

Risk of Diarrhea Related to Iron Content of Infant Formula: Lack of Evidence to Support the Use of Low-iron Formula as a Supplement for Breastfed Infants

Paula D. Scariati, DO, MPH*‡; Laurence M. Grummer-Strawn, PhD‡; Sara Beck Fein, PhD§; and Ray Yip, MD, MPH‡

ABSTRACT. *Background.* Concern has been raised by infant feeding experts that supplementing breastfed infants with iron-fortified formula rather than low-iron formula may have an undesirable impact on their gastrointestinal flora. Thus far, there have been no clinical studies to address this issue directly. We compared the reported frequency of diarrhea for breastfed infants given iron-fortified formula with those fed low-iron formula.

Methods. Mothers participating in a mail panel provided feeding and diarrhea information on their infants at 2, 3, 4, 5, 6, 7, 9, and 12 months (n = 1743). Infants were grouped into five feeding categories: (1) breast milk only, (2) breast milk and low-iron formula, (3) breast milk and iron-fortified formula, (4) low-iron formula only, and (5) iron-fortified formula only. We calculated the number of diarrheal episodes per week for each feeding category and used rate ratios to estimate the relative impact of low-iron and iron-fortified formulas.

Results. Among infants who received both breast milk and formula, the rate ratio for iron-fortified formula versus low-iron formula was 1.06 (confidence interval, 0.84 to 1.34), indicating that the type of formula a breastfed infant receives does not significantly affect the frequency of diarrhea.

Conclusions. We found no evidence to support the hypothesis that breastfed infants given iron-fortified formula are at greater risk of having diarrhea. This, in addition to the fact that iron-fortified formula has played a major role in preventing childhood iron deficiency anemia, supports the current recommendation that any formula given to infants be fortified with iron. *Pediatrics* 1997;99(3). URL: <http://www.pediatrics.org/cgi/content/full/99/3/e2>; *infant food, diarrhea, breastfeeding, iron.*

ABBREVIATION. AAP, American Academy of Pediatrics.

When supplementation is necessary, which is a better supplement to breast milk: low-iron or iron-fortified formula? In a recent article in *AAP News*,¹

From *Epidemic Intelligence Service, Epidemiology Program Office, and ‡Division of Nutrition and Physical Activity, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia; and §Office of Scientific Analysis and Support, Center for Food Safety and Applied Nutrition, Food and Drug Administration, Washington, DC.

Received for publication Mar 5, 1996; accepted May 21, 1996.

Reprint requests to (P.D.S.) Centers for Disease Control and Prevention, Mail Stop K-25, Division of Nutrition and Physical Activity, 4770 Buford Hwy, Atlanta, GA 30341-3724.

PEDIATRICS (ISSN 0031 4005). Copyright © 1997 by the American Academy of Pediatrics.

Lawrence Gartner, MD, chair of the American Academy of Pediatrics (AAP) Group on Breastfeeding, suggested that breastfed infants 6 months or younger be supplemented with low-iron formula. Dr Gartner and others have taken this position on the theoretical grounds that the higher iron content of iron-fortified formula could saturate the breast milk protein lactoferrin, which plays a role in preventing the overgrowth of intestinal *Escherichia coli*.²⁻⁴ If true, the hypothesis continues that this iron-lactoferrin interaction would result in increased intestinal growth of *E coli*. Although in vitro studies and studies in guinea pigs demonstrate the plausibility of this theory,^{3,4} studies of breastfed human infants, supplemented with iron fortified and low-iron formula, are lacking. Furthermore, the clinical consequences of such an alteration, if demonstrated in humans, would require further examination.

Current guidelines on iron-fortified formula issued by the Committee on Nutrition of the AAP in 1989 specify that if infants are supplemented with formula, the formula should be fortified with iron as a strategy to prevent iron deficiency.⁵ Evidence suggests that the iron content of an infant's diet is the major determinant of iron deficiency,⁶ and that the significant decline of iron deficiency anemia among children in the United States is related to the shift from low-iron to iron-fortified formula.^{7,8} Preventing iron deficiency anemia in infants is important, because anemia adversely affects development and behavior.^{9,10}

In this study, we compared the frequency of diarrhea in two groups of breastfed infants, one given low-iron formula and the other given iron-fortified formula. If increased iron has an undesirable impact on the infant's intestinal flora, as hypothesized, breastfed infants given iron-fortified formula should have more episodes of diarrhea than similar infants given low-iron formula.

METHODS

Sampling Frame

The Infant Feeding Practices Study is a panel study of US mother-infant pairs followed from late pregnancy through the infant's first year. The Food and Drug Administration conducted the study between 1993 and 1994. The agency used a consumer mail panel as the sampling frame and sent prenatal intake questionnaires to 3155 households identified as including pregnant women.

Exclusion Criteria

A woman was ineligible for the study at the time of the prenatal questionnaire if she was either not pregnant or her due date was more than 3 months away. A woman was ineligible for the study after the prenatal questionnaire for any of the following reasons: (1) her infant weighed less than 5 lb at birth; (2) she gave birth to multiple infants; (3) she had medical problems that prevented her from feeding the infant for more than 1 week; (4) her infant stayed in the intensive care unit for more than 3 days; (5) her infant had medical problems that affected feeding; (6) she or her infant died at any time during the data collection period; and (7) her infant was born too early for the neonatal questionnaire to be administered on time. Five hundred forty women were excluded from the study because they met ineligibility criteria. This gave a sample base of 2615 women.

Nonresponse

A woman was considered a nonrespondent if she failed to complete the first (prenatal) or second (birth screener) questionnaire or if she failed to complete the first two questionnaires sent after the infant's birth ($n = 812$). We did not eliminate a mother from the study for failure to complete a subsequent questionnaire. The response rate was 69% (1803 of 2615).

For this analysis, we excluded women who failed to complete the demographic questionnaire ($n = 60$), as well, leaving 1743 mother-infant pairs. In any given month, we excluded infants who received neither breast milk nor formula; this exclusion had little impact on the sample size until month 12 (Table 1).

Population Characteristics

To better understand the characteristics of our sample, we compared them with a nationally representative population of mothers participating in the National Maternal and Infant Health Survey. In comparison, our cohort consisted of mothers who were: (1) more from middle- and upper-income groups, (2) predominantly white, (3) older, (4) more likely to be married, (5) more likely to take prenatal classes, and (6) less likely to drink alcohol or smoke.

Data Collection

The Food and Drug Administration used the prenatal questionnaire, which was administered from 90 to 42 days before the mother's due date, to collect information on the mother's health, employment situation, and infant feeding plans. The birth screener questionnaire, administered shortly after the mother gave birth, included questions on the health of the infant and anthropometric indices at birth. A third (neonatal) questionnaire was administered when the child was 1 month old; information about the infant's birth and subsequent feeding was collected. The remaining questionnaires collected information about feeding, health status, allergies, and the infant's social situation and were administered at months 2, 3, 4, 5, 6, 7, 9, and 12. We used data from months 2 through 12 for the analysis presented here.

Classification of Predictor and Outcome Variables

Each month, the mother was asked whether she had breastfed her infant and whether she had given formula to the infant in the previous 7 days. If she had given her infant formula, she was asked whether that formula was iron fortified. We grouped infants into one of five feeding categories: (1) breast milk only, (2) breast

milk and iron-fortified formula, (3) breast milk and low-iron formula, (4) iron-fortified formula only, or (5) low-iron formula only.

Mothers were also asked, "How many times has your baby had diarrhea during the past 2 weeks?" Diarrhea was defined for the mother as three or more watery or semiwatery stools in a 24-hour period. Before this question, the mother had been asked to describe the infant's usual stool. We think this gave her a reference by which to distinguish between normally loose stools and diarrhea.

Analysis

We summed the number of cases of diarrhea (some mothers reported more than one for some 2-week periods) for all periods in which we had responses and divided by 2 (because of the 2-week reporting period) to define the number of diarrhea episodes per infant-week. We examined the five feeding categories described previously in two different groupings. First, to create a framework within which to interpret our results, we compared the rate of diarrhea for three groups: breast milk only, breast milk with formula, and formula only. In this case, the breast milk-only group served as the referent. Next, we compared the rate of diarrhea among infants receiving iron-fortified or low-iron formula in both the breast milk-with-formula and formula-only groups. Here, low-iron formula was the referent group.

To test whether the frequency of diarrhea episodes among breastfed infants differed between those supplemented with iron-fortified formula and those given low-iron formula, we divided the diarrhea rate in the iron-fortified formula group by the rate in the referent group, generating a rate ratio. If the ratio was close to 1.0, we would not reject the null hypothesis that breastfed infants fed with iron-fortified formula have the same frequency of diarrhea as those fed with low-iron formula. A rate ratio significantly greater than 1.0 would suggest that breastfed infants given iron-fortified formula are at greater risk of having diarrhea than their counterparts given low-iron formula. For completeness, we made the comparable calculation for infants given formula only.

The rates were adjusted for the infant's age and gender, mother's education, occupation, and smoking history, household size, household income, and day care use (Table 2). We performed the analysis with Poisson regression (generalized linear model), using the Genmod procedure of SAS for Windows, version 6.08 (SAS Institute, Inc, Cary, NC).

RESULTS

Using the infants fed breast milk only as the referent, we found almost a doubling of the rate of diarrhea among infants fed formula only ($P < .001$; Fig 1). Infants who received both breast milk and formula also had a significantly higher rate of diarrhea ($P = .001$), but it was well below that of the formula-only group.

When we compared infants fed iron-fortified formula with those fed low-iron formula, there was no significant difference in the rates of diarrhea (Fig 2). Among infants who received both breast milk and formula, the rate ratio for fortified versus low-iron formula was 1.06 ($P = .60$; confidence interval, 0.84 to 1.34); among infants receiving formula only, the

TABLE 1. Sample Size by Type of Feeding and Age of Child

Feeding Group	Month								Total
	2	3	4	5	6	7	9	12	
Only breast milk	459	367	335	315	284	263	235	193	2451
Breast milk and formula									
Iron fortified	324	281	228	188	188	175	112	39	1535
Low iron	107	95	77	58	40	34	27	7	445
Only formula									
Iron fortified	565	588	648	685	744	801	840	462	5333
Low iron	162	152	159	165	158	139	123	60	1118
Total	1617	1483	1447	1411	1414	1412	1337	761	10 882

TABLE 2. Confounding Variables Used in Multivariate Analysis

Infants's age	2, 3, 4, 5, 6, 7, 9, and 12 mo
Infant's gender	F M
Mother's education	0-11 y of school 12 y of school 1-4 y of college >4 y of college
Mother's occupation	Full-time homemaker Unemployed, student, or retired Professional or executive Clerical or sales Craftsman, fabricator, technician, farmer, service worker, etc
Mother's smoking	No smoking ≤10 cigarettes/day 11-20 cigarettes/day >20 cigarettes/day
Household size	1-2 people 3 people 4-8 people
Household Income	<\$22 500 \$22 500-\$34 999 \$35 000-\$50 000 >\$50 000
Day care	No care 1-2 days/wk 3-5 days/wk 6-7 days/wk

comparable rate ratio was 0.89 ($P = .02$; confidence interval, 0.80 to 0.99).

DISCUSSION

This study did not find a significant difference between the rate of diarrhea for breastfed infants given iron-fortified formula and the rate for those given low-iron formula. This implies that although supplementation with iron-fortified formula may alter the breastfed infant's intestinal flora, this change is physiologic, not pathologic.

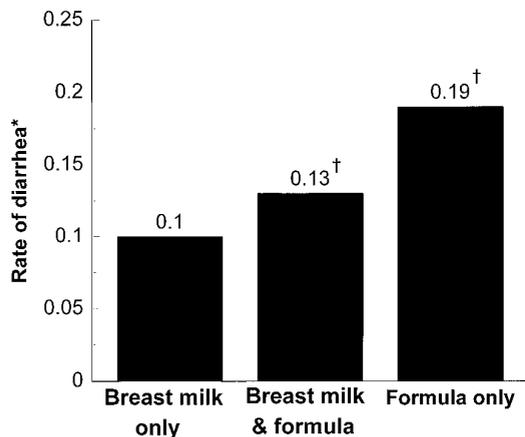


Fig 1. Rate of diarrhea by major feeding group. † indicates $P < .001$ compared with rate for breast milk only; and *, episodes per week, adjusted for age and gender of infant, household income, mother's education, occupation, and smoking history, household size, and use of day care.

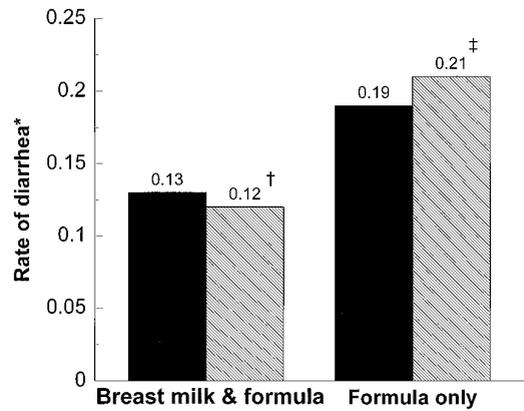


Fig 2. Rate of diarrhea by formula type within two major feeding groups. † indicates not significant compared with breastfed infants given iron-fortified formula; ‡, $P = .02$ compared with formula-only infants given iron-fortified formula; and *, episodes per week, adjusted for age and gender of infant, household income, mother's education, occupation, and smoking history, household size, and use of day care. ■, Iron-fortified; ▨, low iron.

This study also found that among infants receiving formula only, iron-fortified formula provided a small but significant amount of protection against diarrhea when compared with low-iron formula. Other researchers looking at the iron intake of formula-fed infants and the development of diarrhea, in the past, have reported no association.^{11,12}

We did confirm the well-documented finding that infants given formula are at greater risk of having diarrhea than are breastfed infants.¹³⁻¹⁶ Our results also demonstrate that infants receiving both breast milk and formula have diarrhea more often than do infants receiving breast milk exclusively but less often than infants fed formula only. The demonstration of such a dose-response relationship indicates that this study design and sample size have the power to detect differences in clinical outcomes related to feeding practices.

The evidence presented by others to argue that iron may harm an infant's gastrointestinal tract—namely, differences in intestinal flora—without correlation with clinical outcome is not sufficient to recommend the use of low-iron formula. Indeed, we think there is no compelling medical evidence to support the use of low-iron formula in the general population. On the other hand, there is substantial evidence that iron-fortified formula has helped to prevent iron deficiency anemia in the United States. Thus, we urge continued support of the 1989 recommendations of the Committee on Nutrition of the AAP that low-iron formulas have no place in infant feeding and that any formula given to infants be fortified with iron.⁵

ACKNOWLEDGMENTS

We thank Dr Kelley Scanlon, Dr Caryn Bern, and Dr Frederick Trowbridge for their careful review and comments on this manuscript. We also thank Dr Bern for sharing her expertise on matters regarding diarrhea in infancy.

REFERENCES

- Larson L. Warnings fail to slow low-iron formula sales. *AAP News*. 1995;11:1,14

2. Lawrence RA. *Breastfeeding: A Guide for the Medical Profession*. 4th ed. St Louis, MO: Mosby-Year Book, Inc; 1994
3. Baltimore RS, Vecchitto JS, Pearson HA. Growth of *Escherichia coli* and concentration of iron in an infant feeding formula. *Pediatrics*. 1978;62:1072-1073
4. Bullen JJ, Rogers HJ, Leigh L. Iron binding proteins in milk and resistance to *E. coli* infection in infants. *Br Med J*. 1972;1:69-75
5. American Academy of Pediatrics Committee on Nutrition. Iron-fortified infant formulas. *Pediatrics*. 1989;84:1114-1115
6. Pizarro F, Yip R, Dallman PR, Olivares M, Hertrampf E, Walter T. Iron status with different infant feeding regimens: relevance to screening and prevention of iron deficiency. *J Pediatr*. 1991;118:687-692
7. Yip R, Binkin NJ, Fleshood L, Trowbridge FL. Declining prevalence of anemia among low-income children in the United States. *JAMA*. 1987;258:1619-1623
8. Yip R, Walsh KM, Goldfarb MG, Binkin NJ. Declining prevalence of anemia in a middle class setting: a pediatric success story? *Pediatrics*. 1987;80:330-334
9. Lozoff B, Jimenez E, Wolf AW. Long-term developmental outcome of infants with iron deficiency. *N Engl J Med*. 1991;325:687-694
10. Walter T, De Andraca I, Chadud P, Parales CG. Iron deficiency anemia: adverse effects on infant psychomotor development. *Pediatrics*. 1989;84:7-17
11. Oski FA. Iron-fortified formulas and gastrointestinal symptoms in infants: a controlled study. *Pediatrics*. 1980;66:168-170
12. Nelson SE, Zeigler EE, Copeland AM, Edwards BB, Foman JJ. Lack of adverse reactions to iron-fortified formula. *Pediatrics*. 1988;81:360-364
13. Ross CA, Dawes EA. Resistance of the breast-fed to gastroenteritis. *Lancet*. 1954;i:994-998
14. Alexander MB. Infantile diarrhoea and vomiting: a review of 456 infants in a hospital unit for enteritis. *Br Med J*. 1948;ii:973-978
15. Bullen CL, Willis AT. Resistance of the breast-fed infant to gastroenteritis. *Br Med J*. 1971;3:338-343
16. Koopman JS, Turkish VJ, Monto AS. Infant formulas and gastrointestinal illness. *Am J Public Health*. 1985;75:477-480

Risk of Diarrhea Related to Iron Content of Infant Formula: Lack of Evidence to Support the Use of Low-iron Formula as a Supplement for Breastfed Infants

Paula D. Scariati, Laurence M. Grummer-Strawn, Sara Beck Fein and Ray Yip

Pediatrics 1997;99:e2

DOI: 10.1542/peds.99.3.e2

Updated Information & Services	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/99/3/e2
References	This article cites 14 articles, 8 of which you can access for free at: http://pediatrics.aappublications.org/content/99/3/e2#BIBL
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://www.aappublications.org/site/misc/reprints.xhtml

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Risk of Diarrhea Related to Iron Content of Infant Formula: Lack of Evidence to Support the Use of Low-iron Formula as a Supplement for Breastfed Infants

Paula D. Scariati, Laurence M. Grummer-Strawn, Sara Beck Fein and Ray Yip

Pediatrics 1997;99:e2

DOI: 10.1542/peds.99.3.e2

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/99/3/e2>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 1997 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

