Randomised trial of a ready-to-feed compared with powdered formula

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Abstract

Forty three infants were assigned randomly to a ready-to-feed infant formula or a standard formula that required reconstitution from powder. Despite similar nutrient composition of the two formulas those fed the powdered formula had significantly increased body weight and skinfold thickness gains, and became significantly heavier than a further group of 20 breast fed infants by 3 and 6 months. Of those fed the powdered formula 6/19 had become overweight (above the 90th or 97th centile) by 6 months, whereas 1/19 fed the ready-to-feed product was overweight at this age. While differences in fat absorption might have been contributory, our data suggest that errors in reconstitution of formula from powder might be the main cause for the growth differences observed. If it is appropriate to take the breast fed infant as a model, infants fed ready-to-feed formula in this study showed a more physiological pattern of growth than those fed a standard formula reconstituted from powder. These results require replication using other formulas as the findings have potentially important implications for infant feeding.

In some countries infant formulas are presented in liquid form either as a concentrate, requiring dilution, or as a ready-to-feed formulation. In Britain powdered formulas have been used traditionally. Ready-to-feed products are beginning to be introduced into this country, yet there are few clinical trial data on their use. It cannot be assumed that the physiological response in the infant fed these products would necessarily be the same as that found with standard powdered formulas. Heat treatment of a liquid preparation is different from that used for a powder and this might influence biological properties of the milk. Furthermore, reconstitution errors, reported first by Taitz and Byers in 1972,[1] by us,[2] and in a number of other studies on powdered formulas,[3–6] would not occur in a ready-to-feed diet.

In a trial on 43 babies whose mothers had already chosen to bottle feed, we randomly assigned the infants to a ready-to-feed, ultra high temperature (UHT) treated formula or to a standard powdered formula of the same macronutrient composition. As a part of this study we have examined the growth of these babies in the first six months of life and our findings are reported here.

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Subjects and methods

In all, 43 healthy term infants were recruited for study after their delivery in the Rosie Maternity Hospital in Cambridge. The parents were approached on the postnatal ward within 72 hours of delivery only when the mother had already made a firm decision to bottle feed and had commenced doing so. The study was approved by the ethical committees of the Cambridge Health Authority and the Medical Research Council's Dunn Nutrition Unit.

Infants were assigned randomly to diet group using sealed envelopes. Randomisation was based on permuted blocks of variable length and was stratified by sex to ensure a similar sex distribution in each feed group. No infant with a birth weight outside 2 SDs from the mean was included (using Gairdner-Pearson reference data[7]). Of the infants studied, 21 were assigned to a ready-to-feed, UHT treated formula ('First' infant formula, Young Nutrition Ltd) and 21 were assigned a standard powdered formula available in Britain. The diets were very similar in nutrient composition both providing 1·5 g protein/100 ml and 67–68 kcal (280–284 kJ)/100 ml (see table 1 for macronutrient composition). In view of the difference in presentation of the two diets and the need to provide different instructions for their use it was not possible for

Table 1 Composition of the two formulas

Constituents/100 ml	*Powder formula*	*Ready-to-feed formula*
Macronutrients:		
Protein (g)	1·5	1·5
Casein:whey ratio	40:60	40:60
Fat (g)	3·6	3·6
Carbohydrate (g)	7·3	7·2
Type:	100% lactose	100% lactose
Energy (kcal)*	67·6	67·2
Potential renal solute load (mosmol/l)	97	100
Minerals:		
Sodium (mg)	18	19
Chloride (mg)	40	40
Potassium (mg)	65	80
Calcium (mg)	54	40
Phosphorus (mg)	27	34
Magnesium (mg)	5	6
Iron (mg)	0·5	0·7
Copper (μg)	40	40
Zinc (mg)	0·4	0·4
Iodine (μg)	7	7
Vitamins		
A (retinol, μg)	80	80
B1 (thiamin, μg)	40	60
B2 (riboflavin, μg)	100	130
Niacin (mg)	0·4	0·5
B6 (pyridoxine, μg)	40	50
B12 (cyanocobalamin, μg)	0·2	0·2
Folic acid (μg)	10	10
Pantothenic acid (mg)	300	230
Biotin (μg)	1·5	1·2
C (ascorbic acid, mg)	8	8
D3 (cholecalciferol, μg)	1·1	1·0
E (d-α-tocopherol, mg)	1·1	1·0
K (phytomenadione, μg)	5	5

*100 kcal=418 kJ.

the principal field worker (SL) to be blind to dietary assignment.

Infants were monitored at recruitment and at 1, 2, 4, 6, 10, 12, and 26 weeks of age. Further data are being collected currently beyond this period. Monitoring at one or more of these periods included (i) collection of demographic and clinical data; (ii) use of the doubly labelled water method to measure total energy expenditure and energy intake; (iii) measurement of sleeping energy expenditure by indirect calorimetry; (iv) measurement of activity using actometers; (v) assessment of bowel habit, stool volume, and stool consistency; (vi) bacteriological monitoring of the milks when prepared for use; (vii) collection of data on the accuracy of feed reconstitution in the powder formula fed group[2]; and (viii) application of detailed questionnaires to parents. Anthropometry (the focus of this paper) was performed at all the above time periods and included measurement of body weight to the nearest 10 g (using a Seca instrument, model 724), length to the last completed mm (using a Holtain Infantometer), head circumference to the last completed millimetre (using paper tape), and triceps and subscapular skinfold thickness to the nearest 0·1 mm (using Holtain skinfold calipers).

Statistical comparisons were made using Student's *t* test.

Results

There was no difference in mean (SE) birth weight or gestation between infants fed ready-to-feed milk and those fed powdered formula: respectively 3440 (110) g compared with 3480 (100) g and 40·0 (0·2) weeks and 39·5 (0·3) weeks. Both groups had similar numbers of boys and girls. All infants were born vaginally and none had severe birth asphyxia (Apgar score <5 at 5 minutes). One infant, on powdered milk, dropped out of the study at 1 week on account of kidney disease and data are not included in the analyses. Four further infants dropped out as a result of the parents' wish to change formula between 3 weeks and 6 months, three in the ready-to-feed milk group and one on powdered formula (difference in drop out rate not significant). The wish to change formula was no different from that expected from our previous field studies and was usually attributed to minor feeding problems, including possetting. Thus, by 6 months, there were 19 infants in each feed group.

Figure 1 shows the longitudinal changes in weight length, head circumference, and skinfold thickness (triceps plus subscapular). Only weight was recorded at birth; the other measurements were recorded from one week onwards. While length and head size followed a very similar pattern in the two groups, the infants fed the powdered formula developed a higher body weight and skinfold thickness during the first six months. Although the difference between groups in body weight and skinfold, shown in fig 1, did not reach significance at the 5% level at any individual time point, there were significantly faster increments in these measurements during the six month period (see table 2).

Longitudinal changes in SD scores for body weight are shown (both sexes combined) in fig 2. These were calculated (courtesy of Drs T Cole and A Paul) using the Cambridge reference growth centiles for normal infants.[8] Though infants fed the ready-to-feed milk had weight SD scores that remained close to or slightly above 0 (50th centile), the infants fed the powdered formula had a mean SD score which rose to over 0·6 by 6 months (close to the 75th centile). SD scores for head size and body length were generally close to 0 and not different between feed groups.

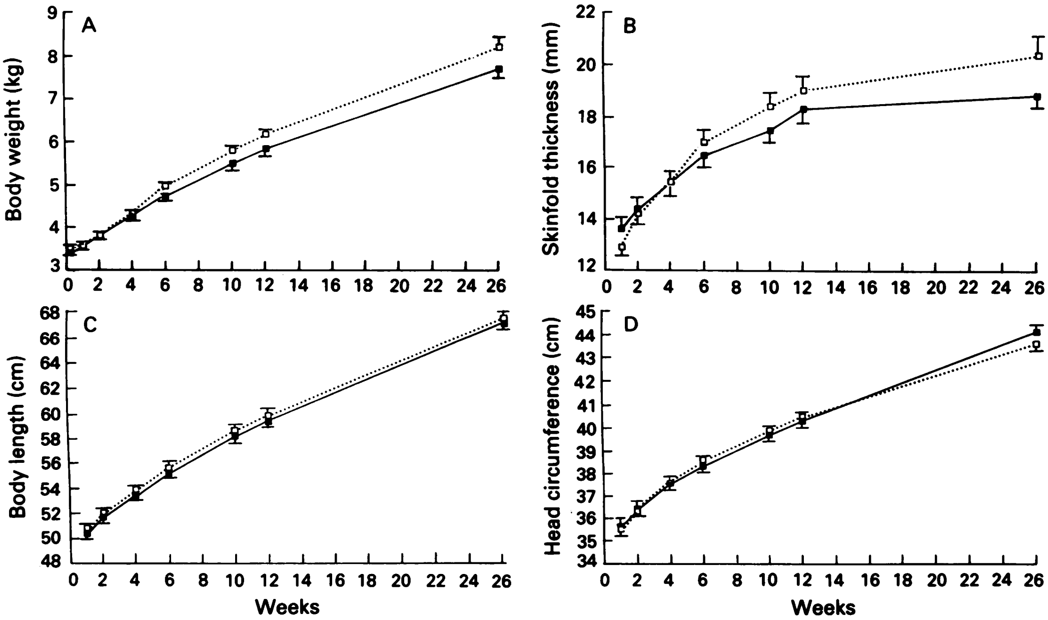

Figure 1 Longitudinal pattern of growth in infants fed a ready-to-feed formula (closed squares, solid line) or reconstituted powdered formula (open squares, dotted line): (A) body weight, (B) triceps plus subscapular skinfold, (C) length, and (D) head circumference. Data are mean (SE).

Mean data for body weight in 20 breast fed babies that we recruited.[9 10] in the same catchment areas at 6, 12, and 26 weeks were compared with corresponding values from babies in the two formula fed groups in this study (see table 3). There were no differenes in body weight at these three ages between breast fed babies or those fed ready-to-feed formula. However, at both 12 and 26 weeks, babies fed the powdered formula were significantly heavier than those who had been breast fed.

Table 4 shows that by 6 months, six out of 19 babies fed on the powdered formula were overweight (>90th or 97th centile for by weight with normal lengths) compared with only one baby in the ready-to-feed formula group. The six babies who became overweight in the powdered formula fed group had a mean (SE) birth weight of 3497 (20) g, which was no different from the mean birth weight of the remaining infants in that feed group.

Milk volume intake on the two formulas was obtained by weighing all formula consumed for a one week period at 5 weeks and again at 11 weeks. There was no significant difference in formula intake at either period (table 5).

We explored the possibility that the greater body weight gain in the powdered formula group was related to formula reconstitution errors. On average on five occasions, at about two weekly intervals, the field worker on this project (SL) obtained a bottle of reconstituted formula provided by mothers whose babies were in the powdered milk group. The mothers were unaware of the purpose of this sampling. Milk potassium concentration was used to calculate formula strength, expressed in terms of kcal per 100 ml of formula (expected value was 68 kcal (284 kJ)/100 ml). These data have been published,[2] but were re-examined in this study in relation to the attained body weight at 26 weeks in the powder formula group. Eighteen of the subjects had both a weight measurement at 6 months and an estimate of average milk energy based on the mean of the samples taken. A linear relationship between body weight at 6 months and the average milk energy did not reach significance at the 5% level. When subjects were divided, however, into two groups, the heaviest and lightest babies, milk energy was found to be significantly higher in the heaviest babies (see table 6).

Table 2 Increments in body weight and skinfold thickness (triceps plus subscapular) in 19 infants fed a ready-to-feed (RTF) formula versus 19 fed a powdered formula. Data are mean (SE)

(A) Body weight increment

Age range (weeks)	*Diet group*	*Total gain for period (kg)*	*Average gain/ day (g)*	*Significance (p value)*
1–6	RTF	1·16 (0·07)	33 (2)	0·003
	Powder	1·42 (0·04)	41 (1)	
1–12	RTF	2·25 (0·08)	29 (1)	0·03
	Powder	2·60 (0·08)	34 (1)	
1–26	RTF	4·13 (0·18)	24 (1)	0·06
	Powder	4·67 (0·18)	27 (1)	

(B) Skinfold thickness increment

Age range (weeks)	*Diet group*	*Total gain for period (mm)*	*Average gain day (g)*	*Significance (p value)*
1–6	RTF	2·9 (0·4)	0·58 (0·07)	0·04
	Powder	4·0 (0·4)	0·81 (0·08)	
1–12	RTF	4·5 (0·5)	0·41 (0·04)	0·05
	Powder	6·0 (0·5)	0·54 (0·05)	
1–26	RTF	5·4 (0·5)	0·21 (0·02)	0·02
	Powder	7·5 (0·7)	0·30 (0·03)	

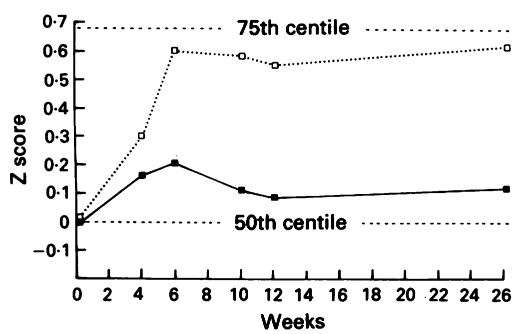

Figure 2 Longitudinal change in weight Z score (derived from Cambridge reference data[8]) for infants fed a ready-to-feed formula (closed squares, solid line) or a reconstituted powdered formula (open squares, dotted line).

Table 3 Body weight compared in breast fed infants and in those fed ready-to-feed or powdered formula. Data in kg are expressed as mean (SE)

Age (weeks)	*Breast fed (n=20)*	*Ready-to-feed (n=19)*	*Powder (n=19)*
6	4·79 (0·09)	4·76 (0·13)	4·98 (0·10)
12	5·78 (0·09)	5·83 (0·15)	6·16* (0·15)
26	7·55 (0·17)	7·70 (0·18)	8·21* (0·29)

*p<0·05 for comparison of breast fed *v* powdered formula fed.

Table 4 Infants >90th centile of weight for age by 6 months among 19 infants fed ready-to-feed formula and 19 infants fed a powdered formula

Diet	*Sex*	*Body weight (kg) at 6 months*	*Centile*
Ready-to-feed formula	F	9·40	>97th
Powder	F	8·82	>90th
Powder	F	9·34	>97th
Powder	F	9·44	>97th
Powder	M	9·55	>90th
Powder	M	9·54	>90th
Powder	F	9·92	>97th

NB. Birth weight of ready-to-feed formula fed baby: 3820 g and mean birth weight of powdered formula fed infants: 3500 (SE 200) g.

Table 5 Mean (SE) milk intakes in g/day by weighing

	Ready-to-feed formula (n=19)	*Powder formula (n=19)*
At 5 weeks	810 (23)	801 (29)
At 11 week	881 (34)	795 (32)*

*Not significant.

*Table 6 Weight at 6 months in relation to strength of reconstitution of powdered formula (as determined by potassium concentration and based on an average of five samples per case taken at intervals of two weeks). Formula strength expressed in kcal/100 ml (SE); manufacturers intended energy content=68 kcal (284 kJ)/100 ml**

Body weight category	*No of subjects*	*Mean body weight in kg (SE)*	*Mean milk energy content in kcal/100 ml (SE)**
<8 kg	9	7·19 (0·17)	67·3 (1·7)
>8 kg	9	9·08 (0·17)	73·3 (1·6)†

*100 kcal=418 kJ.
†Milk energy in >8 kg body weight group significantly higher (p=0·02) than in the <8 kg group.

Discussion

Manufacturers of infant formulas have attempted to copy the macronutrient composition of breast milk. It might be expected therefore that infants fed modern formulas should show patterns of growth, similar to those seen in the breast fed baby. In this randomised study, however, we found that infants fed a standard formula reconstituted from powder had a significantly faster weight gain than that of infants fed a ready-to-feed formula of the same protein and energy content, and with similar contents of other nutrients. That this faster weight gain in the powdered formula fed group reflected greater body fatness was indicated by the higher rate of skinfold thickness gain, while head circumference and length gains were identical on the two formulas. Furthermore, unlike those fed the ready-to-feed formula, the powdered formula group had a higher body weight than that of a reference breast fed group at postnatal ages 3 and 6 months. Also, while only one out of 19 infants fed the ready-to-feed milk was above the 90th centile for weight at 6 months, six out of 19 infants on the powdered formula exceeded this threshold and of these, three were above the 97th centile.

This relatively small study raises a number of questions. Why should two formulas with similar nutrient content but dissimilar preparation and presentation result in such different patterns of growth? What, if any, is the clinical significance of the differences observed; and do these data have potential relevance for the future design of modern infant formulas? With regard to the first question, it is possible that we have observed a chance excess occurrence of overweight infants in the powdered formula group. Against this observation was the fact that the two groups of infants had almost identical mean birth weights, that weight gain was highly significantly greater during the first six weeks (nearly 25% faster) in the powdered formula group, and that the infants on powdered formula that did become overweight by 6 months of age, as a group, did not have higher birth weights than the other infants in the study.

Assuming that the type of formula assigned was the causal factor for the differences in weight gain observed, it is possible that differences in nutrient concentrations between the two formulas were influential. However, all the nutrient concentrations selected fall within the EC guidelines. Protein and energy contents in the two diets were virtually identical, and the concentrations of minerals and micronutrient very similar. There was, however, a difference between formulas in fat blend. Although both formulas contained 3·6 g fat/100 ml and both contained a mixture of vegetable oil and milk fat, the ready-to-feed formula contained a higher proportion of milk fat and therefore, like breast milk, had a higher content of palmitic acid (16:0) and stearic acid (18:0) and a correspondingly lower proportion of oleic acid (18:1) (table 7). Nevertheless, the difference in content of these saturated fatty acids between the ready-to-feed and powdered formula only accounted for about 11% of total fatty acids. If, for instance, there was a 30% decrease in absorption of 16:0 plus 18:0 compared with 18:1, the resultant small decrease in fat absorption in the ready-to-feed formula group (less than 1 g) would theoretically be more than offset by the slightly larger volume (see below) and therefore fat intake in this group, and in any case the decrease would be too small to account for the differences in growth between groups (though data are required on fat balances to reaffirm our calculations).

Table 7 Fatty acid composition of the ready-to-feed and powdered formula

	% Of all fatty acids	
	Ready-to-feed	*Powder*
C4:0 Butyric	3·1	—
C6:0 Caproic	1·8	—
C8:0 Caprylic	1·0	1·5
C10:0 Capric	2·1	1·3
C12:0 Lauric	2·3	9·3
C14:0 Myristic	7·8	4·5
C16:0 Palmitic	22·4	18·1
C18:0 Stearic	11·0	3·9
Other saturated fatty acids	1·1	0·4
C18:1 Oleic	25·3	44·9
C18:2 Linoleic	13·9	11·2
C18:3 α-Linolenic	2·5	2·2
Other unsaturated fatty acids	5·8	2·7

We considered the possibility that the two formulas could have had a differential impact on appetite and that the increased body fatness in the powdered formula group might therefore have been explained if they had consumed an increased volume intake. However, the data obtained by weighing the formula consumed over one week periods did not show a difference in milk volume intake between groups, and indeed the ready-to-feed formula fed infants had, if anything, a higher intake. The required heat treatment of powdered milk is necessarily quite different from that of a liquid. The UHT treatment of the ready-to-feed formula we used here would be less severe and theoretically would be expected to have less damaging effects on biologically important proteins. This might influence digestion or nutrient availability and hence the rate of weight gain.

Our data, however, provide a further, perhaps more plausible explanation for the greater fatness of babies in the powdered formula fed group. We and others have shown previously that reconstitution errors using powdered formula are common, often large, and that individual mothers rank in their tendency to over or under reconstitute the feeds they prepare.[2] Table 4 demonstrates that the heaviest 50% of babies at 6 months in the powdered formula group were given milk containing on average 6 kcal (25 kJ)/100 ml more than that received by the lightest 50% of babies at this age. In the powdered formula group the heavier babies gained weight on average at 10 g/day faster over the first six months than the lighter babies. Assuming that the samples of milk provided by the mother were representative, the heavier babies would have received up to 50 kcal (209 kJ)/day more in their diet which could explain their higher weight gain, assuming around 4 kcal (17 kJ)/g of weight gain based on our data using the doubly labelled water method.[9 10] The difference in weight gain between the babies fed ready-to-feed and powdered milk was 5 g/day averaged over the first three months and 3 g/day over the first six months. This difference could be related, theoretically, to formula reconstitution errors. Our previous work suggests that not all extra energy ingested is stored,[11] but the differences in weight gain between diet groups that we have observed could be explained by a plausible 5–7% increase in powdered formula strength over that in the ready-to-feed product, even if only 30–50% of the extra ingested energy was stored in new tissue.

As a group, babies fed powder formula approached the 75th weight centile by 6 months of age, whereas those fed ready-to-feed formula along with those fed by breast lay close to the 50th centile for this unit's reference data. It might be argued that this difference was not clinically important. Nevertheless, a greater proportion of frankly overweight infants among those given powdered rather than ready-to-feed formula could be regarded as undesirable. The difference between groups in overweight infants (6/19 compared with 1/19), though suggestive, did not reach significance at the 5% level, and a larger sample would be needed to explore this further.

Optimal patterns of growth in infancy are unknown as appropriate long term outcome studies have never been undertaken. In the absence of such data, it seems reasonable to take the breast fed baby as a model for performance. In this study, infants fed a ready-to-feed formula had a pattern of weight gain that closely resembled the physiological pattern seen in breast fed infants. In contrast, use of a powdered formula, perhaps because of the risk of formula reconstitution errors, appeared to be associated with a greater rate of fat deposition. If our data are confirmed, they would indicate a potential advantage for ready-to-feed formulations, though we recognise that currently they are too expensive for many families.

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