

Intestinal Blood Loss by Normal Infants Fed Cow's Milk

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In the 1960s, it was recognized that intestinal blood loss could cause iron deficiency anemia (1,2). Furthermore, Wilson et al. (3), using ⁵¹Cr-tagged erythrocytes, furnished convincing evidence that intestinal blood loss could be provoked by the feeding of cow's milk. These investigators also showed that the effect of cow's milk was dose-dependent and could be abolished by heat treatment of cow's milk (of a more extensive kind than mere pasteurization). The studies of Elian et al. (4), also using ⁵¹Cr-tagged erythrocytes, showed that virtually all otherwise normal infants lose small amounts of blood with their stool. However, the number of infants in this study (4) was small, and it remained unclear whether intestinal blood loss was a universal phenomenon. Also, it has remained unclear whether cow's milk could induce intestinal blood loss in normal (nonanemic) infants and, if so, whether blood loss by normal infants could be of sufficient magnitude to affect iron nutritional status.

Initial information on this question was provided by Woodruff et al. (5) from a prospective study of normal infants. The infants were breast-fed or formula-fed up to 2 months of age and then fed whole cow's milk (13 infants) or a non-iron-fortified formula (25 infants). A sensitive guaiac test was used to detect the presence of blood in the stools, and a number of positive reactions were detected even in feces of fully breast-fed infants. Among formula-fed infants at 3, 6, 9, and 12 months of age, guaiac-positive stools were detected in 44, 52, 67, and 54% of stools, respectively. Among infants fed cow's milk, the corresponding percentages were 92, 69, 83, and 64% at 3, 6, 9, and 12 months of age, respectively. Thus, a greater percentage of guaiac-positive stools was seen in infants fed whole cow's milk than in infants fed formula, although it was not possible to judge the nutritional significance of the blood loss in either group. The study failed to provide evidence that younger infants were more susceptible than older infants to cow's milk-provoked gastrointestinal blood loss.

In this study by Woodruff et al. (5), intakes of iron were similar for the

infants fed the non-iron-fortified formula and those fed cow's milk. Blood samples were obtained at 3, 6, 9, and 12 months of age. In the group fed whole cow's milk, hemoglobin concentration was significantly less at ages 9 and 12 months, and mean corpuscular volume and percent saturation of transferrin were significantly less at 6 and 9 months of age. Thus, this study provided some evidence that the feeding of cow's milk had adverse effects on iron nutritional status over a long period.

In a study somewhat similar in design to that of Woodruff et al., except that the observation periods were shorter, Fomon et al. (6) observed 81 normal infants from 112 to 196 days of age who were divided into three feeding groups. One group was fed a low-iron, milk-based formula, one group was fed homogenized whole cow's milk heat-treated in the same manner as the infant formula, and one group was fed pasteurized, homogenized whole cow's milk. All infants received a daily supplement providing 12 mg of iron as ferrous sulfate. In most instances, a stool sample was collected each week and tested with the guaiac reaction. Figure 1 indicates the percent guaiac-positive stools in each group at baseline (112 days of age), from 119 to 140 days of age, from 147 to 168 days of age, and from 175 to 196 days of age. The number of infants with guaiac-positive stools and the total number of guaiac-positive stools during the first 28 days of the trial (from 119 to 140 days of age) was significantly greater in the group fed whole cow's milk than in the other groups ($p < 0.01$ and < 0.001 , respectively). During the later

n. Also, it has remained unclear whether cow's intestinal blood loss in normal (nonanemic) infants and blood loss by normal infants could be of sufficient magnitude to affect nutritional status. Information on this question was provided by Woodruff et al. in a prospective study of normal infants. The infants were breast-fed up to 2 months of age and then fed whole cow's milk or a non-iron-fortified formula (25 infants). A sensitive guaiac test to detect the presence of blood in the stools, and a number of guaiac-positive stools were detected even in feces of fully breast-fed infants. At 3, 6, 9, and 12 months of age, guaiac-positive stools were detected in 44, 52, 67, and 54% of stools, respectively. Among infants fed whole cow's milk, the corresponding percentages were 92, 69, 83, and 83% at 3, 6, 9, and 12 months of age, respectively. Thus, a greater percentage of guaiac-positive stools was seen in infants fed whole cow's milk than in those fed formula.

Age intervals (days)	Formula	Heat-treated cow's milk	Cow's milk
112	44	92	92
119-140	52	69	69
147-168	67	83	83
175-196	54	83	83

Age intervals (days)

FIG. 1. Percent of stools with positive guaiac reaction (•) of infants fed formula or heat-treated cow's milk and (d) of infants fed cow's milk after 112 days of age. (Reproduced from ref. 6 with permission, © C.V. Mosby Co., 1981.)

periods, differences in percent of subjects with guaiac-positive stools and in total number of guaiac-positive stools in the three feeding groups were small and not statistically significant. As was the case with the study reported by Woodruff et al. (5), the clinical significance of these observations was difficult to evaluate because guaiac tests do not yield quantitative data on blood loss. No differences were detected in iron nutritional status between the various feeding groups. However, iron intakes were generous, and the observation period was short.

With the availability in recent years of quantitative tests of fecal hemoglobin, it has become possible to determine the extent of fecal blood loss. In a recently completed study of normal infants fed either cow's milk or a milk-based formula (Ziegler et al., to be published), we have used a sensitive and specific method (7) for the quantitative determination of fecal loss of hemoglobin. With this method, it is possible to detect 0.02 mg of hemoglobin/g of wet feces. From 168 through 252 days of age, 26 infants were fed cow's milk, and 26 infants were fed a low-iron, milk-based formula. Selected other foods low in iron content were permitted, and one jar per day of a specially prepared cereal-fruit combination providing 3.65 mg of iron in the form of ferrous sulfate was provided. Before entering the trial, all infants had been fed a milk-based formula with 12 mg of iron per liter for 28 days or more. Thirty-one infants had been breast-fed, whereas 21 infants had never been breast-fed. Stool samples were collected before the start of the trial (at 140, 166, 167, and 168 days of age) and at weekly intervals thereafter for determination of hemoglobin concentration. In addition, stools were tested for occult blood with the guaiac reaction (Hemoccult, Smith Kline Diagnostics, Sunnyvale, CA, U.S.A.). Venous blood was obtained in most cases at 140 days of age and during the trial at 168, 196, 224, and 252 days of age for determination of hematocrit, hemoglobin concentration, erythrocyte protoporphyrin, serum iron, and ferritin.

As shown in Fig. 2, the percent of guaiac-positive stools was significantly greater ($p < 0.01$) in the group fed cow's milk than in the group fed formula during the first 28 days of the trial (175 to 196 days of age). Differences in the percent of guaiac-positive stools were smaller and not statistically significant during the two subsequent 28-day periods. Results of quantitative determinations of fecal hemoglobin indicated that the group fed cow's milk had much higher fecal hemoglobin losses than the group fed formula (Fig. 3). The difference was statistically significant in each 28-day period. Closer inspection of the data revealed that six infants fed cow's milk showed no appreciable increase above baseline in fecal hemoglobin loss ("nonresponders"). Responses of the other 20 ("responders") infants were highly variable, and most infants had increased hemoglobin loss even in the first stool sample obtained after starting on cow's milk (at 175 days of age). In many infants, fecal hemoglobin loss declined later, but a few infants had sustained high hemoglobin losses. In some infants, fecal hemoglobin loss did not

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In the 1960s, it was recognized that intestinal blood loss could cause iron deficiency anemia in normal (nonanemic) infants and that the magnitude of blood loss by normal infants could be of sufficient magnitude to cause iron deficiency anemia. Information on this question was provided by Woodruff et al. in a comparative study of normal infants. The infants were breast-fed to 2 months of age and then fed whole cow's milk or iron-iron-fortified formula (25 infants). A sensitive guaiac test detected the presence of blood in the stools, and a number of infants at 3, 6, 9, and 12 months of age, guaiac-positive stools were detected even in feces of fully breast-fed infants. Among infants at 3, 6, 9, and 12 months of age, guaiac-positive stools were detected in 44, 52, 67, and 54% of stools, respectively. Among infants at 3, 6, 9, and 12 months of age, fecal hemoglobin concentrations were 140, 166-168, 175-196, 203-224, and 231-252 mg/dl, respectively. Bars indicate standard error.

Age intervals (days)

FIG. 2. Percent of stools with positive guaiac reaction (•) of infants fed formula and WE) of infants fed cow's milk after 168 days of age.

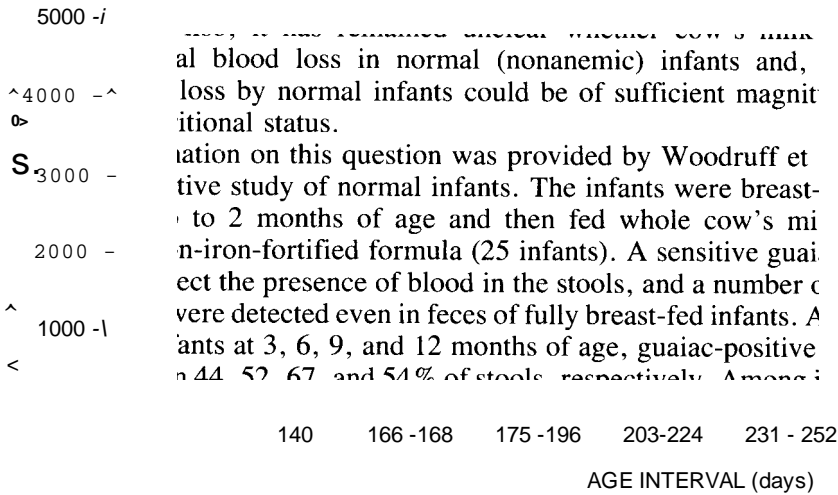


FIG. 3. Fecal hemoglobin concentration of infants (0) fed formula and infants (•) fed cow's milk after 168 days of age. Bars indicate standard error.

TABLE 1. Indices of iron nutritional status

	Age (days)									
	140		168		196		224		252	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Hemoglobin (g/dl)										
Cow's milk	11.8	1.1	11.8	0.9	11.7	0.9	11.8	1.0	12.0	0.9
Formula	11.9	1.0	12.1	1.1	11.8	1.0	11.9	1.0	12.1	0.6

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increase until several weeks after cow's milk feeding was started. Mean fecal hemoglobin of the 20 responders was 4,773 µg/g of dry stool during the period 175 to 196 days of age.

Assuming a wet stool weight of 60 g/day with 20% dry solids, a fecal hemoglobin concentration of 4,773 µg/g of dry stool represents an iron loss of 0.20 mg/day, a quantity we consider nutritionally significant.

Biochemical indices of iron nutritional status did not differ between the group fed cow's milk and the group fed formula. As shown in Table 1, hematocrit and concentrations of hemoglobin, erythrocyte protoporphyrin, serum iron, and ferritin provided no evidence for deterioration of iron nutritional status among infants fed cow's milk. There was also no difference in iron nutritional status between responders and nonresponders in the group fed cow's milk. However, one infant with high fecal blood loss developed clear evidence of iron deficiency within 4 weeks after cow's milk was introduced.

CONCLUSIONS

The literature and our own studies provide convincing evidence that consumption of cow's milk leads to increased gastrointestinal blood loss in the majority of normal, nonanemic infants. The data do not suggest that suscep-

tibility to cow's milk-induced blood loss is age-dependent during the first year of life. However, blood loss is most severe when cow's milk is first introduced and diminishes in most infants with the duration of feeding cow's milk. A few infants experience quite large blood loss, but the data are insufficient to estimate the prevalence of this phenomenon.

In our studies, few adverse effects on iron nutritional status have been evident, presumably because of the relatively short exposure to cow's milk (3 months). Studies with longer periods of cow's milk feeding have generally demonstrated impaired iron nutritional status. Thus, there can be little question that the feeding of cow's milk to infants and young children for a prolonged period is likely to lead to poor iron nutritional status and, in some infants, to outright iron deficiency. The relative importance of gastrointestinal blood loss, displacement by cow's milk of more iron-rich foods, and inhibition of iron absorption remains to be determined. We conclude that cow's milk is an unsuitable food during the first year of life.

REFERENCES

1. Rasch, C. A., Cotton, E. K., Harris, J. W., and Griggs, R. C. (1960): Blood loss as a contributing factor in the etiology of iron-lack anemia of infancy. *Am. J. Dis. Child.*, 100:627(Abstract)
2. Hoag, M. S., Wallerstein, R. O., and Pollycove, M. (1961): Occult blood loss in iron deficiency anemia of infancy. *Pediatrics*, 27:199-203.
3. Wilson, J. F., Lahey, M. E., and Heiner, D. C. (1974): Studies on iron metabolism *J. Pediatr.* 84:335-344.
4. Elian, E., Bar-Shani, S., Liberman, A., and Matoth, Y. (1966): Intestinal blood loss: a factor in calculations of body iron in late infancy. *J. Pediatr.*, 69:215-219
5. Woodruff, C. W., Wright, S. W., and Wright, R. P. (1972): The role of fresh cow's milk in iron deficiency. *Am. J. Dis. Child.*, 124:26-30.
6. Fomon, S. J., Ziegler, E. E., Nelson, S. E., and Edwards, B. B. (1981): Cow milk feeding in infancy: gastrointestinal blood loss and iron nutritional status. *J. Pediatr.*, 98:540-545
7. Schwartz, S., Dahl, J., Ellefson, M., and Ahlquist, D. (1983): The HemoQuant test: a specific and quantitative determination of heme (hemoglobin) in feces and other materials, *clin. Chem.*, 29:2061-2067.

Discussion

Dr. Filer: In the study comparing cow's milk with heat-treated cow milk, was the ascorbic acid intake controlled?

Dr. Ziegler: Ascorbic acid was not given to the infants fed cow's milk; however, the formula contained at least 50 mg/liter; thus, infants fed formula received more vitamin C.

Dr. Walravens: Which fruits did you use in the iron-fortified cereal-fruit combination?

Dr. Ziegler: Bananas and pears. These products were fortified with vitamin C.

Dr. Walter: Did the infants receive meat?

Dr. Ziegler: No.

Dr. Dallman: In your second study in which you changed the feedings of formula-fed and breast-fed infants to cow's milk, how many were breast-fed?

Dr. Ziegler: Thirty-one were breast-fed, and the other 21 were formula-fed.

Dr. Walravens: What was the weight of the dry stool in this study?

Dr. Ziegler: We assumed that it was 10 to 12 g. Stool dry solids account for around 23% to 25% of stool weight.

Dr. Filer: Was there any relationship between iron loss and the use of solid foods?

Dr. Ziegler: No. Solid foods were started at 140 days and were limited to one jar of the fruit-cereal mixture.

Dr. Filer: So, you never eliminated solid foods.

Dr. Ziegler: In this study, we did not.

Dr. Walter: Was the infant who had the high iron loss breast-fed in early life?

Dr. Ziegler: Yes, she was, but only for about 1 month.

Dr. Walter: In our study, infants who were fed fresh cow's milk had almost double the stool volume than infants receiving either milk or soy formula and somewhat more stool volume than when they were fed powdered milk.

Dr. Ziegler: That parallels our observations. Infants fed cow's milk had lower dry solid concentrations in their stools than infants who were fed formulas.

Dr. Walter: In our longitudinal studies, about one-third of infants, despite having the same birth weight and living in the same environment and receiv-

ing the same diet, develop iron deficiency anemia. Another one-third have biochemical evidence of iron deficiency and another one-third have normal iron status. Our question has always been: why is there a difference in large groups of infants who are essentially the same? Our current longitudinal study is a follow-up of a large number of infants to find out if there is a group of infants who have increased iron loss and, as a result, eventually become anemic. These infants are receiving modified formula and powdered milk. None of the infants are receiving fresh cow's milk, which is normally not consumed by infants in Chile. From our daily stool collections, we have found that a few of the infants tend to lose more blood, as indicated by Dr. Ziegler.

Dr. Dallman: Did you obtain a family history of allergy?

Dr. Ziegler: No, we did not obtain such histories. We recently inquired about the infant who had high stool blood losses to determine how she was doing. She is a perfectly normal child without any signs of gastrointestinal illness.

Dr. Oski: Did she have atopic dermatitis? Sometimes, cow's milk protein causes both gastrointestinal symptoms and atopic dermatitis.

Dr. Ziegler: There was no clinical evidence of atopic dermatitis.

Dr. Filer: Allergic infants may also have colitis. At what age are stool blood losses an issue? It is frequently recommended that cow's milk not be introduced before 1 year of age, but is 1 year too early?

Dr. Ziegler: Our study went only to age 252 days. Wilson et al. (1974) observed that some infants have blood loss into the second year of life. But, in addition, they showed that infants who have this problem in infancy have no blood loss when they ingest cow's milk later in life. Formerly, my primary reason for recommending against cow's milk feeding during infancy was renal solute load. Now, I feel the main concern is blood loss.