Iron status of very-low-birth-weight infants during the first 15 months of infancy

James K. Friel, PhD; Wayne L. Andrews, MD; J. Derek Matthew, MD; David R. Long, MD; Anna M. Cornel, MD; Margaret Cox, MD; Craig T. Skinner, RT

The adequacy of iron stores in infants of very low birth weight (defined as less than 1500 g) in Canada is unknown. We monitored the iron status of 81 such infants at 3, 6, 9, 12 and 15 months of age. All of the infants were fed formula fortified with iron (13 mg/L) for at least 6 months, starting at 2 months of age. The plasma ferritin level decreased after the formula was no longer used. Although 90% of the infants were given cereal fortified with iron (30 mg of iron per 100 g) by 9 months of age, the plasma ferritin level continued to decrease. The level was less than 10 μg/L in 54% of the infants at 12 months of age and in 74% at 15 months; this indicated depleted iron stores. Because of delayed development very-low-birth-weight infants eat small amounts of cereal and therefore require iron-fortified formula throughout infancy.

On ne sait pas si, au Canada, les nourrissons de très faible poids de naissance (moins de 1500 g) ont des réserves suffisantes de fer. Nous avons examiné en série ces réserves chez 81 de ces nourrissons à l'âge de 3, 6, 9, 12 et 15 mois. Ils ont tous été alimentés, dès l'âge de 2 mois et pendant au moins 6 mois, au moyen d'un lait enrichi en fer (13 mg/L). Lorsqu'on cesse d'utiliser ce lait, le taux de ferritine plasmatique s'abaisse. Bien que 90% des sujets commencent dès 9 mois à consommer des céréales enrichies en fer (30 mg de fer par 100 g), le taux de ferritine continue de baisser. Il est inférieure à 10 μg/L chez 54% des sujets à l'âge de 12 mois et chez 74% à l'âge de 15 mois, ce qui fait croire à un épuisement des réserves de fer. Vu la lenteur de leur développement, les nourrissons de très faible poids de naissance consomment peu de céréales. Aussi ont-ils besoin d'un lait enrichi en fer pendant toute la petite enfance.

Infants of very low birth weight (defined as less than 1500 g) are at high risk for iron deficiency because of low stores of iron at birth,[1] rapid growth in the erythrocyte mass, which depletes the iron reserves,[2] and uncertainty about their iron requirements.[3] The Canadian Paediatric Society[4] has recommended that the low-birth-weight infant receive iron in the amount of 2 mg/kg daily, either in formula or as a supplement, from about 2 months of age onward. The American Academy of Pediatrics[3] has recommended 2 to 3 mg/kg daily for very-low-birth-weight infants and has stated that formulas with iron usually contain sufficient supplemental iron. Siimes,[5] a Finnish investigator, has recommended even higher daily doses, 3 to 4 mg/kg, for low-birth-weight infants.

Because most studies examining iron requirements of infants have continued for about 6 months[6-8] little is known about the long-term iron status of very-low-birth-weight infants on various iron regimens. Although there have been reports on the iron status of term infants in Canada, most notably that of Yeung and associates,[9] no researchers have studied iron stores in very-low-birth-weight infants. We examined the iron status of very-low-birth-weight infants given iron-fortified formula during early infancy who were part of a prospective study of the effects of zinc supplements on growth

From the departments of Biochemistry and Pediatrics, Memorial University of Newfoundland, and the Dr. Charles A. Janeway Child Health Centre, St. John's

Reprint requests to: Dr. James K. Friel, Department of Biochemistry, Memorial University of Newfoundland, St. John's, Nfld. A1B 3X9

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and development. Although the amount of zinc varied the amount of iron did not (13 mg/L of formula). To monitor the possible interaction between zinc and iron we assessed the plasma ferritin level, which is a measure of iron stores.

Methods

Subjects

From June 1, 1985, to July 1, 1989, we selected all infants whose birth weight was less than 1500 g from the neonatal intensive care units of the Dr. Charles A. Janeway Child Health Centre, the Grace General Hospital and St. Clare's Mercy Hospital, St. John's. The mean weight was 1116 (standard deviation [SD] 279) g and the mean gestational age 29 (SD 3) weeks. The study was approved by the Faculty of Medicine Human Investigations Committee and the three hospital human investigation committees. Infants were excluded if they were being breast-fed, had severe bronchopulmonary dysplasia that required more than 2 weeks of oxygen therapy or had hydrocephalus, liver dysfunction or any congenital malformation. Of the parents of the eligible infants 85% consented to enrolment in the study. Of the 84 eligible infants 2 died in hospital and 1 was admitted to another hospital; therefore, there were 81 infants for whom data were available at discharge.

We calculated the gestational age of the infants from the last menstrual period of the mother and by using the Dubowitz method.[10] If there was a discrepancy of more than 2 weeks between the two assessments we used the latter. Size for gestational age was considered appropriate if the birth weight was within two standard deviations of weight for gestational age, according to the growth curves of Lubchenco and collaborators.[11]

All of the infants received uniform management, as established in the respective neonatal intensive care units, and were fed a special formula for premature infants (Ross Laboratories, Columbus, Ohio), which contained about 100 kJ/30 ml and 13 mg of iron per litre, until they could tolerate a formula with about 85 kJ/30 ml. About 1 month before discharge random number tables were used to assign the infants to receive either Similac with Whey or Low Birthweight Formula (Ross Laboratories), both of which contained 13 mg of iron per litre but had different amounts of supplemental zinc. When the infants were discharged formula was provided for a minimum of 5 months, after which the parents were responsible for purchasing it. A total of 36 infants discharged from the Grace General Hospital were given one 15-ml bottle of ferrous sulfate drops, 0.3 ml/d, which provided 7.5 mg of elemental iron daily.

Sample collection and analysis

The data were collected in the hospital when the infants were 3 months of age and at the Perinatal Follow-up Clinic when they were 6, 9, 12 and 15 months. Heparinized blood samples (0.5 to 1 ml) were obtained through heel or finger prick by the hematology staff; the samples were centrifuged and separated, and the plasma was frozen at −20°C until analysis. Three-day dietary records were completed by the nursing staff at discharge and by the parents or guardians before each visit. Each record was verified for accuracy and completeness by a trained research assistant. The infants were weighed on a calibrated scale at each visit. Data on the amount of blood drawn in hospital for routine tests such as determination of blood gas values were not available, but hospital records were used to determine whether the infants had had transfusions to compensate for excessive blood drawing or to correct abnormally low hemoglobin levels.

The plasma samples were shipped on dry ice to Abbott Laboratories, Chicago, where the ferritin level was determined with Abbott's Ferrizyme radioassay technique. The hemoglobin level was determined with an automated Coulter counter. Measurements of both the ferritin and hemoglobin levels were not available for all of the subjects.

The iron and food intakes for all subjects who were seen at follow-up were calculated from the coded dietary records.[12] All the data were entered into a computerized database, and differences between adjacent sampling times for iron intake and for ferritin and hemoglobin values were assessed by means of the paired Student's *t*-test, with correction for multiple comparisons. Differences between zinc treatment groups, sex, size for gestational age and iron intake at the same sampling times were assessed through one-way analysis of variance or through unpaired *t*-tests. Pearson correlation coefficients were determined to assess the relation between iron intake, ferritin and hemoglobin levels, birth weight, velocity of weight gain and size for gestational age. All computations were done with SPSS-X.[13] Statistically significant differences had a p value less than 0.05.

Results

The mean weight for the 81 infants at the beginning of the study was 1851 (SD 107) g and at discharge 2527 (SD 294) g. The plasma ferritin level, iron intake and hemoglobin level did not differ for those infants of different gender who received different formulas and different levels of zinc; therefore, we pooled the results. Fig. 1 shows the plasma ferritin level over time. Table 1 shows the mean

dietary iron intake and the proportion of samples with a plasma ferritin level of less than 10 μg/L, the level indicating depletion of iron stores.[14] The hemoglobin level (g/L) rose significantly in early infancy, from 106 (SD 12) in 47 infants at 3 months of age to 125 (SD 10) in 28 infants at 6, but did not differ significantly in 28 infants at 9 months (125 [SD 16]), in 21 infants at 12 months (124 [SD 10]) and in 20 infants at 15 months (121 [SD 13]).

No patient was excluded from the study once the in-hospital data had been collected. Some of the infants were lost to follow-up because of personal reasons, the expense of travelling to the clinic or relocation outside of the province.

Some of the blood samples that were collected at the follow-up visits could not be analysed for the ferritin level because they were lost during shipping. There was no difference in the daily iron intake between the infants for whom samples were available for ferritin analysis and those for whom they were not at 9 months of age (1.2 [SD 1.0] v. 1.6 [SD 0.9] mg/kg), at 12 months (1.0 [SD 0.7] v. 1.0 [SD 0.8] mg/kg) or at 15 months (0.7 [SD 0.3] v. 0.7 [SD 0.3] mg/kg). A positive correlation was found between iron intake and ferritin level only at 15 months of age ($p = 0.03$, $r = 0.43$). The ferritin level at any sampling time was not related to birth weight. Regardless of whether the infants were small or of appropriate size for gestational age the ferritin level decreased as the velocity of weight gain increased between 12 and 15 months of age ($p = 0.03$, $r = -0.45$).

The ferritin level was lower in 51 infants at 3 months (51 [SD 32] μg/L) and 27 infants at 6 months (14 [SD 8] μg/L) who had not received blood transfusions than in 17 infants at 3 months (90 [SD 53] μg/L) and 11 infants at 6 months (29 [SD 22] μg/L) who had. There was no effect of transfusion on the plasma ferritin level after 6 months of age and no effect of the ferrous sulfate supplementation on the level at any sampling time.

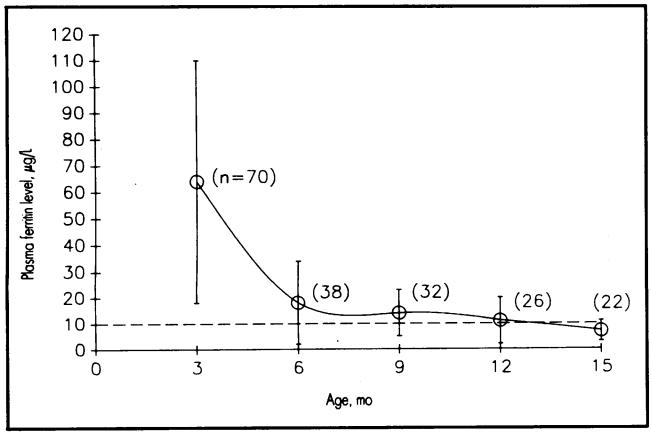

Fig. 1: Mean plasma ferritin level (and standard deviation) in very-low-birth-weight infants by age at follow-up visit. Broken line represents level indicative of depleted iron stores.

Because of various rates of food intake 36% of the infants had sufficient iron-fortified formula to last until 9 months of age; at that time 57% of them were given a non-iron-fortified formula whose iron content was only 1.5 mg/L. These infants consumed 810 (SD 266) ml of formula at 6 months of age, 774 (SD 391) ml at 9 months, 392 (SD 386) ml at 12 months and 95 (SD 200) ml at 15 months.

The proportion of infants who consumed iron-fortified cereal (30 mg of iron per 100 g) was 38% at 6 months of age, 90% at 9 months, 73% at 12 months and 30% at 15 months. The average intake of cereal was 4 to 12 g daily. By 12 months of age the infants had begun to consume adult foods.

Discussion

Oski[14] and Lundstrom, Siimes and Dallman[8] characterized iron depletion without anemia as the disappearance of storage forms of iron and a decrease in the plasma ferritin level to less than 10 μg/L. In our study the plasma ferritin level greatly decreased from 3 to 6 months of age, a physiologic sign previously reported in very-low-birth-weight infants.[8] All of the infants in our study received iron-fortified formula until they were at least 8 months of age; at 9 months 36% were still consuming it. While the infants consumed iron-fortified formula their plasma ferritin level was comparable to the level in other very-low-birth-weight infants who were given supplemental iron.[8] The level dropped after the infants stopped consuming iron-fortified formula. By 9 months of age 90% of the infants were consuming iron-fortified cereal; however, the intake of iron from the cereal was insufficient to stop the decrease in the plasma ferritin level.

The proportion of infants with a clinically low plasma ferritin level was remarkably high (74%) among those for whom samples were analysed at 15 months of age. Because the ferritin level was not

Table 1: Mean daily dietary iron intake of very-low-birth-weight infants and proportion of such infants with plasma ferritin level less than 10 μg/L by age at follow-up visits

Age at follow-up, mo	Mean iron intake (and standard deviation), mg/kg*	Plasma ferritin level < 10 μg/L, % of infants
3 (n = 81)	3.7 (1.6)	0
6 (n = 67)	2.3 (0.6)	24
9 (n = 55)	1.3 (0.8)	31
12 (n = 49)	1.0 (0.7)	54
15 (n = 41)	0.8 (0.4)	74

*$p < 0.05$ for amounts between adjacent months.

available for all of the study subjects there was a potential bias in the interpretation of the results. None the less, the high number of infants with a clinically abnormal ferritin level at 12 and 15 months of age is representative of the total study population because the daily iron intake did not differ between the subjects for whom the ferritin level was available and those for whom it was not at 9, 12 and 15 months of age and because all of the infants were given iron-fortified formula.

An increased velocity of weight gain between 12 and 15 months of age was significantly correlated with a decrease in the plasma ferritin level, as demonstrated by Arad and colleagues.[15] This decrease confirms that the iron intake was insufficient to meet the demands for growth and tissue storage. Two infants in our study had documented anemia at 15 months of age; no other obvious clinical signs of iron depletion were evident. We are concerned that depleted iron stores in infancy owing to the lack of iron supplementation will ultimately result in frank anemia once non-iron-fortified table foods are introduced. Furthermore, it is not known to what degree iron depletion rather than iron deficiency may affect cognition.[14,16] A decreased level of iron in tissue that leads to suboptimal levels of iron-dependent enzymes[17] may alter neurologic development; this suggests that low iron stores are not desirable at any time during infancy.

Arad and colleagues[15] found a beneficial effect of blood transfusions on the plasma ferritin level in infants aged up to about 6 months. We also found an increased ferritin level in infants in the same age group who received transfusions but no effect at 12 and 15 months of age. Infusing packed erythrocytes early in infancy did not appear to influence the ferritin level later in infancy. In addition, the 36 infants who received ferrous sulfate at discharge did not have better iron stores at any sampling time.

Infants in our study appeared to consume even greater amounts of iron than other very-low-birth-weight infants in Canada. About 80% of infants in Canada consume non-iron-fortified formulas, as compared with 20% in the United States (Helen Churella, Ross Laboratories: personal communication, 1989). Almost all formulas consumed in Japan,[6] Sweden[7] and Finland[18] are iron-fortified. We are uncertain what proportion of iron-fortified formulas used in Canada are given to very-low-birth-weight infants. However, data from our study and those of Gibson and DeWolfe[19] suggest that few, if any, of the parents of very-low-birth-weight infants will purchase iron-supplemented formula unless it is specifically recommended.

Although term infants regularly consume solid food by 4 to 6 months of age,[9] usually starting with an iron-fortified infant cereal, we and Gibson and DeWolfe[19] found that very-low-birth-weight infants consume less solid food at the same age as term infants because of delayed development.[20] The infants in our study ate 4 to 12 g of solid food daily from 6 to 12 months of age, as compared with the 18 to 20 g reportedly consumed in Canada by term infants 3 to 10 months of age.[9] Such small amounts of iron-fortified cereals will not provide enough iron to meet the infants' needs. Furthermore, Fomon[21] suggested that such cereal is not a good source of iron for infants, and Gorten and Cross[1] reported that low-birth-weight infants given iron-fortified cereal without additional iron-supplemented formula had anemia at 3 months of age. Very-low-birth-weight infants in Canada appear to be vulnerable to iron depletion, especially if they do not consume iron-fortified formula throughout infancy.

The Canadian Paediatric Society[4] and the American Academy of Pediatrics[3] have recommended that very-low-birth-weight infants receive iron in the amount of 2 to 3 mg/kg daily throughout infancy. Dallman[22] has suggested that the issue of exactly when to provide an additional source of iron to very-low-birth-weight infants is unresolved. From the results of our study and others[1,5,8,21] we believe that such infants in Canada who are bottle-fed should receive iron-fortified formula as soon as they can tolerate about 85 kJ/30 ml and that they should be given this formula for the remainder of infancy.

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Conferences

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Nov. 30, 1990: Violence Within the Therapeutic Milieu (Annual Clinical Day, Department of Psychiatry)
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Dec. 1-2, 1990: Society of Toxicology of Canada 23rd Annual Symposium
Holiday Inn Crowne Plaza, Montreal
Dr. Gordon Krip, executive director, Society of Toxicology of Canada, PO Box 517, Beaconsfield, PQ H9W 5V1

Dec. 5, 1990: Innovations in Cardiovascular Nursing Practice Conference
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Dec. 6-7, 1990: Contemporary Management of Cardiovascular Disease
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Dec. 7-9, 1990: British Columbia Anaesthetists' Society/Washington State Society of Anesthetists Annual Meeting — Myths and Controversies in Anaesthesia
Four Seasons Hotel, Vancouver
Ms. Ellen MacNeill, British Columbia Anaesthetists' Society, c/o British Columbia Medical Association, 115-1665 W Broadway, Vancouver, BC V6J 5A4; (604) 736-5551, ext. 234, FAX (604) 736-4566

Feb. 7-9, 1991: Conference on Medicine and the Humanities
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Feb. 21-24, 1991: Pan-American Doctors' Club (Canadian section) 45th Meeting
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Feb. 25-Mar. 1, 1991: College of Family Physicians of Canada (Alberta Chapter) 36th Annual Scientific Assembly
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Feb. 26-Mar. 2, 1991: 7th International Hypoxia Symposium — High Altitude Physiology and Medicine (sponsored by McMaster University and the Arctic Institute of North America in conjunction with the International Society for Mountain Medicine)
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