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 infant feeding experts that supplementing breastfed infants with iron-fortified formula should be supplemented 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 women. 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 women 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 semifluid 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

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<th>TABLE 1. Sample Size by Type of Feeding and Age of Child</th>
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<td>Feeding Group</td>
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<tr>
<td>Breast milk and formula</td>
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2 of 4    IRON-FORTIFIED FORMULA SAFE FOR BREASTFED INFANTS

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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.

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 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**

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