Infant Formulas and Gastrointestinal Illness

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Abstract: Infants under age one in a pediatric practice were followed prospectively, and the determinants of acute gastrointestinal illness were evaluated in case-control pairs, matched by birth month. The risk of acute gastrointestinal illness in infants receiving formula was six times greater than in infants receiving breast milk and 2.5 times greater than in infants receiving cow milk. In the second six months of life, infants on formula had 0.38 more gastrointestinal illness episodes per child than infants on cow milk. Episodes without rotavirus or bacterial agents accounted for most of the increased risk of formula. The increased risk could not be explained by iron fortification of the formulas, prescription of non-milk based formulas to high-risk infants, case ascertainment bias, control selection bias, or numerous control factors. Non-antibody anti-infection properties found in cow milk are one possible explanation for these findings. (*Am J Public Health* 1985; 75:477–480.)

Introduction

Bottle feeding is associated with a higher frequency of gastrointestinal illness than is breast feeding.[1–5] Whether different types of bottle feedings have different risks is not established. Most formulas are now iron fortified and the iron content of formulas promotes the growth of bacteria.[6] Different types of bottle feedings could also have different anti-infective properties. Whole milk has been shown to have antiviral properties not found in infant formulas.[7]

The present study addresses the risk of gastrointestinal illness associated with formula, cow milk, and breast milk feedings in infants.

Methods

Study Design and Population

The private practice of one of the authors (VJT) provided the population base. The practice sees mostly lower and lower middle class patients from Ypsilanti, Michigan. A prospective, population based case-control study was conducted from August 1979 to April 1980 and from July 1980 to April 1981. For this study, cohort lists of patients in the practice were established in July 1979. Separate lists were made for each month of birth. Sex and residence inside or outside of Ypsilanti were specified on these lists. The lists were subsequently updated as patients came into or left the practice.

Patients on these lists were followed prospectively. Cases of acute gastrointestinal illness were ascertained when the parents called the practice. A patient with onset in the past ten days of abnormal frequency and consistency of stools or vomiting not explained by another condition was defined as a case. Controls were matched to cases by age, sex, and geographic area using random number selection from the cohort lists on which the case occurred.

When a parent telephoned the practice regarding a gastrointestinal illness, the study was explained to the parent and the patient was seen free of charge. No patient refused to participate in the study. A suitable control whose parents affirmed that he or she had not had a gastrointestinal illness in the prior two weeks was found for 97 per cent of the cases. Since having one episode of acute gastrointestinal illness does not substantially reduce the risk of a subsequent episode, controls included patients who at other times were cases. Less than 5 per cent of selected controls could not be contacted or refused to participate. When this occurred, a second control was drawn.

Both cases and controls were interviewed using a one-page protocol. Parents of patients were interviewed by the physician or an office assistant at the time of their visit. They were followed up at one week intervals by phone. Parents of controls were interviewed by the office assistant over the telephone. The following were ascertained: exposure to other cases of gastrointestinal illness inside or outside of the household, race, income, medical payment plan, pet exposures, number and ages of siblings, day care or school attendance by the patient or siblings, baby sitting arrangements, church attendance, and type of milk feeding in the period prior to the onset of the acute illness. At first the only types of milk feedings recorded were breast milk, cow milk, and/or formula. Beginning in January of 1980, the fat content of cow milk and commercial brand of formula were also ascertained.

Overall gastrointestinal illness rates were estimated for the practice from January 1979 to April 1981. Since some months of the year occur twice and other months three times between these dates, the 12 average monthly rates were summed to get the final rate. The denominators used were the age-specific effective population sizes in June 1980. This was determined by contacting all parents with an infant's record in the practice to determine if they considered their child a patient of the practice. Repeated efforts resulted in contacting all but a few parents. Those not contacted were not considered part of the practice.

In practice patients the number of acute illnesses attended by the practice and elsewhere was determined. There were 79 practice patient infants under age six months; 65 per cent of their acute illness care was in the practice giving an effective population size of 51. There were 98 practice patient infants in the second six months of life; 70 per cent of their acute illness care was in the practice giving an effective population size of 68.

Laboratory Methods

Stool or rectal swabs of patients with gastrointestinal illness were collected in the office and transported the same day to the University of Michigan. Rotavirus was detected by an indirect enzyme linked immunosorbant assay using goat antirotavirus serum as the capture antibody.[8] Results were confirmed by comparisons to controls using preimmune goat sera from the same animal. Beginning in January 1980, specimens were examined for a full range of bacterial

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pathogens including enterotoxigenic *E. coli* and colonization factor positive *E. coli*. The laboratory methods used are described in greater detail elsewhere.[9]

Statistical Analyses

Associations of feeding type with gastrointestinal illness were assessed by use of matched pair odds ratios. Confidence intervals were calculated with reference to tables of the exact confidence limits of the binomial distribution as outlined by Fleiss.[10] Attributable risks were estimated as outlined by Schlesselman.[11] Confounding of the associations by measured third variables was controlled by logistic regression of the discordant pairs.[12]

Results

The average yearly incidence of acute gastrointestinal illness seen in this practice was 0.88 per child below age one year, 0.46 in the first six months of life and 0.42 in the second six months of life.

Thirteen per cent of the cases under age six months and 29 per cent of the cases between six and 12 months had rotaviruses identified in their stools. The only bacterial pathogen identified in the 99 bacteriologically examined specimens was one enteropathogenic *E. coli* serotype 055:B5.

Analysis of Feeding Type

There were 143 case-control pairs: 60 under six months of age and 83 from six to 12 months of age. The distribution of milk feeding types prior to illness in the age matched pairs of cases and controls is presented in Tables 1 and 2 for the first and the second six months of life, respectively. Being selected by a random procedure from practice cohort lists, the controls should be representative of the practice population. Under age six months, 17 of 60 (27 per cent) of the controls had some breast-feeding in the weeks prior to illness onset, 64 per cent had some formula feedings, and 20 per cent had some cow milk feedings. As shown in Table 2, in the second six months of life, only 13 per cent of controls had some breast-feedings, 41 per cent had some formula feedings, and 51 per cent had cow milk feedings.

The association of each type of feeding with gastrointestinal illness was assessed by matched pair odds ratios. In Table 3, various comparisons derived from Tables 1 and 2 are summarized.* Infants taking any formula feedings in the weeks prior to illness had a 2.44-fold increased risk of gastrointestinal illness compared to infants not taking any formula. Cow milk and breast milk, on the other hand, appear to be protective. Using the presented odds ratios, rates of illness, and frequencies of feedings, we can estimate that 62 per cent of acute gastrointestinal illness under age six months in this population might be attributable to formula feeding and that the rate of illness per infant on formula during the first six months is 0.45 higher than the similar rate in infants not on formula.

In the second six months of life, 29 per cent of the acute gastrointestinal illnesses might be due to formula use. The rate per infant on formula is 0.30 higher than in infants not on formula.

Overall for the first year, 42 per cent of acute gastrointestinal illness could be attributable to formula and the rate in infants on formula is 0.74 per infant higher than in infants not on formula.

The odds ratio of acute gastrointestinal illness is greater in the breast milk formula comparison than in the cow milk formula comparison. But the gastrointestinal illness risk of formula fed infants in relation to cow milk fed infants is significant. Moreover, most of the risk of formula feeding in the second six months of life is in relation to cow milk rather than breast milk.

In the second six months of life we can estimate the difference in the rates of acute gastrointestinal illness between cow milk and formula consumers by using the restricted population of only formula or only cow milk consumers. In this population, approximately 43 per cent are formula consumers and the overall rate of illness is 0.45 episodes per child. Using these figures, we can estimate that formula fed babies experience 0.38 more episodes of acute gastrointestinal illness per infant than do infants fed only cow milk during the second six months of life.

The higher risk of gastrointestinal illness in formula fed as compared to cow milk fed infants tended to be stronger for non-rotavirus illness than for rotavirus positive illness. The OR of exclusive formula feeding versus exclusive cow milk feeding for rotavirus positive cases was 1.6 (13/8; 95 per cent C.I. = 0.6 to 9.5). The OR for cases without rotavirus was 3.2 (29/9; 95 per cent C.I. = 1.5 to 6.4).

Analysis by Specified Formula Types

There were ninety-one case-control pairs where the brand or type of milk consumption was specified; 34 were in the first six months of life and 61 were in the second.

Analysis of these pairs gives no indication that infants taking identical brands with and without iron have differences in risk. The unmatched odds ratio over the entire first year for brands without iron was five (15 cases and three

*The comparison between breast milk and cow milk is not presented because the different ages at which these feedings are commonly given means there are very few age matched pairs with just these feedings.

TABLE 1—Case-Control Pairs under Age Six Months by Type of Milk or Formula Consumption

	Cases					
Controls	Total	Formula	Breast Milk	Cow Milk	Breast Milk and Formula	Cow Milk and Breast Milk
Total	60	48	2	5	4	1
Formula	32	26	1	2	2	1
Breast Milk	10	10	0	0	0	0
Cow Milk	10	7	0	3	0	0
Breast Milk and Formula	5	3	1	0	1	0
Cow Milk and Breast Milk	1	0	0	0	1	0
Cow Milk and Formula	1	1	0	0	0	0
Breast Milk and Unspecified Other Milk	1	1	0	0	0	0

TABLE 2—Case-Control Pairs from Ages Six to 12 Months by Type of Milk or Formula Consumption

Controls	Cases						
	Total	Formula	Breast Milk	Cow Milk	Breast Milk and Formula	Cow Milk and Breast Milk	Cow Milk and Formula
Total	78	44	5	23	2	2	2
Formula	28	17	1	9	1	0	0
Breast Milk	6	2	0	3	0	0	1
Cow Milk	37	21	3	10	1	1	1
Breast Milk and Formula	1	0	1	0	0	0	0
Cow Milk and Formula	3	2	0	1	0	0	0
Breast Milk and Unspecified Other Milk	3	2	0	0	0	1	0

controls). The odds ratio for the same brands with iron was 3.9 (35 cases and nine controls).

Analysis of risks by fat content of cow milk showed that whole milk had a protective effect while low fat milk did not. In all cases but one, low fat milk means 2 per cent milk. The unmatched odds ratio over the entire first year for whole milk was 0.55 (24 cases and 44 controls). The same ratio for low fat milk was one (four cases and four controls).

The different brands of formula included three brands comprising two different types of milk based formulas and five brands of non-milk based formulas. The unmatched odds ratio of milk based formulas for acute gastrointestinal illness in the second six months of life was 2.5 (15 cases and six controls). The same ratio for the non-milk based formulas was 1.75 (14 cases and six controls). Thus there is no indication that the association of formula use with illness is due to infants being placed on non-milk based formulas because of a tendency to increased illness.

Use of the two similar brands of milk based formula was associated with a considerably higher risk of illness than was the third brand of milk based formula.

Bias Assessment

The possibility that case selection bias caused the apparent increased risk of infants on formula as compared to milk was assessed by examining symptoms in the 92 infants receiving formula only and in the 28 infants receiving cow milk only. If the parents of infants receiving only cow milk are less likely to consult the doctor for mild illness, then the cases they do bring to the doctor should have more severe symptoms. Table 4 shows that this is not the case. None of the differences are statistically significant and most are in the opposite direction expected if selection bias had occurred.

The possibility of confounding bias was assessed through logistic regression of discordant pairs. All recorded variables presented under methods were used. The main confounding factors were income and availability of help in child care. Adding other variables to the model with these two factors raised rather than lowered the odds ratio. Controlling for these factors, the 2.44 increased risk of any formula feeding compared to no formula feeding was reduced to 2.2 but remained highly significant. The 2.54 increased risk of only formula feeding compared to only cow milk feeding remained unchanged and was significant at less than the 0.01 level.

Discussion

This study observed a lower risk of acute gastrointestinal illness in infants receiving cow milk than in infants

TABLE 3—Matched Pair Case-Control Contrasts of Acute Gastrointestinal Illness Risk in Breast Milk, Cow Milk or Formula Fed Infants.

Comparison	All under Age One		Under Age Six Months		Age Six to 12 Months	
	prs*	OR# 95% C.I.	prs	OR# 95% C.I.	prs	OR# 95% C.I.
Any Formula vs No Formula	44	2.44	18	3.6	26	2.0
	—	(1.4–4.5)	—	(1.3–8.6)	—	(.98–4.2)
	18		5		13	
Any Breast Milk vs No Breast Milk	11	0.5	4	0.28	7	0.88
	—	(.2–1.06)	—	(0.08–0.89)	—	
	22		14		8	
Any Cow Milk vs No Cow Milk	17	0.47	3	0.33	14	0.52
	—	(.25–.86)	—	(.06–1.4)	—	(.25–1.01)
	36		9		27	
Just Formula vs Just Breast Milk	12	6	10	10	2	2
	—	(1.33–>10)	—	(1.2–>10)	—	
	2		1		1	
Just Formula vs Just Cow Milk	28	2.54	7	3.5	21	2.33
	—	(1.3–5.7)	—	(.7–>10)	—	(1.03–6.0)
	11		2		9	

*The numerator is the number of pairs where the case had the first element in the comparison and the control had the second. The denominator is the number of pairs where the control had the first element and the case had the second.

#The matched pair odds ratio estimate and the 95% confidence interval.

TABLE 4—Symptom Frequencies in Acute Gastrointestinal Illness Cases under One Year of Age by Feeding Type

Symptom	Exclusively Formula Fed (%)	Exclusively Milk Fed (%)
Diarrhea	98	100
Vomiting	54	45
Fever	42	31
Apparent Abdominal Pain	30	21
Mucus in Stool	36	21
Anorexia	34	43
6 or More Stools	53	62
10 or More Stools	12	10
Cough	68	55
Rhinorrhea	57	45

receiving formula. Most of the comparison between these two types of feedings occurred in the second six months of life. This observation is especially important as there is a current trend toward greater frequency of formula feedings with formula being promoted as a good source of iron in the second six months of life.

Microbiological observations could support hypotheses that either iron fortification or formula preparation processes might increase the risk of gastrointestinal illness in infants taking formula. Iron fortification might increase the risk of bacterial growth[7] and processing might eliminate natural antiviral properties.[8,13] Our data, like that of another study,[14] do not support the contention that iron fortification increases the risk of gastrointestinal illness. In contrast to the previous study on this issue,[14] our study assesses the effect of iron fortification on gastrointestinal illness without taking measures that might protect against bacterial contamination.

Our data cannot assess the effect of antiviral properties in formula or cow milk. But they do suggest that if there is such an effect, it might be stronger for the unrecognized agents than for rotavirus.

This study also observed that whole fat milk, but not low fat milk, was associated with a reduced risk of illness. This is consistent with our observation in the same practice that children over age one year taking low fat milk have a five-fold increased risk of acute gastrointestinal illness compared to children on whole milk.[15] Both the increased risk of formula and low fat milk could be due to a lack of antiviral properties in the lipid fractions of these feedings. Such antiviral properties are found in human milk.[13] The increased risks of formula and low fat milk might also be due to the same mechanisms that create an association between low fat milk consumption and chronic nonspecific diarrhea.[16,17]

This study was not designed to identify causal mechanisms. Any causal conclusions to be drawn from the observed associations must therefore rest on our conviction that the associations are not due to artifacts of the study or to confounding variables. Let us evaluate the factors that could have created noncausal associations.

The use of all ascertained cases from prospectively followed cohort lists and the use of the same lists to randomly select controls eliminates the usual sources of control selection bias in case-control studies. The possibility of case selection bias persists. It was evaluated by examining symptoms. The symptoms of infants receiving formula were somewhat more severe than the symptoms of infants receiving cow milk; thus case selection bias might have acted to decrease rather than increase our observed associations.

A potential source of observer bias is that the cases were interviewed in the office and the controls over the phone. Recall bias seems unlikely as formula versus cow milk is a readily made distinction that does not involve any prolonged recall.

Nipple use, bottle refrigeration, and other dietary components were not assessed and may have created some confounding. It seems likely, however, that the parents who switch to milk first also add other dietary components earlier; if so, they should be at an increased and not a decreased risk of exposure.

Non-milk based formulas might have some reversed direction relationship to acute gastrointestinal illness as children prone to gastrointestinal illness might be placed on such formulas. This was not commonly done, however, in the practice studied. Given the lack of a greater odds ratio for non-milk based formulas than for milk based formulas, this reversed direction relationship becomes unlikely.

Since all sources of confounding or observer bias cannot be ruled out, it seems unwise to base any public health decision on formula use after six months of age on this study. The high attributable risks observed, however, should create a priority for further studies to confirm the associations observed and to investigate the composition of fats or other factors that might relate to anti-infective properties in cow milk.

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