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Breastfeeding and Infant Growth: Biology or Bias?

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ABSTRACT. ***Background.*** **Available evidence suggests that prolonged and exclusive breastfeeding is associated with lower infant weight and length by 6 to 12 months of age. This evidence, however, is based on observational studies, which are unable to separate the effects of feeding mode per se from selection bias, reverse causality, and the confounding effects of maternal attitudinal factors.**

Design/Methods. **A cluster-randomized trial in the Republic of Belarus of a breastfeeding promotion intervention modeled on the World Health Organization (WHO)/UNICEF Baby-Friendly Hospital Initiative versus control (then current) infant feeding practices. Healthy, full-term, singleton breastfed infants (n = 17 046) weighing ≥2500 g were enrolled soon after birth and followed up at 1, 2, 3, 6, 9, and 12 months old for measurements of weight, length, and head circumference. Data were analyzed according to intention-to-treat, while accounting for within-cluster correlation. To assess the potential for bias in observational studies of breastfeeding, we also analyzed our data as if we had conducted an observational study by ignoring treatment, combining the 2 randomized groups, and comparing 1378 infants weaned in the first month and those breastfed for the full 12 months of follow-up with either ≥3 months (n = 1271) or ≥6 months (n = 251) of exclusive breastfeeding.**

Results. **Infants from the experimental sites were significantly more likely to be breastfed (to any degree) at 3, 6, 9, and 12 months and were far more likely to be exclusively breastfed at 3 months (43.3% vs 6.4%). Mean birth weight was nearly identical in the 2 groups (3448 g, experimental; 3446 g, control). Mean weight was significantly higher in the experimental group by 1 month of age (4341 vs 4280 g). The difference increased through 3 months (6153 g vs 6047 g), declined slowly thereafter, and disappeared by 12 months (10564 g vs 10571 g). Analysis by z scores confirmed that infants in both groups gained more weight than the WHO/Centers for Disease Control and Prevention reference, with no evidence of undernutrition in the control group. Length followed a similar pattern. In the observational analyses, infants weaned in the first month were slightly lighter and shorter at birth and their weight-for-age and length-for-age z scores declined by 1 month, but they caught up to both experimental and the other observational groups by 6 months and were heavier and longer by 12 months. Among infants in the 2 prolonged and exclusive breastfeeding groups, weight-for-age z scores fell slightly between 3 and 12 months; length-for-age fell below the reference by 6 months with catch-up to the reference by 12 months. Head circumference showed no significant differences at any age between the 2 trial groups or among the observational groups.**

Conclusions. **Our data, the first in humans based on a randomized experiment, suggest that prolonged and exclusive breastfeeding may actually accelerate weight and length gain in the first few months, with no detectable deficit by 12 months old. These results add support to current WHO and UNICEF feeding recommendations. Our observational analysis showing faster weight and length gains with early weaning and slower gains with prolonged and exclusive breastfeeding may reflect unmeasured confounding differences or a true biological effect of formula feeding.** ***Pediatrics*** **2002;110:343–347;** ***breastfeeding, infant growth, infant nutrition, randomized, controlled trial.***

ABBREVIATIONS. WHO, World Health Organization; CDC, Centers for Disease Control and Prevention; PROBIT, Promotion of Breastfeeding Intervention Trial.

Infants following World Health Organization (WHO) recommendations for prolonged and exclusive breastfeeding appear to show a fall-off in weight and length in the first year of life compared with the existing WHO/Centers for Disease Control and Prevention (CDC) reference,[1] which is based on predominantly formula-fed infants. Previous studies are fairly consistent in showing a downward trajectory in z scores beginning at 2 or 3 months until ~12 months, with considerable but not complete catch-up by the age of 24 months.[2–11] The data for length-for-age z scores generally follow the same pattern, although the magnitude of the z score deficit for length is lower.[2–11] Based on this evidence, WHO is currently developing a new international infant growth reference based on infants who follow WHO feeding recommendations.[12,13]

Is the robust association between prolonged, exclusive breastfeeding and reduced growth causal? All the existing evidence is based on observational studies with considerable potential for bias, including confounding, reverse causality, and selection bias. With respect to confounding, breastfeeding

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mothers in developed countries differ considerably from formula-feeding mothers. In particular, they tend to be of higher socioeconomic status and may therefore be more "nutrition-conscious."[14] As a result, they may be more aware of the risks of obesity and hence less likely to overfeed their infants independently of the choice of feeding mode. Reverse causality can create a bias in the opposite direction: slow-growing infants who are "falling off" their growth curve trajectories may be deliberately supplemented or weaned in an effort to reverse those trends. If the supplementation or weaning does not lead to catch-up growth, it may be wrongly "blamed" for the continued poor growth.

Selection bias is another concern. Breastfeeding is a "1-way street"; once breastfed infants are weaned, they seldom, if ever, return to breastfeeding.[15,16] Fast-growing infants may tax their mothers' milk supply; their hunger may then lead to crying and poor sleeping, which may subsequently lead to supplementation. Once supplementation begins, the writing is on the wall for some infants, leading to reduced suckling, a reduced milk supply, and the hastening of weaning. Thus, infants who continue breastfeeding may be a select subgroup whose modest growth does not tax their mothers' milk supply.

The best solution to these problems of confounding, reverse causality, and selection biases is a randomized, controlled trial with intention-to-treat analysis. In the remainder of this study, we describe the methods and results of such a trial, which is to our knowledge the first attempted.

METHODS

Promotion of Breastfeeding Intervention Trial (PROBIT) is a cluster-randomized trial in the Republic of Belarus.[17] The clusters that served as units of randomization (and intervention) consisted of maternity hospitals and their affiliated polyclinics (outpatient clinics where the children are followed for routine health care). Cluster randomization was preferred over individual randomization in this trial, because randomizing individual women within the same maternity hospital to different interventions would inevitably have led to "contamination" and consequent dilution of the effect of the intervention. For maternity hospitals in the largest cities (Minsk, Brest, Vitebsk, and Mogilev) affiliated with 2 or more polyclinics, enrollment was restricted to infants followed at a single polyclinic to simplify the intervention and follow-up procedures. We anticipated enrolling between 250 and 1000 mother-infant pairs per maternity hospital. Thirty-two hospitals were calculated to provide over 80% power to detect a decrease from 60% to 54% in incidence of 1 or more episodes of gastrointestinal infection, the primary outcome for PROBIT. The estimated total sample size was 15 000 to 20 000. One of 32 study sites was removed from the trial because of documented falsification of outcome data, leaving a sample size of 17 046 randomized mother-infant pairs.[17]

The experimental intervention was based on the WHO/UNICEF Baby-Friendly Hospital Initiative,[18] which comprises 10 steps that maternity hospitals must implement to become certified as "baby friendly." Details of the study methods and infant illness outcomes are outlined in our previous report.[17] In brief, the WHO/UNICEF 18-hour Baby-Friendly Hospital Initiative training course was provided to the chief obstetrician at the maternity hospital and the chief pediatrician at the corresponding polyclinic. Those physicians then embarked on a 1-year program of training all medical and nursing staff at both sites. The control intervention consisted of the continued current maternity hospital and polyclinic practices that existed at the time of randomization, which were characterized by delayed onset of breastfeeding, routine separation of mother and infant, scheduled feeding, frequent supplementation with formula and other liquids, and early introduction of solid foods. Monitoring visits were conducted both before and during recruitment and again during the follow-up to ensure compliance with and maintenance of the practices and policies specified by the experimental and control interventions.

Healthy newborns weighing at least 2500 g at birth were enrolled during their postpartum hospital stay. Follow-up data forms were completed at polyclinic visits at 1, 2, 3, 6, 9, and 12 months; at each of these visits, data were obtained on infant feeding, infections, and rash, and measurements were obtained of weight, length, and head circumference. Because differences in growth were not major hypotheses of PROBIT (which focused on reduced infection and atopic eczema),[17] no attempts were made to standardize measurements of weight, length, and head circumference among the study sites. As previously reported, random audits at all 31 participating polyclinics showed excellent concordance between the data recorded on the PROBIT data sheets and both the polyclinic charts and maternal interviews.[17] For continued breastfeeding at 3 months, for example, the κ values (and 95% confidence intervals) were 0.93 (0.88–0.98) and 0.91 (0.87–0.96) for the polyclinic charts in the experimental and control groups, respectively, and 0.89 (0.81–0.97) and 0.94 (0.89–0.99) for the maternal interviews.[17]

Study sites were stratified by region (West [Brest and Grodno regions] vs East [all other regions]) and urban versus rural location, because women in the West and in rural areas have traditionally breastfed for longer and more exclusively than those in the East and those in urban regions. Weight-for-age and length-for-age z scores were based on the WHO/CDC reference and calculated using EpiInfo 2000 (CDC, Atlanta, GA), where

$$z = \frac{\text{observed value} - \text{reference mean}}{\text{reference standard deviation}}$$

Statistical analysis was based on intention-to-treat, while accounting for the cluster as the unit of randomization and adjustment for both cluster-level (East vs West region, urban vs rural location, study site) and individual-level (maternal education and birth anthropometric measures) covariates using a repeated-measure multilevel regression model with an autoregressive covariance structure (PROC MIXED in SAS, version 8.2) (SAS Institute, Cary, NC). Baseline characteristics of the 2 trial groups were compared using PROC MIXED to account for intracluster correlation and the variable number of infants per cluster.

To assess the potential for confounding, reverse causality, and selection bias, we also analyzed the data as if we had conducted an observational study, ie, ignoring treatment by combining the 2 randomized groups. Infants who were weaned in the first month ($n = 1378$) were used to approximate a formula-fed cohort. We compared this early weaning group with 2 overlapping (ie, nonmutually exclusive) groups: 1 exclusively breastfeeding for ≥3 months with continued breastfeeding (to some degree) for ≥12 months ($n = 1271$), and the other exclusively breastfeeding for ≥6 months with continued breastfeeding (to some degree) for ≥12 months ($n = 251$). These latter 2 groups are not mutually exclusive but were defined deliberately to approximate the then current feeding recommendations of WHO and UNICEF, respectively. The data were analyzed using the same multivariate mixed model as for the intention-to-treat (experimental) approach described above.

RESULTS

As shown in Table 1, randomized allocation resulted in similar gestational age, birth weight, birth

TABLE 1. Baseline Comparison of Study Infants in Trial

Variable	Control ($n = 8181$)	Experimental ($n = 8865$)
Gestational age (wk)	39.3	39.4
Birth weight (g)	3446	3448
Birth length (cm)	52.2	51.9
Birth head circumference (cm)	34.8	35.1
5-min Apgar score	8.5	8.6
Male sex (%)	51.6	51.8

TABLE 2. Effect of Intervention on Weight (g)

Age	Control (n)	Experimental (n)	Difference	P Value
1 mo	4280 (8062)	4341 (8630)	61	.001
2 mo	5170 (7961)	5258 (8459)	88	<.001
3 mo	6047 (8009)	6153 (8620)	106	<.001
6 mo	8042 (7896)	8131 (8509)	89	<.001
9 mo	9451 (7750)	9509 (8339)	58	.002
12 mo	10571 (7918)	10564 (8553)	−7	.726

TABLE 3. Effect of Intervention on Length (cm)

Age	Control (n)	Experimental (n)	Difference	P Value
1 mo	54.63 (8062)	54.79 (8618)	0.16	.258
2 mo	57.57 (7959)	57.89 (8412)	0.32	.030
3 mo	60.63 (8007)	61.13 (8619)	0.50	.001
6 mo	66.90 (7893)	67.36 (8504)	0.46	.002
9 mo	71.62 (7749)	71.93 (8333)	0.31	.039
12 mo	75.75 (7918)	75.93 (8551)	0.18	.226

length, birth head circumference, 5-minute Apgar score, and sex distribution in the 2 treatment groups. Overall, only 3.3% of study infants were lost to complete follow-up.[17]

As reported previously,[17] the experimental intervention was highly successful in prolonging the duration of any breastfeeding. Substantial and highly significant differences of ~12% or 13% in the proportion of infants still breastfeeding (to any degree) were seen by the second or third month and continued throughout the 12 months of follow-up. The intervention was particularly effective in increasing the degree of breastfeeding. The proportion of women who were exclusively breastfeeding was sevenfold higher in the experimental group at 3 months (43.3 vs 6.4%; $P < .001$ by unpaired t test) and >12-fold higher at 6 months (7.9 vs 0.6%; $P < .01$).

Table 2 shows the results for weight in grams. The weight in the experimental group exceeded that of the control group by 61 g at 1 month, and the difference increased through 3 months, declined somewhat thereafter, and then disappeared by 12 months. As shown in Fig 1, weight-for-age z scores were well above the reference mean of 0 and rose throughout the first year in both trial groups, indicating that the observed differences in weight did not reflect undernutrition in the control group. For the 2 prolonged and exclusive breastfeeding (observational) groups, weight-for-age z scores exceeded those in the 2 trial groups until 3 months, after which they fell progressively below the trial groups. Mean weight-for-age among infants weaned within the first month fell substantially by 1 month but then rose quickly to catch up to the other groups by 6 months and even exceed the other groups by 12 months.

Table 3 and Fig 2 show the corresponding results for length and length-for-age z score, respectively. Length-for-age showed a similar pattern to that seen for weight-for-age, except that the 2 prolonged and exclusive breastfeeding groups actually fell below the reference value at 6 months, with subsequent catch-up to the reference by 12 months. As shown in Table 4, we found no significant differences in head circumference at any age between the 2 trial groups. Nor did we observe any significant differences in head circumference among the early weaned group and either of the prolonged and exclusive breastfeeding observational groups (observational data not shown).

DISCUSSION

As reported previously, the experimental intervention, which was based on the WHO/UNICEF Baby-Friendly Hospital Initiative, succeeded in increasing

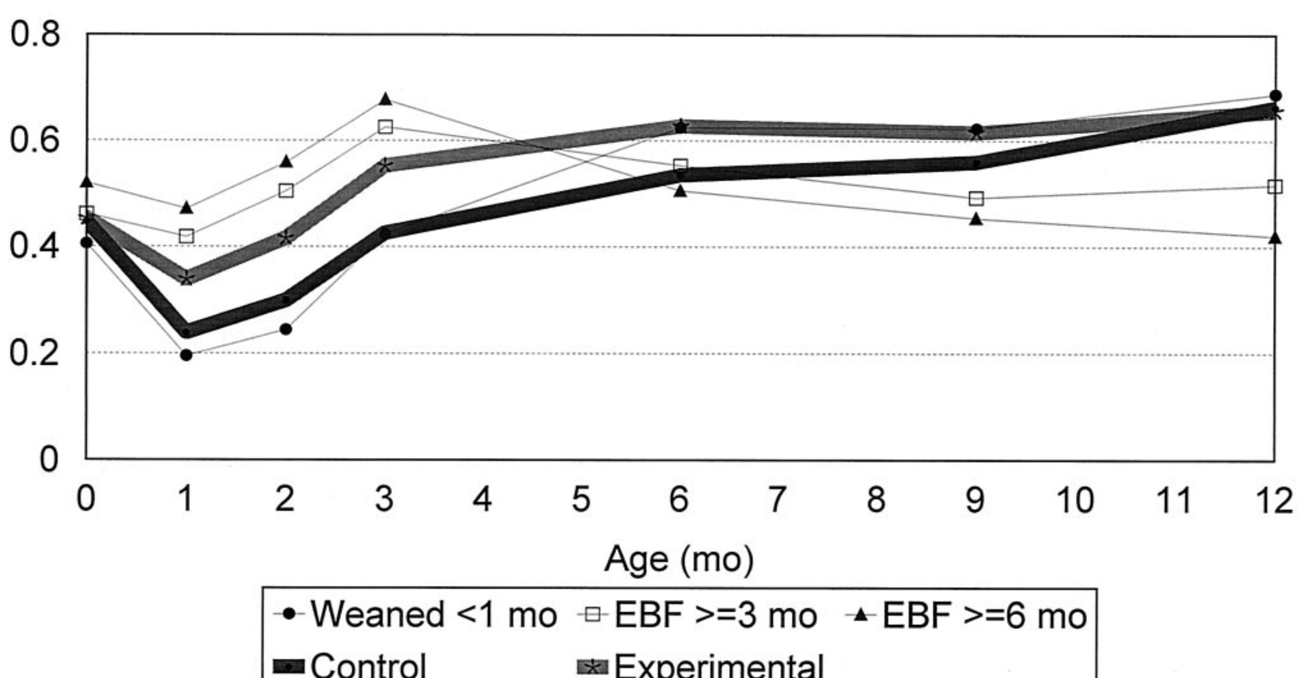

Fig 1. Weight-for-age z score in experimental versus control trial groups and 3 observational groups.

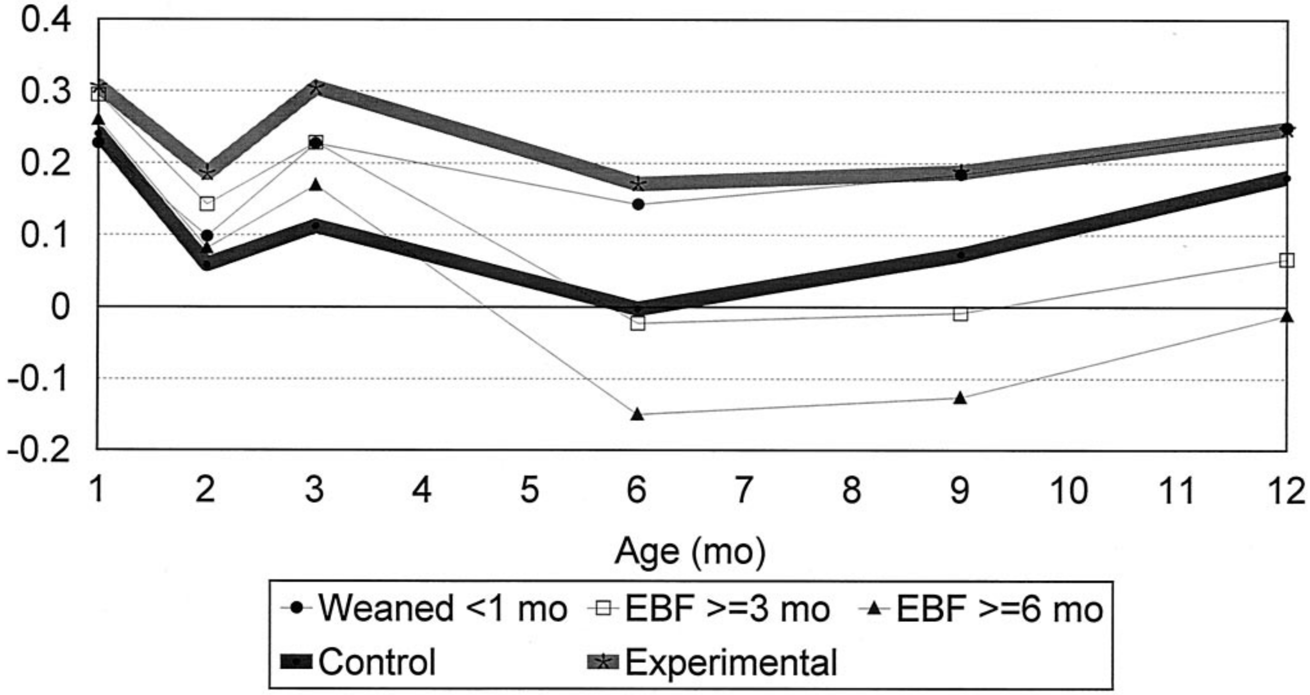

Fig 2. Length-for-age *z* score in experimental versus control trial groups and 3 observational groups.

TABLE 4. Effect of Intervention on Head Circumference (cm)

Age	Control (*n*)	Experimental (*n*)	Difference	*P* Value
1 mo	37.09 (8061)	37.28 (8592)	0.19	.287
2 mo	38.71 (7959)	38.89 (8431)	0.18	.313
3 mo	40.29 (8006)	40.47 (8608)	0.18	.301
6 mo	43.22 (7894)	43.36 (8477)	0.14	.394
9 mo	45.37 (7748)	45.35 (8317)	−0.02	.925
12 mo	47.08 (7915)	46.90 (8541)	−0.18	.303

both breastfeeding duration and exclusivity.[17] The intervention also resulted in higher infant weight and length gain in the first 3 months but no discernible differences by 12 months old. Our observational analysis suggests that prolonged and exclusive breastfeeding led to slower weight and length gains between 3 and 12 months, while remaining, on average, at or above the WHO/CDC reference.

Previous observational studies have reported reduced weight gain and length gain in infants who receive exclusive and prolonged breastfeeding.[2–11] Infants in our experimental group, however, grew faster than those in our control group; the *z* score results clearly demonstrate that the observed differences were not attributable to undernutrition in the controls. The difference in growth between the 2 trial groups may reflect the sevenfold higher proportion of experimental versus control infants who were exclusively breastfed at 3 months and the previously reported acceleration in growth from birth to 3 months among exclusively breastfed infants.[2–11] It is important to emphasize that our randomized treatment allocation obligates an intention-to-treat analysis, and thus the observed differences between the 2 randomized groups are likely to be small. These differences represent the best estimates of the expected average effects on growth of the experimental breastfeeding promotion intervention. But because of the substantial overlap in breastfeeding duration and exclusivity in the 2 randomized groups, these average effects substantially underestimate the differences in outcome caused by prolonged, exclusive breastfeeding (vs a shorter duration and/or lesser exclusivity). The magnitude of the causal effects on growth attributable to breastfeeding duration and exclusivity cannot be estimated without bias, however, because it was not the breastfeeding behavior itself that was randomized—only the exposure to the experimental versus control intervention.

In contrast, the observational results in infants weaned within the first month suggest that these infants were selected by virtue of their falling growth trajectories, ie, the mother's and/or physician's decision to wean was likely related to the perception of insufficient growth. Nonetheless, these infants grew faster in weight and length even beyond the time of "catch-up," suggesting either intentional overfeeding by their mothers to promote maximal growth or a true biological effect of formula feeding (with supplementation by solids) in accelerating growth trajectories in the first 12 months of life.[19] Similarly, those infants with prolonged and exclusive breastfeeding showed growth patterns similar to those reported in previous observational studies,[2–11] with a rise in weight-for-age and length-for-age *z* scores through 3 months and a fall thereafter. Unlike previous reports, however, the *z* scores for weight-for-age never fell below 0 (the mean of the WHO/CDC reference), and those for length-for-age caught up to the reference by 12 months. Again, these data cannot distinguish whether the observed growth trajectories represent a true biological effect of prolonged breastfeeding or are confounded by other differences, eg, a (hypothetical) preference for thinner infants among mothers who practice exclusive and prolonged breastfeeding. Nonetheless, the consistency of the growth trajectories during the first 3 months between the experimental group from the trial and the 2 observational groups with prolonged and exclusive breastfeeding seem more consistent with a true biological effect.

Several limitations of our study require discussion. First, anthropometric measurements were not standardized among study sites (see "Methods") and probably led to increased (random) error in measuring weight, length, and head circumference. This lack of standardization should therefore have been nondifferential with respect to the study intervention and biased the results toward the null, ie, toward finding no differences between the experimental and control groups and among the 3 "observational" groups. Second, although the infants in both trial groups grew at rates exceeding those of the WHO/CDC reference, cultural factors affecting infant feeding in Belarus may differ from other developed countries, particularly those in the West, and may therefore limit the generalizability of our findings. Nonetheless, our results offer no support to the prevailing premise that prolonged and exclusive breastfeeding inexorably leads to deficits in weight and length during the first year of life. Instead, our results showing faster weight and length gains in infants exposed to the experimental intervention support the current WHO and UNICEF recommendations for prolonged and exclusive breastfeeding.

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REFERENCES

1. US Department of Health Education and Welfare. *NCHS Growth Curves for Children, Birth–18 Years*. Washington, DC: US Department of Health Education and Welfare; 1977. DHEW Publication (PHS) 78-1650
2. Whitehead R, Paul A. Growth charts and the assessment of infant feeding practices in the western world and in developing countries. *Early Hum Dev.* 1984;9:187–207
3. Hitchcock N, Gracey M, Gilmour A. The growth of breast fed and artificially fed infants from birth to twelve months. *Acta Paediatr Scand.* 1985;74:240–245
4. Dewey K, Heinig M, Nommsen L, Peerson J, Lonnerdal B. Growth of breast-fed and formula-fed infants from 0 to 18 months: the DARLING study. *Pediatrics.* 1992;89:1035–1041
5. Whitehead R, Paul A, Cole T. Diet and the growth of healthy infants. *Nutr Diet.* 1989;2:83–84
6. Salmenpera L, Perheentupa J, Siimes M. Exclusively breast-fed healthy infants grow slower than reference infants. *Pediatr Res.* 1985;19:307–312
7. Persson L. Infant feeding and growth—a longitudinal study in three Swedish communities. *Ann Hum Biol.* 1985;12:41–52
8. Dewey K, Peerson J, Brown K, et al. Growth of breast-fed infants deviates from current reference data: a pooled analysis of US, Canadian, and European data sets. *Pediatrics.* 1995;96:495–503
9. Nielsen G, Thomsen B, Michaelsen K. Influence of breastfeeding and complementary food on growth between 5 and 10 months. *Acta Paediatr.* 1998;87:911–917
10. Hediger M, Overpeck M, Ruan W, Troendle J. Early infant feeding and growth status of US-born infants and children aged 4–71 mo: analyses from the third National Health and Nutrition Examination Survey, 1988–1994. *Am J Clin Nutr.* 2000;72:159–167
11. Haschke F, van't Hof M. Euro-growth study groups. Euro-Growth references for breast-fed boys and girls: influence of breast-feeding and solids on growth until 36 months of age. *J Pediatr Gastroenterol Nutr.* 2000;31:S60–S71
12. de Onis M, Garza C, Habicht J. Time for a new growth reference. *Pediatrics.* 1997;100(5). Available at: www.pediatrics.org/cgi/content/full/100/5/e8
13. WHO Working Group on the Growth Reference Protocol and WHO Task Force on Methods for the Natural Regulation of Fertility. Growth patterns of breastfed infants in seven countries. *Acta Paediatr.* 2000; 89:215–222
14. Bauchner H, Leventhal J, Shapiro E. Studies of breast-feeding and infections: how good is the evidence? *JAMA.* 1986;256:887–892
15. Hill A. *A Short Textbook of Medical Statistics*. London, England: Hodder & Stoughton; 1977
16. Sauls H. Potential effect of demographic and other variables in studies comparing morbidity of breast-fed and bottle-fed infants. *Pediatrics.* 1979;64:523–527
17. Kramer MS, Chalmers B, Hodnett ED, et al. Promotion of breastfeeding intervention trial (PROBIT): a randomized trial in the Republic of Belarus. *JAMA.* 2001;285:413–420
18. WHO/UNICEF. *Protecting, Promoting and Supporting Breastfeeding: The Special Role of Maternity Services*. Geneva, Switzerland: World Health Organization; 1989
19. Hörnell A, Hofvander Y, Kylberg E. Solids and formula: association with pattern and duration of breastfeeding. *Pediatrics.* 2001;107(3). Available at: www.pediatrics.org/cgi/content/full/107/3/e38