

Zinc deficiency in rapidly growing preterm infants

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Symptomatic zinc deficiency was observed in a 24-week gestation, 640 g birthweight infant fed exclusively with maternal breast milk. Our hypothesis was that subclinical Zn deficiency is not uncommon in very low birthweight infants because fortified human milk and preterm formula may contain little Zn. Zinc serum concentrations determined in 26 consecutive very low birthweight infants (gestational age 23–32, median 27 weeks), prior to discharge, at a chronological age of 37–121 (median 72) d, were found between 1.0 and 14.0 (median 6.4) $\mu\text{mol/l}$, in 14 infants they were below the normal range of 7.6–15.0 $\mu\text{mol/l}$. Serum alkaline phosphatase and iron intake did not correlate with Zn concentrations. Nutritional supply of Zn and other trace elements by breast milk fortifiers and infant formulas currently used in Germany does not appear to meet the demands of rapidly growing extremely low birthweight infants during the first months of life. □ *B- and T-lymphocytes, breastfeeding, human milk, iron supplementation, preterm infant, zinc deficiency*

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With the majority of extremely low birthweight infants now surviving in industrialized countries, neonatologists realise how severely many of these infants are malnourished. We report a case of severe zinc deficiency with recurrent infection and a series of serum Zn measurements carried out in 26 very low birthweight (VLBW) infants. Zinc is necessary for the function of T-helper lymphocytes, natural killer cell activity, and normal structure and function of lymphatic tissues. We hypothesized that subclinical Zn deficiency is not uncommon in immature infants, that it is mainly due to malnutrition, and that it may contribute to immune deficiency and nosocomial infection. To facilitate enteral nutrition of VLBW infants, we compiled the information on mineral content in human milk (HM) fortifiers, and preterm formulae (PTF) frequently used to feed these infants.

Patients and methods

Study group

We prospectively investigated serum Zn concentrations in all 26 VLBW infants admitted from March to December 1996 and surviving up to discharge, birthweight 430–1430 (median 940) g, gestational age 23–32 (median 27) weeks, data given in Table 1. From 28 eligible infants, 1 was excluded because of intestinal surgery owing to volvulus on d 3, and another because Zn determination failed. As nutritional inadequacies will occur late, infants were studied at the latest possible time before discharge, at chronological age of 37–121 (median 72) d. The investigations were in accord with the Helsinki declaration of 1983.

Nutritional protocol

Infants received parenteral nutrition (defined as intravenous fluid exceeding 1.5 ml/h, neglecting smaller volumes for drug administration) with electrolytes, glucose, and amino acids (Aminopäd 10%, Pharmacia & Upjohn, Erlangen, Germany) during the first 10–41 (median 22) days of life. Fourteen infants were given intralipid 20% (2 g/kg per day, Pharmacia & Upjohn, Erlangen, Germany) and trace elements (Inzolen Infantibus sine Na K Köhler Chemie, Alsbach-Hähnlein, Germany) containing Zn aspartate, 0.49 mg/kg per day = 1.5 $\mu\text{mol Zn}^{2+}$ /kg per day, for 3 to 23 days. As soon as tolerated, infants received their own mother's breast milk by gavage, fortified with 5% FM85 (Nestlé, München, Germany). Breast milk constituted from 0.2 to 95% (median 52%) of the cumulated feeding volume. If maternal breast milk was not available, we fed donated breast milk or PTF (Humana O, Humana Milchwerke, Herford, Germany). Composition and quantity of feedings and body weight were noted in the daily protocol. We calculated iron intake from parenteral, oral and iron in HM/formulae, but neglected iron intake by transfusion and iron loss by diagnostic sampling.

Zinc determination

Zinc was determined by atomic absorption spectrophotometry, described by Makino and Talahara (1981) using a Solar 939 (Unicam, Kassel, Germany), which enables to measure samples as small as 20 μl of serum (1). No haemolysed samples were used. Normal serum range was 9.9–19.9 $\mu\text{mol/l}$ for adults and 7.6–15 $\mu\text{mol/l}$ for infants aged 1–3 months (2, 3). Internal standards included

Table 1. Data of 26 VLBW infants, in ascending order of serum Zn concentration near the time of discharge.

Case No.	Birthweight (g)	GA (weeks + d)	Intake of mother's own milk (%)	Parenteral nutrition (d)	Mean daily iron intake (mg/kg)	Age at Zn determination (d)	Recent weight gain (g/d)	Alkaline phosphatase (U/l)	Total serum protein (g/l)	Serum Zn concentration (μ mol/l)
1 ^a	640	24 + 1	92	23	3.4	102	11.5	92	5.1	1.0
11	1185	29 + 1	6	11	5.7	37	17.7	377	4.6	4.2
10	1140	29 + 0	14	14	6.2	49	6.2	410	4.4	4.6
5	860	27 + 3	93	28	7.6	57	15.1	384	4.0	4.7
16	1235	32 + 1	81	16	3.7	41	16.9	754	4.1	4.9
20	1230	31 + 4	0	11	7.7	50	17.1	595	4.3	4.9
24	900	25 + 4	43	15 ^b	7.3	59	23.1	406	3.4	5.8
14	904	26 + 2	72	41 ^b	6.6	71	9.8	424	3.8	5.9
13	606	23 + 2	51	37 ^b	10.7	117	12.9	413	4.9	6.0
15	995	28 + 4	1	16 ^b	6.3	74	11.9	364	3.9	6.3
21	1430	30 + 5	31	17	5.1	51	18.5	280	4.2	6.4
18	650	24 + 0	26	34 ^b	4.9	97	8.5	543	4.7	6.6
6	825	27 + 2	60	32 ^b	5.3	85	10.5	534	4.7	6.7
25	990	25 + 4	44	21 ^b	5.7	59	26.4	664	3.5	6.9
19	580	24 + 2	84	35 ^b	5.1	92	19.7	297	3.9	7.7
2	895	25 + 1	69	8	5.1	92	10.3	461	4.3	7.8
4	960	31 + 0	26	29	2.8	73	7.8	400	4.0	8.3
12	1130	32 + 2	93	10	3.8	85	19.4	944	4.0	8.6
22	1125	27 + 4	32	13	6.2	42	17.7	470	3.8	8.6
23	920	26 + 3	95	35 ^b	6.3	73	20.5	540	3.9	8.7
17	1190	31 + 1	53	13 ^b	6.8	41	15.1	398	3.7	9.1
26	825	25 + 4	76	17 ^b	5.8	66	12.2	409	4.1	9.4
8	430	25 + 6	77	28 ^b	3.7	102	15.8	649	5.0	9.8
7	1065	30 + 5	46	28 ^b	5.0	64	15.8	520	3.6	10.2
3	720	24 + 1	56	39 ^b	4.7	121	15.7	440	4.1	12.8
9	1380	32 + 3	28	11	5.4	73	18.6	339	3.8	14.0

^aIndex case ^bparenteral nutrition including intralipid and trace elements.

a zero-standard of 0.1 M HNO₃ diluted in glycerin (Merck, Darmstadt, Germany) and a Zn-standard (Kontrollrogen Precipath U, Ciba Corning Diagnostics, Fernwald, Germany). Breast milk samples were diluted 1:5 in zero-standard and aspirated into the flame. Coefficients of variance were <10%. The laboratory regularly participates in internal and external (Instand Ltd, Düsseldorf, Germany) quality management programs. Each sample was run in duplicate. The relative distribution of lymphocyte subpopulations was analysed by flow cytometry as previously published (4).

Statistics

The Spearman rank correlation coefficient *R* (software SPSS, PC+, Chicago, IL, USA) was calculated to estimate the relationship between serum Zn concentration, serum alkaline phosphatase activity, and cumulative iron administration. Inter-group differences were analysed with the Mann-Whitney *U* test, significance was assumed for *p* < 0.05.

Results

Case report

The mother was a 34-y old gravida, para 1, whose pregnancy was uneventful up to 23 weeks, when severe amniotic infection was treated with cefotiam. Contractions were

stopped with fenoterol, and β-methasone was given to accelerate lung maturation. At 24 + 1 weeks a C-section was performed because of prolapsed membranes and breech presentation. The girl's weight of 640g was appropriate for gestational age. Apgar scores were 5, 7 and 7 at 1, 5 and 10 min, respectively, umbilical artery pH was 7.34. She was intubated at the age of 3 min, ventilated with FiO₂ of 0.40; surfactant (2 × 40 mg Curosurf, Serono, Germany) was substituted. Antibiotics were given for 7 d because of leukocytosis (38 200/μl), I:T-ratio of 0.50, and purulent tracheal secretion. A patent ductus arteriosus was ligated on d 9. Artificial ventilation ended on d 19 after a 6-d course of dexamethasone. From d 69 to d 77 antibiotics were given again for suspected septicaemia with severe apnea, distended abdomen, skin discoloration and acrocyanosis. No bacteria were isolated. Subcutaneous recombinant human erythropoietin, 3 × 250 IU/kg/week (Recormon, Boehringer Mannheim, Germany) and enteral iron (Ferro 66, Promonta, Hamburg, Germany) were given to prevent anaemia of prematurity. The mean daily iron intake until d 102 was 3.4 mg/kg and the cumulated iron intake was 609 mg. In total, 104 ml blood was administered in seven transfusions. Glucose and electrolytes were infused during the first 23 d of life, but no amino acids, lipids or trace elements. From day 3 to day 102, we fed mother's breast milk fortified with 5% FM 85 (Nestlé, München, Germany) by gavage. Figure 1 shows the infant's gain in weight and length.

When the girl was 93 d old, she fell acutely sick with

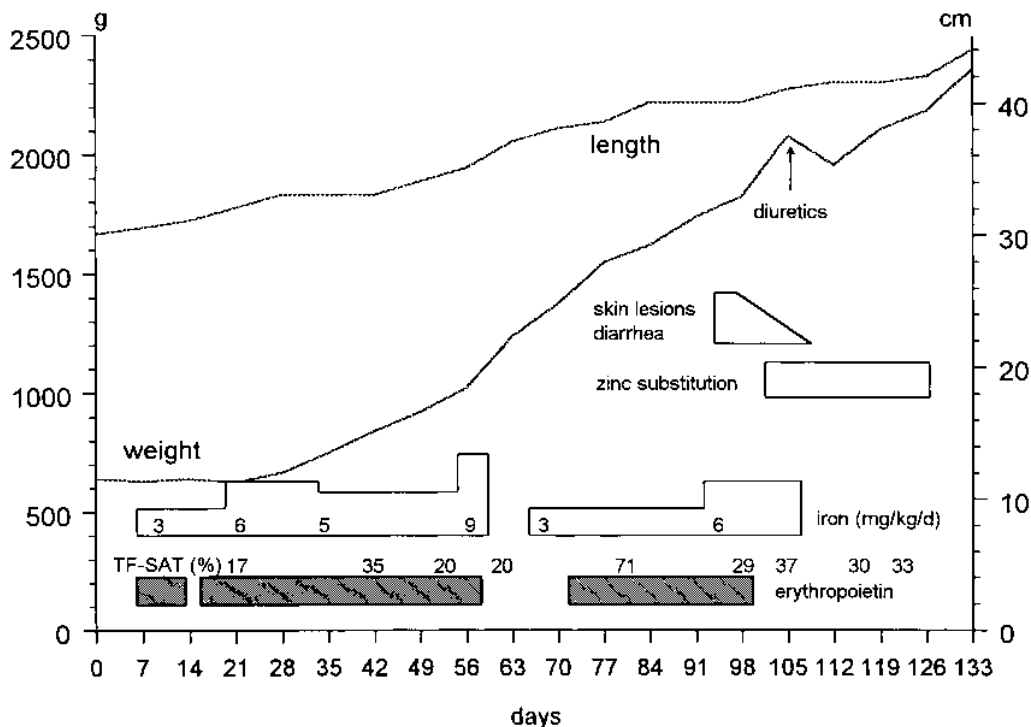


Fig. 1. Gain in weight and length, erythropoietin, iron administration and transferrin saturation in the 640 g preterm infant of 24 + 1 gestational weeks shown in Fig. 2. TF-SAT: transferrin saturation (%).

green-watery diarrhoea and herpes-like vesicular skin lesions in the genital area which rapidly progressed to severe dermatitis on legs, feet, and abdomen (Fig. 2). No bacteria could be isolated from vesicle liquid and EIA and PCR for herpes simplex virus type I and II, and varicella-zoster virus were negative. A serum sample obtained on d 102 contained $1.0 \mu\text{mol/l}$ Zn. As the mother produced much more milk than we could feed to the girl, we could determine Zn in frozen milk samples: the concentration decreased from an initial $31.2 \mu\text{mol/l}$ (d 36) to $16.6 \mu\text{mol/l}$ (d 65), $12.6 \mu\text{mol/l}$ (d 99) and $7.4 \mu\text{mol/l}$ (d 129). The maternal serum Zn concentration on d 124 after delivery was $10.2 \mu\text{mol/l}$.

The baby's symptoms were assumed to result from Zn deficiency and high iron intake. On d 123, breast milk was replaced by PTF, iron administration was discontinued and 1.4 mg/kg/d Zn-bis-(DL)-hydrogen aspartate was administered parenterally ($4.4 \mu\text{mol Zn}^{2+}/\text{kg/d}$, Inzolen-Infantibus sine Na K, Köhler Chemie, Alsbach-Hähnlein, Germany) for 5 d, followed by enteral administration of $2 \times 20 \text{ mg zincorotate/d}$ (2.9 mg/kg Zn/d) for 12 d (Zinkorotat, Ursapharm, Germany). This treatment resulted in the healing of skin eruptions and diarrhoea within 4 d. On d 130, serum Zn concentration was $19.4 \mu\text{mol/l}$, and Zn treatment

was reduced to 1.4 mg/kg/d for 11 d and then abandoned. No symptoms of Zn deficiency recurred.

Bone demineralization was detected in X-rays and alkaline phosphatase activity was 1400 (normal range 70–350) U/l on d 67 of life, and milk was additionally supplemented with calcium and phosphorus. Despite continuing osteopenia, alkaline phosphatase dropped to 92 U/l on d 102 (time of detecting Zn depletion), but rose again to 1003 U/l when serum Zn concentration had normalized (d 135). On d 121 (2 d prior to parenteral Zn substitution), granulocytes were $1580/\mu\text{l}$ and lymphocytes $2885/\mu\text{l}$. Analysis of T-lymphocyte subsets revealed a low number of CD4 (31%; $894/\mu\text{l}$) and CD8 (12%; $346/\mu\text{l}$) cells. After correction of serum Zn concentration on d 137, granulocytes rose to $2640/\mu\text{l}$ and lymphocytes to $4160/\mu\text{l}$, with a selective increase in CD4 T-cells (32%; $1331/\mu\text{l}$) and B cells (43% compared to 30% before Zn therapy). T-cell activation markers remained within the normal range.

Serum zinc measurements in 26 VLBW infants

Fourteen VLBW infants had serum Zn concentration below $7.6 \mu\text{mol/l}$ (Table 1). Twelve of the infants with low plasma Zn had not been predominantly fed with breast milk but

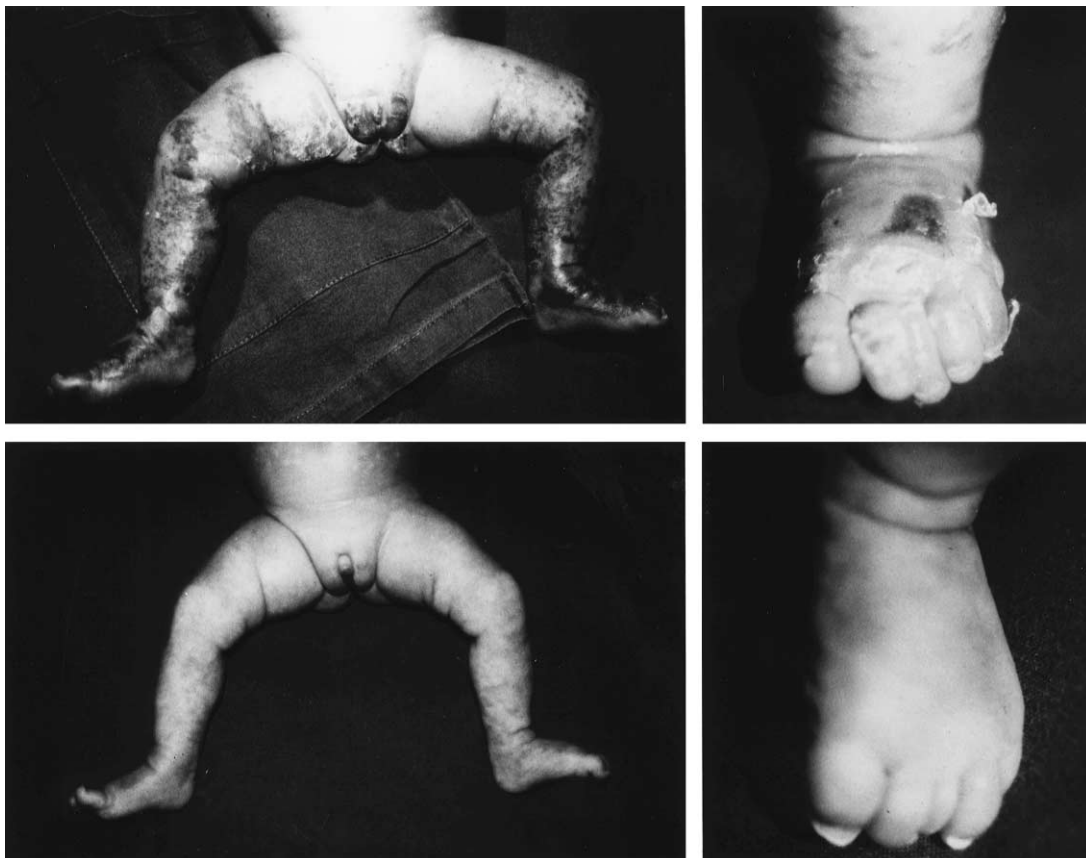


Fig. 2. Lower extremities of the infant with skin changes resembling acrodermatitis enteropathica. Top: d 102, serum Zn concentration $1.0 \mu\text{mol/l}$; bottom: after 20 d of Zn supplementation, serum Zn concentration $19.4 \mu\text{mol/l}$.

with PTF (Humana O-F plus, Milchwerke Westfalen, Herford, Germany). In addition to the infant described previously, no other infant had clinical signs of Zn deficiency. Seven infants whose cumulated enteral intake contained <29% breast milk had insignificantly lower median serum Zn concentration than eight infants in whom breast milk exceeded 75% of enteral intake (6.3 vs 8.1 $\mu\text{mol/l}$, $p = 0.53$).

Recombinant human erythropoietin was administered in a dose of 750 IU/kg/week for 15–96 (median 51) d, always combined with enteral iron intake. The daily iron administration ranged from 2.8 to 10.7 (median 5.6) mg/kg and the cumulated iron dose from 241 to 1084 (median 545) mg. Cumulative parenteral Zn administration given to 14 infants ranged from 1.7 to 7.1 mg (5–22 μmol). The other 12 VLBW infants required no prolonged parenteral nutrition and received no supplementation of trace elements. Serum alkaline phosphatase ($R_s = 0.31$, $p = 0.125$) and cumulative iron administration ($R_s = 0.164$, $p = 0.424$) showed poor correlation with serum Zn concentration.

Mineral content in different preterm formulae and human milk fortifiers

Table 2 shows Zn content in different nutrients for preterm infants and represents intake per kg, assuming that preterm infants receive 160 ml/kg/d. Daily Zn intake ranges from 590 to 1936 $\mu\text{g/kg}$, Fe intake from 0.13 to 2.32 mg/kg. Copper and iodine content is remarkably low in some PTF.

Discussion

Severe Zn deficiency leads to dermatitis, diarrhoea, and alopecia. Skin lesions appear as small moist, erythematous lesions around orifices and on extremities, progressing to vesiculobullous eruptions as observed in our case and shown in Fig. 1 (7). Zinc deficiency has been described in exclusively breastfed neonates (8) and premature infants (9), and Zn supplementation has been shown to enhance growth and weight gain of breastfed infants (10). The mechanisms underlying growth retardation owing to Zn deficiency are not known (11). Zinc is an essential cofactor of many enzymes in all areas of metabolism. Several Zn metalloenzymes are related to specific disorders and problems of preterm infants: carboanhydrase (metabolic acidosis), DNA- and RNA-polymerases (impaired growth), alkaline phosphatase (osteopenia praematurorum), superoxide dismutase (bronchopulmonary dysplasia), pancreatic protease (impaired digestion).

Zinc affects T- and B-lymphocytes, depresses baseline and antibody-dependent cytotoxic activity of killer lymphocytes, and phagocytic and bactericidal capacities of neutrophils (7). Correspondingly, we found diminished granulocytes in our case together with T- and B-cells before therapy. The relatively high CD4/CD8 ratio was most likely due to infection, and the low frequency of

activated T-cells points to impaired immune function. After 2 weeks of therapy, CD4 T-cell and B-cell numbers in particular increased, but it remains unclear whether this rise was due to Zn therapy or to eradication of infection.

Premature birth may be associated with suboptimal maternal intake of trace elements during pregnancy (12) resulting in low stores of trace elements in preterm infants. Very rapid postnatal growth predisposes them to progressive deficiency of virtually all minerals and trace elements (3, 13). Assuming a Zn content of 30 $\mu\text{g/g}$ fat-free tissue, a weight gain of 1000 g necessitates a net Zn intake of 30 mg. For a period of 50 d, this amounts to 600 $\mu\text{g Zn/d}$.

Colostrum is rich in Zn, but during lactation Zn declines from above 45 to about 12 $\mu\text{mol/l}$ in HM (9, 14–16). As in our patient's mother, very low Zn milk levels have been observed after several months of breastfeeding (8, 17) and may be associated with low maternal intake. Owing to low mineral and protein content of breast milk, fortifiers are widely used in breastfed preterm infants. Lucas et al. showed the beneficial effects of fortified HM on long-term development of preterm infants (18). As shown in Table 2, minerals other than calcium and phosphorous, however, may be very low or even absent in fortified HM.

Intake of one trace element influences the absorption of others. Excess iron administration may contribute to Zn deficiency (19), because iron and Zn metabolism are closely linked (20, 21). When erythropoiesis of the preterm infant is stimulated by erythropoietin, enteral administration of 3 mg/kg up to 12 mg/kg/d is strongly recommended (22). We cannot exclude the possibility that high iron intake has contributed to the Zn depletion of our infant. Our data, however, show no correlation of EPO-treatment or iron intake with serum Zn concentration.

Serum Zn concentrations do not necessarily reflect body Zn content (23–25), and fluctuate widely depending on nutrition, time of sampling, stress, infection or other causes of cytokine release, and albumin concentration. Decreasing alkaline phosphatase, often welcomed by the clinician as a sign of improving osteopenia praematurorum, may signal subclinical Zn deficiency. As fortifiers produced in Germany are not supplemented with trace elements, and as most feeding protocols are similar to ours, we assume that subclinical deficiencies may be common.

We speculate that part of the preterm infant's disposition to infection is caused by subclinical Zn deficiency. In both acrodermatitis enteropathica and nutritional deficiency, immune function is severely compromised. Already modest deficits cause lymphopenia (especially of B-lymphocytes) and the antibody-mediated responses to both T-cell-dependent and T-cell-independent antigens are significantly reduced (7, 9).

AAP-CON and ESPGAN recommendations for PTF asking for at least 1.5 mg Fe, and 550 $\mu\text{g Zn/100 kcal}$ are not sufficient to feed an infant of <1000 g. Our nutritional protocol as well as those used in many nurseries was below this target. Neonatologists should be aware that some commercial PTF and fortifiers supplementing preterm

Table 2. Mineral content in different preterm formulae and in human milk supplemented with different fortifiers according to of the manufacturer's directions and information. The table corresponds to intake per kg body weight assuming that full enteral feeding is achieved with 160 ml/kg.

Recommended daily intake/kg for growing stable preterm infants ^a	Ca (mg) 120–230	P (mg) 60–140	Mg (mg) 8–15	Fe (mg) 2	Zn (µg) 600–1400	Cu (µg) 110–150	Mn (µg) 5–8	Se (µg) 1.3–3.0	I (µg) 30–60
Preterm Formulae									
Prematil (Milupa, Germany)	112	56	8.9	0.13	615	102	15.6	–	16.0
Beba Frühgeborenen-Nahrung (Nestlé, Germany)	160	85	13.3	1.9	960	112	8.9	–	19.2
Humana O (Humana, Germany)	128	64	12.8	1.6	1328	160	80	–	16.8
Similac Special Care (Ross, USA)	232	116	15.5	0.48	1936	323	15.5	2.3	25.8
Preemie SMA 24 (Wyeth, USA)	115	64	11.0	0.49	1280	110	32	–	12.8
Nenatal (Nutricia, The Netherlands)	160	80	16.0	1.44	1120	128	16.5	3.0	40.0
Enfamil Premature-24 (Mead Johnson, USA)	213	107	8.8	0.32	1936	161	8.1	2.3	32.2
Enfamil Premature-24 + Fe (Mead Johnson, USA)	213	107	8.8	2.32	1936	161	8.1	2.3	32.2
Human milk, 2–4 weeks postpartum	41	24	5.3	0.14	597	61	0.58	–	28.8
Fortified with									
5% FM 85 (Nestlé, Germany)	114	74	8.1	0.14	590	60	0.58	–	28.8
3% Eoprotin (Milupa, Germany)	103	67	8.9	0.17	609	65	5.7	–	28.3
3% BMF (Nutricia, The Netherlands)	139	89	14.9	0.14	1070	100	1.54	–	46.3
Similac Natural Care (Ross, USA)	157	80	10.5	0.31	1267	192	8.0	–	28.2
4% Enfamil HMF (Mead Johnson, USA)	186	96	6.9	0.14	1742	161	8.1	–	28.4

^aPer 160 ml; ESPGAN-CON and AAP-CON (5, 6).

human milk might fail to reach even this minimal amount of Zn and iron required. We do not propose uncontrolled administration of iron and Zn. In rapidly growing VLBW infants, nutritional deficiency must be avoided by careful examination and individual mineral substitution.

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