of Health may have been misplaced as there was evidence of an insufficiency of vitamin A but not of toxicity. Because of the high incidence of low birthweight and associated morbidity and mortality in the socially deprived area of the UK, and the role of vitamin A in normal cell division and development, immune functions and vision, the focus of the advice should have been primarily on meeting requirements. For low income-bracket mothers, liver and liver products are the cheapest and the best source of vitamin A, E, haem iron, B vitamins and several other essential nutrients.

Vitamin A toxicity is a potential problem [5] for pregnant women if they regularly consumed liver and liver products as well as vitamin A supplements. For this group, counselling should be provided through family planning, general practice and antenatal clinics.

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