Formula Tolerance in Postbreastfed and Exclusively Formula-fed Infants

ABSTRACT. *Objective.* **Perceived intolerance to infant formula is a frequently reported reason for formula switching. Formula intolerance may be related to perceived symptoms of constipation, fussiness, abdominal cramps, and excessive spit-up or vomit. Commercially available formulas differ from each other in processing and in sources and levels of protein, lipids, and micronutrients. These differences may affect tolerance. The objective of this article was to compare the tolerance of two commercially available powder infant formulas that differ in composition. Measures of tolerance in exclusively breastfed infants weaned to an infant formula and exclusively formula-fed infants were evaluated.**

Methods. **Two clinical studies were conducted. In study 1, 82 healthy, full-term infants who were exclusively breastfed at the time of enrollment were randomized at weaning to formula A (commercially available Similac With Iron Powder) or formula B (previously available Enfamil With Iron Powder). Parents completed daily records of tolerance during exclusive breast milk feeding, during the weaning period, and for a 2-week exclusive formula-feeding period. In study 2, 87 healthy, full-term infants who were exclusively formula-fed at the time of study enrollment (by 2 weeks of age) were fed a standard cow milk-based formula (previously commercially available Similac With Iron Powder) and then randomized to receive formula A or B for a 2-week period. Parents completed daily records of tolerance throughout the study. Formula A was a cow milk-based formula with a whey:casein ratio of 48:52 and a fat blend of 42% high-oleic safflower, 30% coconut, and 28% soy oils. Formula B was a cow milk-based formula with a whey:casein ratio of 60:40 and a fat blend of 45% palm olein, 20% soy, 20% coconut, and 15% high-oleic sunflower oils. Both formulas had lactose as the source of carbohydrate and contained 12 mg of iron per liter. Only formula A contained nucleotides at the time of the study. Measures of tolerance included volume of each formula feeding, occurrences of spit-up and/or vomit, and the color (yellow, green, brown, or black) and consistency (water, loose/mushy, soft, formed, or hard) of each stool.**

Results. **In both studies, volume of formula intake, weight gain, and incidence of spit-up or vomit did not differ between feeding groups. In study 1, stool frequency decreased significantly from the exclusive breast milk period to weaning. Stools also became firmer as infants moved from breast milk to weaning and to exclusive formula feeding. When formula was introduced into the diet, stools became less yellow and more green. Infants weaned to formula B had less frequent stools, fewer brown stools, and more yellow stools than did infants fed formula A. In both studies, infants fed formula B experienced significantly firmer stools than did those fed formula A.**

Conclusions. **The present clinical studies indicate that the composition and/or processing of milk-based powder iron-fortified infant formulas affect stool characteristics experienced by infants. The inclusion of palm olein oil in formula B may be the reason for the observed differences in stool characteristics. Palm olein is used in infant formulas to provide palmitic acid at a level similar to that found in breast milk. However, palmitic acid from palm olein is arranged differently from that in breast milk triglyceride and is poorly absorbed. Unabsorbed palmitic acid tends to react with calcium to form insoluble soaps, and the level of these soaps is correlated with stool hardness. The pattern of softer stools and greater frequency of stooling associated with formula A is similar to the stool pattern in the exclusively breastfed infant. Thus, the use of formula A may ease the transition from breast milk to formula feeding and ameliorate parents' perception that constipation is associated with iron-fortified formula.** *Pediatrics* **1999;103(1). URL: http://www.pediatrics.org/cgi/content/full/103/1/e7;** ***breastfeeding, bottle feeding, human milk, weaning, stools, formula tolerance, constipation.***

ABBREVIATION. FF, formula-fed.

Parents are very concerned about their infant's tolerance to feedings. One of the primary concerns is whether an infant formula produces "constipation," a term that is used often to describe a condition in which stools are firm and perceived by parents to be passed with excessive effort and discomfort. Perceived intolerance also may be related to the fact that infants, whether breastfed or formula-fed (FF), for unknown reasons are sometimes fussy, appear to have abdominal cramps, cry at inconvenient times, and regurgitate. Parents often switch their infant's formula as the result of these symptoms.[1] The perceived presence of an allergy to milk protein may explain formula-switching as well. However, the incidence of true allergy to milk protein is far less common than the incidence of formula-switching.[2] This suggests that other components of formulas produce symptoms in some infants that are viewed by parents as undesirable. Commercially available formulas differ from each other in processing and in sources and levels of protein, lipids, and micronutrients; there is reason to believe that these differences affect tolerance.

Despite the great frequency of formula-switching, data comparing the tolerance to various infant formulas are limited. Whether infants who are initially breastfed differ in their reaction to infant formula from those who are FF from birth also is unclear. The present investigation compares the tolerance of two commercially available powder formulas (formula A and formula B) that differ in composition. One of the formulas is a commercially available formula and the

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other is a reformulation of another leading formula that was being developed at the time of the study and now is commercially available. Measures of tolerance among exclusively breastfed and FF infants are considered in two clinical studies.

METHODS AND MATERIALS

Study Design and Data Collection

Two studies were conducted. Protocols for both studies were approved by institutional review boards at all participating sites, and informed written consent was obtained from legal guardians of all infants.

Study 1

Study 1 considered 82 infants who were exclusively breastfed at the time of recruitment. Infants were recruited from four US pediatric offices at the 2-week posthospital discharge well-baby visit and were enrolled into the study between September 1994 and July 1995. Infants were eligible to participate if they were born full-term, were considered to be in good health, were exclusively fed breast milk since birth, and the mother had expressed an interest in weaning her infant from breast milk to formula within the infant's first 6 months of life. Throughout the weaning period and for 2 weeks of exclusive formula-feeding, infants were fed either formula A or formula B. Infants were allowed to receive vitamin or mineral supplements during the period of exclusive breastfeeding, but were allowed only fluoride supplements once formula-feeding was initiated. Infants were allowed to consume solid foods throughout the study.

Parents completed daily dietary intake and stool records during a 3-day period of exclusive breastfeeding (prestudy period), during the weaning period (daily during the first 2 weeks of formula introduction, and 3 days per week thereafter until weaning was completed), and for the 2-week exclusive formula-feeding period (defined as no more than one breastfeeding per day). The volume of each formula feeding; occurrences of spit-up and/or vomit; color (yellow, green, brown, or black); and consistency (watery, loose/mushy, soft, formed, or hard) of each stool were recorded. Other foods (juice, fruit, cereal, meat, vegetables) consumed were described but not quantified. The assigned study formula was given to the parents at the completion of the prestudy period (study day 1). Study office visits occurred at the completion of each of the feeding periods. During each office visit, parents returned completed record forms, and each infant was weighed naked according to standardized procedures.[3]

Study 2

Infants in study 2 were exclusively FF at the time of enrollment. Infants were healthy, full-term infants who were recruited from four hospitals in Canada within the first 2 weeks of life. All infants were exclusively FF at the time of study entry and were enrolled into the study between September 1994 and February 1995.

Parents were provided with a standard cow milk-based formula (previously commercially available Similac With Iron Powder, which had a 50% corn oil, 38% coconut oil, and 12% soy oil fat blend and a whey:casein ratio of 18:82) from the time of enrollment until the 2-week well-baby visit. At the 2-week visit (study day 1), parents were given clinically labeled Similac With Iron Powder as provided at the time of enrollment; this formula was administered for a 1-week baseline period. At the study day 8 office visit, parents returned all unused baseline formula and were provided the assigned study formula (formula A or formula B) based on the randomization schedule. Infants were fed the assigned study formula for 2 weeks. Parents completed daily dietary and stool records throughout the baseline and study feeding periods. Weight was measured on study days 8 and 22. Infants were not administered any solid foods or vitamins or mineral supplements for the duration of the study.

Study Feedings

Formula A was a cow milk-based formula with a whey:casein ratio of 48:52 and a fat blend of 42% high-oleic safflower, 30% coconut, and 28% soy oils (Table 1). Formula B was a cow milk-based formula with a whey:casein ratio of 60:40 and a fat blend of 45% palm olein, 20% soy, 20% coconut, and 15% high-oleic sunflower oils (Table 1). Both formulas had lactose as the source of carbohydrate and contained 12 mg of iron per liter. Only formula A was fortified with nucleotides. The study formulas were provided as powder in cans and provided 20 calories per fl oz when prepared. Formula cans and cases were labeled with codes to mask the identity of the study feedings. For both studies, assignment of infants to formula A or B was based on computer-generated randomization schedules. The randomization for both studies were stratified by gender. The randomization for study 1 was stratified by age at onset of weaning (≤2 months, >2 months).

TABLE 1. Partial Composition of Study Formulas (Per Liter)

Nutrient	Formula A*	Formula B†
Protein, g‡	14.0	14.2
Source	Nonfat milk and whey protein concentrate	Reduced minerals whey and nonfat milk
Fat, g‡	36.5	35.8
Source	42% High-oleic safflower, 30% coconut oil, and 28% soy oil	45% Palm olein, 20% soy, 20% coconut, and 15% high-oleic sunflower oil
Carbohydrate, g‡	73.0	73.7
Source	Lactose	Lactose
Iron, mg‡	12	12
Fatty acid (weight%)§		
6:0	0.2	0.2
8:0	2.5	1.7
10:0	1.8	1.2
12:0	13.6	8.4
14:0	5.4	3.9
16:0	8.2	22.1
16:1	0.1	0.1
18:0	3.5	4.7
18:1	39	36.7
18:2	22	18.1
18:3	2.2	1.7
20:0	0.3	0.3
20:1	0.3	0.2
22:0	0.2	0.3
24:0	0.1	0.2

* Improved Similac With Iron (Ross Products Division, Abbott Laboratories, Columbus, OH).
† Enfamil With Iron (Mead Johnson Nutritionals, Evansville, IN).
‡ Values based on label claims when mixed to standard solution.
§ Analytical values.

Statistical Methods

The primary outcome variable for both studies was tolerance, defined as formula intake, incidence of spit-up and/or vomit, and stool characteristics. Statistical analyses were performed using SAS.[4] Data collected at each time period (exclusive breastfeeding, weaning, and exclusive formula-feeding periods for study 1, and baseline and study feeding periods for study 2) were analyzed separately. Although some infants did not complete the study, an intent-to-treat analysis was used for all available infants. Stool consistency was expressed in three ways: 1) average stool consistency, calculated by assigning a score to each consistency (1 = watery, 2 = loose/mushy, 3 = soft, 4 = formed, 5 = hard), multiplying this value by the frequency of stools for the specified consistency and dividing the resulting value by the total number of stools; 2) predominant stool consistency represented by the greatest percentage of stools across the stool consistency types; and 3) the percentage of stools in each consistency.

Categoric data were analyzed using Pearson's χ^2 or Fisher's exact test. Continuous and ordinal data were analyzed using analysis of covariance (study 1) and analysis of variance (study 2). Age at initiation of weaning and gender were covariates in study 1. Site was incorporated as a blocking factor, and ranking was applied when appropriate. To evaluate whether tolerance changed within each feeding group as infants progressed from breastfeeding to formula-feeding (study 1), the exclusive breastfeeding and exclusive formula-feeding periods were compared with the weaning period (characterized by breastfeedings >1/d and formula feedings >2/d) using Wilcoxon's signed rank test for each feeding. Time to weaning was analyzed using a log-rank test. Exit status was analyzed by the χ^2 test according to the following criteria: study completion, poor compliance or illness/condition not associated with the study formula, and withdrawal based on evidence of formula intolerance. All statistical tests were two-sided using an $\alpha = .05$ to determine statistical significance. *P* values are reported where appropriate.

RESULTS

Study 1

Of 82 infants enrolled into the study, 43 were randomized to formula A and 39 to formula B. Of these, 85% successfully completed the study according to the protocol (35 infants in each group). In the formula A group, 8 infants failed to complete the study: 4 were removed by parents because of reported diarrhea, fussiness, family vacation, and family emergency; 1 infant was removed by the investigator for protocol noncompliance; 2 infants were removed because of illness unrelated to the study feeding; and 1 infant exited because of antibiotic use for sinus infection. Four infants in the formula B group were removed from study participation because 2 mothers chose to continue breastfeeding, 1 infant experienced colic, and 1 infant refused to drink the study formula. There were no significant differences between feeding groups in exit status.

There were no significant differences between feeding groups in demographic characteristics at study entrance (Table 2). The time that infants were weaned from breast milk to either formula A or formula B was similar (30 ± 5 vs 32 ± 6 days, respectively).

Volume of formula intake did not differ between feeding groups. Infants consumed an average of 780 ± 31 mL/d and 775 ± 26 mL/d of formulas A and B, respectively, during the exclusive formula-feeding period. Infants were fed more frequently during the weaning period (8.4 feedings/d) than during the exclusive formula-feeding period (6.6 feedings/d). The frequency of nonformula food consumption did not differ between the feeding groups.

There were no significant differences in weight gain between feeding groups. The average weight gain for infants fed formula A was 32 ± 4 g/d during the weaning period and 26 ± 3 g/d during exclusive formula feeding. Infants fed formula B had an average weight gain of 26 ± 3 g/d during both the weaning and exclusive formula feeding periods.

There were no significant differences in incidence of spit-up or vomit between the feeding groups (Table 3). During exclusive formula-feeding, emesis occurred with 16% ± 3% of feedings in infants fed formula A and 25% ± 4% among those fed formula B. Infants fed formula A experienced a significant reduction in spit-up or vomit between the weaning and exclusive formula-feeding periods.

In both feeding groups, several significant changes in stool tolerance characteristics occurred as infants progressed from exclusive breastfeeding, to weaning, to exclusive formula-feeding (Table 3). Analysis of covariance indicated that after adjusting for the effect of gender, the effects of feeding on characteristics of stool tolerance remained unchanged. Age at onset of weaning had a significant ($P < .05$) effect on stool frequency during the prestudy and weaning periods, and on the percentage of loose/mushy, formed, and hard stools ($P < .05$), and percentage of yellow and brown stools during all study periods ($P < .05$). Stool frequency significantly ($P < .05$) decreased from the exclusive breast milk period to weaning. The stools also became firmer as infants

TABLE 2. Sample Characteristics

	Study 1		Study 2	
	Formula A	*Formula B*	*Formula A*	*Formula B*
Enrolled *(n)*	43	39	45	42
Gender (% male)	56	46	53	55
Gestational age (wk)	39.4 ± 0.2*	39.9 ± 0.2	39.6 ± 0.2	39.3 ± 0.2
Ethnicity *(n)*				
Caucasian	33	35	29	37
African-American	3	1	5	1
Asian	1	0	5	3
Other	6	3	6	1
Age at study day 1 (days)	4–188†	8–181	12–16	12–17
Weight at study day 1 (g)	5570 ± 235*	5425 ± 205	3624 ± 80	3609 ± 62

* Mean ± SEM.
† Range.

TABLE 3. Study 1: Tolerance Data

	Exclusive Breast Milk-feeding Period*		Weaning Period†		Exclusive Formula-feeding Period‡	
	Formula A (n = 42)	*Formula B* (n = 39)	*Formula A* (n = 38)	*Formula B* (n = 35)	*Formula A* (n = 37)	*Formula B* (n = 35)
Spit-up or vomit (% of feedings)	19 ± 3§	22 ± 4	20 ± 3	22 ± 4	16 ± 3‖	25 ± 4
Stool frequency (number of stools per day)	3.4 ± 0.3	3.5 ± 0.3	2.5 ± 0.2‖	2.1 ± 0.2‖¶	2.0 ± 0.2	1.6 ± 0.1¶
Stool color (% of stools)						
% Yellow	77 ± 5	70 ± 6	42 ± 6‖	56 ± 6‖	12 ± 4‖	26 ± 5‖¶
% Green	8 ± 3	12 ± 4	38 ± 6‖	37 ± 6‖	65 ± 6‖	64 ± 5‖
% Brown	13 ± 5	17 ± 5	20 ± 5	7 ± 3¶	21 ± 4	9 ± 3¶
% Black	2 ± 2	0	0	0	3 ± 1	2 ± 1
Average stool consistency#	2.0 ± 0.1	2.1 ± 0.1	2.3 ± 0.1‖	2.5 ± 0.1‖¶	2.6 ± 0.1‖	3.0 ± 0.1‖¶
Stool consistency (% of stools)						
Watery	29 ± 6	22 ± 6	15 ± 4‖	9 ± 4‖	7 ± 2	1 ± 0‖¶
Loose/mushy	52 ± 6	50 ± 7	52 ± 5	34 ± 5‖	37 ± 5‖	19 ± 4‖¶
Soft	13 ± 4	23 ± 6	25 ± 4‖	51 ± 5‖¶	41 ± 6‖	59 ± 5¶
Formed	6 ± 3	5 ± 3	7 ± 3	5 ± 2	12 ± 4	20 ± 4‖¶
Hard	0	0	0	1 ± 1	2 ± 1	2 ± 1
Predominant stool consistency (% of subjects)	Formula A	Formula B*	Formula A	Formula B*	Formula A	Formula B*
Watery	32	21	11	6	6	0
Loose/mushy	59	50	64	29	39	9
Soft	5	26	17	65	44	71
Formed	5	3	8	0	11	21
Hard	0	0	0	0	0	0

* ≤2 Formula feedings/day.
† >1 Breast milk and 2 formula feedings per day, respectively.
‡ ≤1 Breast milk feeding/day.
§ Mean ± SEM.
‖ Significantly different from the data for the same feeding group at the earlier study period, $P < 0.05$.
¶ Significantly different from formula A during this study period, $P < 0.05$.
# A five-point scale was used, with 1, watery; 2, loose/mushy; 3, soft; 4, formed; 5, hard.

moved from breast milk to weaning to exclusive formula-feeding ($P < .05$). When formula was introduced into the diet, stools became less yellow and more green ($P < .05$).

Significant differences in stool tolerance characteristics between the feeding groups also were observed (Table 3). Infants fed formula B had significantly fewer brown stools than those fed formula A during both the weaning ($P < .05$) and the exclusive formula-feeding ($P < .05$) period, and more yellow stools during exclusive formula-feeding ($P < .01$) period. Infants weaned to formula B had significantly less frequent stools than those fed formula A ($P < .05$). This difference persisted during the 2 weeks of exclusive formula-feeding ($P < .05$). Infants fed formula B also experienced significantly firmer stools than did infants fed formula A for both the weaning ($P < .05$) and the exclusive formula-feeding ($P < .01$) periods. Specifically, infants exclusively fed formula A had significantly more watery ($P < .01$) and loose/mushy ($P < .01$) stools than did those fed formula B, and those fed formula B had significantly more soft ($P < .05$) and formed ($P < .01$) stools than those fed formula A. Predominant stool consistency reflected the same patterns, with more infants fed formula B experiencing soft or formed stools and fewer infants experiencing watery or loose/mushy stools than those fed formula A.

Study 2

Of the 87 infants enrolled into the study, 45 infants were randomized to formula A and 42 to formula B. Six infants exited the study during the baseline period. Of the infants entering the study feeding period, 10/43 (23%) infants in the formula A group and 6/38 (16%) infants in the formula B group failed to complete the protocol. Five infants in the formula A group were withdrawn because of reported intolerance (3 for fussiness or gas, 2 for diarrhea); 1 exited because of illness unrelated to the study feeding; 1 exited because of medication use for colic; and 3 were removed because of failure to comply with the protocol. Two infants in the formula B group exited because of intolerance (1 for constipation, 1 for vomiting); 2 exited because of illness unrelated to the study feeding; and 2 were withdrawn for failure to comply with the protocol. As in study 1, there were no significant differences between the feeding groups in exit status. Additionally, there were no significant differences between study 1 and study 2 in the frequency of infants who failed to complete the protocol.

Birth and enrollment characteristics did not differ between the feeding groups (Table 2). Most infants (95%) were fed Similac With Iron before study entry (Table 2). Infants fed formula A consumed an average of 755 ± 21 mL/d, and infants fed formula B consumed 743 ± 21 mL/d. There were no significant differences in weight gain between feeding groups. The average weight gain during the study period was 17 ± 1 g/d among infants fed formula A and 16 ± 1 g/d among those fed formula B. There were no significant differences between the feeding groups in the incidence of spit-up or vomit (Table 4). Infants fed formula A experienced emesis with 24% ± 4% of feedings, and infants fed formula B had emesis with 25% ± 4% of feedings.

Stool frequency and color did not differ during

TABLE 4. Study 2: Tolerance Characteristics

	Formula A	Formula B
	(n = 40)	(n = 37)
Spit-up or vomit (% of feedings)	24 ± 4*	25 ± 4
Stool frequency (number of stools per day)	2.5 ± 0.2	2.3 ± 0.2
Stool color (% of stools)		
Yellow	58 ± 6	66 ± 5
Green	31 ± 6	32 ± 5
Brown	10 ± 4	2 ± 1
Black	1 ± 1	0
Average stool consistency†	2.7 ± 0.1	3.2 ± 0.1‡
Stool consistency (% of stools)		
Watery	9 ± 3	1 ± 1‡
Loose/mushy	31 ± 5	12 ± 2‖
Soft	44 ± 5	54 ± 4
Formed	12 ± 3	24 ± 4‡
Hard	3 ± 1	7 ± 2‖
Predominant stool consistency (% of subjects)	Formula A	Formula B‖
Watery	11	0
Loose/mushy	35	9
Soft	46	65
Formed	5	21
Hard	3	6

* Mean ± SEM.
† A five-point scale was used, with 1, water; 2, loose/mushy; 3, soft; 4, formed; 5, hard.
‡ Significantly different from formula A, $P < 0.01$.
‖ Significantly different from formula A, $P < 0.05$.

either the baseline or the study feeding period. However, significant differences were observed during the study feeding period for the three measures of stool consistency (Table 4). Infants fed formula B had a significantly ($P < .01$) higher average stool consistency (ie, firmer stools) than did those fed formula A, experienced a significantly greater percentage of hard ($P < .05$) and formed stools ($P < .01$), and had a significantly lower percentage of watery ($P < .01$) and loose/mushy stools ($P < 0$ .05) (Table 4). The pattern for predominant stool consistency was similar: a greater percentage of infants fed formula A had looser stools ($P < .01$) than did those fed formula B.

DISCUSSION

The present studies clearly demonstrate that cow milk-based, iron-fortified formulas in the form of powder and differing in composition are tolerated differently by infants. Formulas A and B produced significantly different characteristics of stool tolerance. In both studies, formula B was associated with firmer stools than was formula A in FF and initially breastfed infants. Additionally, compared with formula A, formula B also was associated with less frequent stooling in infants weaned from breast milk.

In the present studies, stool characteristics were evaluated using daily record forms; these are probably more accurate than questionnaires typically provided at the end of the study,[5,6] which require the recall of detailed information. Unlike previous studies that considered one measure of stool consistency,[7–9] the present studies considered three measures. Use of all three measures appears to provide a more comprehensive description of stool consistency. For example, average stool consistency is a general description of stools for a sample of infants and indicates whether there was a shift in the distribution of stool consistency (eg, from looser to firmer stools). Predominant stool consistency indicates the consistency for the greatest percentage of stools for the majority of infants, and percentage of stools in each category shows the specific types of stools experienced. The three measures of stool consistency from the present studies show a clear pattern that stools associated with formula A were softer than those associated with formula B, that the predominant consistency for the majority of infants fed formula A were loose/mushy or soft, and that loose/mushy and soft stools were the consistencies experienced most frequently in infants fed formula A.

We speculate that the reason for the observed differences in characteristics of stool consistency is the source of lipids. Both formulas contain soy and coconut oils, but differ in the other lipid (high-oleic safflower oil in formula A and palm olein in formula B). Nelson and associates [10,11] found that a palm olein-containing formula was associated with greater fat excretion and less fat absorption than a formula without palm olein. Palm olein is used in infant formulas to provide palmitic acid at a level similar to that in breast milk. However, palmitic acid from palm olein is arranged differently from palmitic acid in breast milk triglyceride and is poorly absorbed.[12–16] Unabsorbed palmitic acid tends to react with calcium to form insoluble soaps, and the level of fecal fatty acid soaps is highly correlated with stool hardness.[17]

The formulas considered in the present studies had similar whey:casein ratios (48:52 vs 60:40); thus, this factor alone is unlikely to explain the difference in stool consistency. In addition, previous studies have shown that whey-predominant formulas and not casein-predominant formulas (formula A) are associated with looser stools.[18,19] The addition of nucleotides in formula A also is an unlikely explanation for the differences in stool consistency. Pickering and colleagues[20] have shown that addition of nucleotides has no impact on stool consistency.

Stool color also differed between infants fed formula A and those fed formula B, but only after breastfed infants were weaned to formula. Infants fed formula A had more brown stools and fewer yellow stools than did those fed formula B, but had a similar number of green stools. The level of iron in whey-predominant formulas affects stool color, with iron-fortified formulas producing a high incidence of green stools compared with low-iron formulas.[8,18] Changes in stool color also are associated with increasing age and the introduction of solid foods.[7] However, both feeding groups in the present studies were fed formulas with similar levels of iron fortification and were similar in age and timing of solid food introduction. Thus, there seems to be no obvious explanation for the difference in stool color.

The findings that formula introduced into the diet of breastfed infants resulted in fewer and firmer stools and produced a change in stool color is consistent with results from previous studies.[7–9,21,22] The results from study 1 extends the previous studies by

demonstrating that there is a progressive change in stool consistency and stool color from exclusive breastfeeding, to weaning, to exclusive formula-feeding. Stools became firmer as infants were weaned from the breast to exclusive formula-feeding. Stool frequency also decreased from exclusive breastfeeding to weaning. When formula was introduced, stools became less yellow and more green and brown. It also is apparent that age at weaning affects measures of tolerance. That infants weaned to formula at a later age have less frequent stools is consistent with results from previous studies.[7,9,22,23] Infants weaned at an earlier age also had a higher percentage of feedings with spit-up or vomit than did infants weaned after 2 months of age. These data shed light on the types of changes mothers can expect when their infants are weaned from breast milk to formula.

The results reported here have important implications for infant feeding practices. The pattern of softer stools associated with formula A, including the greater frequency of stooling among infants weaned from breast milk to formula A, in contrast to formula B, is remarkably similar to the stool pattern of the exclusively breastfed infant. Thus, the use of formula A may facilitate a smoother transition from breast milk to formula-feeding than the use of other formulas that produce firmer stools. Moreover, formula A may be perceived by mothers to be less "constipating." Although this term is not well-defined,[24] parents most often associate reduced frequency of stooling, firmer stools, and the inability or difficulty to pass stools with constipation.[25] Perceived bowel dysfunction in infancy, particularly among those fed formula, is a common cause of parental anxiety.[26] Furthermore, the widespread use of low-iron formulas often is attributed to the belief that iron contributes to constipation and/or other gastrointestinal problems despite the evidence to the contrary.[27,28] If parents view formula A as less constipating, this could reduce concerns regarding iron-fortified formulas and help eliminate the use of low-iron formulas.

Notably, the results presented reflect infants' tolerance to the powdered form of iron-fortified infant formula. Additional research is needed to determine whether other forms of formula (concentrated liquid and ready-to-feed) produce similar results. Nevertheless, it is important for those making decisions concerning infant feeding to be aware that infants can have different tolerances to formulas. These differences should be considered when selecting the appropriate formula for infants.

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