Objective: To determine whether utilization of iron from infant cereal and pureed meat was sufficient to prevent iron depletion and/or anaemia in infants 6 to 12 months old fed whole cow milk (WCM) as their primary milk source.

Design: Six-month-old infants were randomized into a treatment group (n=43) receiving iron-fortified infant cereal (10.2 mg iron), pureed meat (0.75–1.7 mg iron) and WCM for six months or a control group (n=54) receiving no dietary intervention. Haemoglobin < 110 g/L or ferritin < 10 µg/L (measured bi-monthly), confirmed in a second blood sample, defined end-points.

Results: Proportion reaching end-point was similar between the treatment (3/43) and control infants (5/54) (p=0.66). Infants not complying with the protocol were at greater risk of reaching end-point (p=0.0002). Change in haemoglobin and ferritin across age was similar in both groups.

Conclusions: Iron deficiency is not a concern in WCM-fed infants after six months of age if iron-containing complementary foods are concurrently ingested.

Iron deficiency (ID) is the most prevalent nutrient problem in the world, affecting two thirds of children and infants in most developing countries. It also affects up to one third of Canadian infants from disadvantaged households. The most severe form, iron deficiency anaemia (IDA), is associated with depressed mental and motor function in infants and children. Despite controversy regarding the efficacy of treatment with iron to reverse these effects, there is universal consensus that the prevention of IDA is essential for every infant. Programs such as the U.S. Special Supplemental Food Program for Women, Infants and Children (WIC) are effective but expensive solutions and are not widely available throughout Canada.

In light of this, the Canadian Paediatric Society (CPS) has recommended prolonged exclusive breastfeeding or the use of iron-fortified formula for the prevention of IDA. However, a large segment of the Canadian population, primarily from low-income households, either cannot or will choose not to breastfeed or use iron-fortified formula throughout the first year of life. Instead they often use cow milk as an inexpensive alternative to formula.

The CPS recommends delaying introduction of whole cow milk (WCM) until 9 to 12 months while the American Academy of Pediatrics (AAP) recommends delaying its introduction until one year of age. Occult blood loss has been used as the argument to support the recommendation opposing the use of WCM; however, evidence suggests that this is a concern in infants before six months of age but not after. Although it is a poor source of iron, we suggest that if consumed along with iron-rich foods such as iron-fortified cereal and meat, WCM after six months of age may be an acceptable lower cost alternative to iron-fortified formula.

Thus, the objective of this study was to determine whether the utilization of iron from infant cereal and pureed meat was sufficient to prevent iron depletion and/or anaemia in infants 6 to 12 months old fed WCM as their primary milk source.

METHODS

General design

We hypothesized that the incidence of iron depletion/anaemia in infants 6 to 12 months old from low-income households consuming iron-fortified cereals, pureed meat and WCM as their only milk source would be lowered when compared to similar infants receiving no dietary intervention. Healthy, full-term infants from low-income households (based on Statistics Canada, 2000) were eligible if they were born at term, breastfed or not breastfed for at least 6 months, and not on any dietary supplements other than vitamins. Infants were recruited from public health clinics in the City of Toronto.

Infants were enrolled at 4 months of age and randomized into a treatment group (n=43) or a control group (n=54). The treatment group received iron-fortified infant cereal (10.2 mg iron), pureed meat (0.75–1.7 mg iron) and WCM as their primary milk source. The control group received WCM as their primary milk source.

RESULTS

Proportion reaching end-point was similar between the treatment (3/43) and control infants (5/54) (p=0.66). Infants not complying with the protocol were at greater risk of reaching end-point (p=0.0002). Change in haemoglobin and ferritin across age was similar in both groups.

CONCLUSIONS

Iron deficiency is not a concern in WCM-fed infants after six months of age if iron-containing complementary foods are concurrently ingested.
Iron status ‘end-points’

An end-point was declared on evidence of iron depletion (ferritin (Ferr) < 10 µg/L) or early anaemia (haemoglobin (HgB) < 110 g/L) on two consecutive blood samples (the second sample was collected on a revisit to the home within seven days). If ‘end-point’ was declared, the infant was discharged from the study and treated with iron drops, otherwise they continued until 12 months of age.

Feeding instructions and restrictions

Caregivers in the treatment group were asked to feed their infant one to two jars of pureed meat (0.75-1.50 mg of iron), 2/3 cup of iron-fortified infant cereals (10.2 mg of iron) per day and WCM (ad libitum). Food items were provided to the families at no cost and coupons were provided to obtain the milk from local grocery stores. Other than vitamin/mineral supplements containing iron and iron-fortified formulas, all other foods were allowed at the parents’ discretion.

The control group was not provided with feeding instructions or food products. To equalize financial advantages of being in one group or the other, control families were provided with laundry detergent and infant clothing worth an equivalent dollar value to the food provided to the treatment group.

Recruitment

Infants were recruited in Toronto by direct mailings using lists (supplied by Carnation Canada Ltd.) targeted at families with infants younger than six months and in postal zones where the median household income was below low-income cut-off levels and by direct solicitations in participating community health centres.

Infants were randomized, by random number generator, after initial contact was made. More infants from the treatment withdrew from the study than the control group because, once in the treatment group, they decided to continue breastfeeding or were unwilling to feed WCM (Figure 1). None of the infants dropped out due to allergic reactions to the milk. Infant characteristics (Table I) were similar between treatment and control groups. Family backgrounds were also similar, except for maternal education, which was higher in control families (Table II).

Sample size calculation

The rate of iron depletion (Ferr < 10 µg/L) in infants from socio-economically disadvantaged families in Winnipeg was reported to be 53%2 and in Montreal 37%.3 In average-income families across Canada, the rate was 33.9%.22 In Toronto, 20% of infants from average-income households had Ferr < 10 µg/L confirmed in a second sample.23 Thus, it was estimated that at least 30% of the control infants (from low-income families) would reach end-point. We assumed that a decrease to 10% in the treatment group would represent a clinically significant result. With a type I error of 5% and type II error of 20%, a two-tailed sample size estimate yielded 55 infants per group.

Analytical methods

Blood samples were collected from infants in their homes and kept cool in anticoagulant treated tubes. The cyan-
methemoglobin method was used to assay HgB in triplicate using standard haemoglobin solution to control for accuracy. Plasma ferritin was assayed in duplicate by an immunoradiometric assay using ‘Fer-Iron’ kits. The Lyphocheck Anemia Control was used as an external reference standard. Samples were analyzed weekly upon receipt.

Nude body-weight, recumbent length and head circumference were measured in triplicate during home visits (6, 8, 10 and 12 months of age) by trained nurses. Parents maintained daily records of morbidity and answered food use questionnaires every second month. Parents in the treatment group recorded qualitative estimates of cereal and meat usage daily and answered a monthly compliance check questionnaire that asked, among other questions, if their infants consumed any meat and if they consumed any cereal in the last month. Six mothers consistently said ‘no’ to one or the other of these questions each month. In each of these cases, the lack of meat or cereal intake was confirmed by the daily meat and cereal use records. Infants from these families were treated as non-compliers.

**Statistical analysis**

The primary analysis compared the occurrence of end-points between the infants in the treatment group excluding non-compliers and the infants in the control group using Mantel-Haenszel Chi-square analysis. Secondary analysis included comparison of slope of change for HgB and Ferr using an age-based regression model that recognized repeated measures within individuals, treatments and treatment x age interactions (under the general linear models procedure of SAS).

Analysis was conducted with SAS version 6.12 (SAS Institute, Inc., Cary, NC). The acceptable level of statistical significance for all tests was p<0.05.

**RESULTS**

Infants in the control group were generally fed formula or breastfed. Cow milk use was delayed until the tenth month in the vast majority of infants. In contrast, all of the infants in the treatment group were fed WCM as their only milk source throughout the study (Table III).

Daily estimates show that most infants in both groups consumed infant cereal (treatment mean intake = 28±9 g/day) and meat throughout the study (treatment mean intake = 98±21 g/day). Only six treatment infants were identified as non-compliers.

There was no difference in ‘end-point’ incidence (p=0.78) between treatment (3 of 43) and control infants (5 of 49). In...
the treatment group, all end-points were by low ferritin; in the control group three were by low ferritin while two were by low HgB (Table IV).

Three out of 43 infants who complied with the treatment reached end-point compared to 5 of 6 infants who did not comply (p=0.0002) (Table V).

Slope of change in log Ferr fell progressively with age in both the treatment (-0.08±0.02, p=0.0001) and control (-0.07±0.02, p=0.0001) groups at a similar rate (p=0.49). In contrast, slopes of haemoglobin did not change significantly across age for the treatment (-0.03±0.30, p=0.30) or control groups (0.02±0.31, p=0.95). Again, there was no difference between groups (p=0.44).

Other effects of treatment

There was no detectable effect of the treatment diet versus control on anthropometric indices at any age. Neither was there any detectable association between morbidity and the occurrence of end-point. The inference is that neither growth nor morbidity was influenced by the treatment diet and that differentials in growth and morbidity rates did not confound interpretation of main effect measures.

DISCUSSION

Based on data from previous Canadian studies,2,3,22,23 our hypothesis assumed that the incidence of iron depletion in the control group (low-income families without dietary intervention) would be 30% or higher and that the intervention would reduce this to an incidence of 10% or less. This assumption was incorrect. Despite having incomes below the defined Canadian poverty level, the families in the control group differed from other low-income families described in the literature2,3 in that they were generally better educated. Unexpectedly, families in the control group were generally fed in accordance with current Canadian recommendations. These were established as guidelines for parents to meet the nutritional needs and prevent ID in their infants.11,12

By following these recommendations, the incidence of iron depletion in the control group was much lower than anticipated. Thus, it was not possible to test the original hypothesis.

Despite this, three lines of evidence from our results suggest that the iron from cereal and meat was well utilized and prevented ID in WCM-fed infants. First, the proportion of infants reaching end-point in the treatment was as low as in the control group who were generally fed in accordance with CPS guidelines. If, as had originally been anticipated, 30% of the control infants were iron deficient, the reduction to 3/43 in intervention group would have been both statistically and clinically significant.

Second, all but one of the infants (i.e., 5 of 6) in the treatment group who consumed WCM but did not consume either meat or cereal reached ‘end-point’. This indirectly suggests that the iron from the combination of meat and cereal prevented iron depletion in WCM-fed infants.

Third, changes in Ferr and HgB across age were similar between study groups. Ferritin levels declined with age at similar rates in both groups. Haemoglobin levels did not change significantly with age in either group. These results are as expected in normal healthy infants since iron stores are generally being utilized at this age due to the rapidly expanding blood volume but functional iron should remain unaffected in the absence of ID.27

CPS recommendations suggest delaying introduction of WCM until 9 to 12 months of age11,12 because WCM is a poor source of iron and its use is associated with occult gastrointestinal blood loss. The current data suggest that ID is not a concern in WCM-fed infants after six months of age as long as iron-containing complementary foods are concurrently ingested. The only major sources of iron for infants who complied with the treatment diet were the meat and iron-fortified cereal. The individual contributions of infant cereal versus meat could not be determined; however, the results of this study are consistent with others showing that infant cereal and iron-fortified meat and cereal contribute substantially to preventing ID.23,28-30

Although, occult blood loss has been shown to be a concern before six months of age,17,19-21 the current data indirectly support a number of studies that demonstrate that it rarely occurs after six months.17,19-21 The observation that only 3/43 WCM-fed infants consuming meat and cereal, after six months, became iron deplete implies that the intake of iron was adequate and loss was not excessive.

In Toronto, WCM is about one third the cost of formula. Substituting formula with WCM after six months, while otherwise following CPS guidelines (which suggest the use of iron-rich supplementary foods) can result in substantial savings. However, in the current trial, cereal, meat and milk were provided without cost to iron-replete infants. In a non-study setting the effectiveness of this intervention in preventing ID would be seriously compromised if cost, availability and/or acceptability limited the use of meat and cereal. This is illustrated by the fact that nearly all of the infants in the treatment group who did not consume meat or cereal developed iron depletion. The results of this study suggest that WCM is an acceptable alternative for families who cannot or choose not to feed breastmilk or formula after six months of age if the infant is regularly consuming meat and iron-fortified infant cereal.

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