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Randomized, double-blind comparison of growth in infants receiving goat milk formula versus cow milk infant formula

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Objective: To compare growth of infants fed goat milk infant formula (GMF) or cow milk infant formula (CMF) and to compare tolerability and safety of the two formulas.

Methods: The study was conducted in Auckland, New Zealand. This was a double-blind randomized controlled trial. Newborn term infants were randomized within 72 h of birth to GMF or CMF. Milk formula powder in single serve sachets were reconstituted and fed to infants from trial commencement until age 168 days. No other formula given from randomization until age 168 days. Infant weight, length and head circumference were measured at birth and age 14, 28, 56, 84, 112, 140 and 168 days. Bowel motion frequency and consistency, sleeping and crying patterns and adverse events were also measured.

Results: Seventy-two infants were randomized, 36 each to GMF or CMF, with 62 infants completing the intervention. At enrolment the average weight of infants in the GMF group (mean $\pm$ SD) was 3.33 ± 0.43 kg and in the CMF group 3.43 ± 0.47 kg; and at study completion 8.07 ± 0.90 kg (GMF) and 7.87 ± 0.99 kg (CMF). The difference in average weight gain over the study period for the GMF group versus the CMF group was not significant (+309 g; 95% CI = −49 to +668, $P = 0.09$). Median daily bowel motion frequency was greater in the GMF group than the CMF group (2.4 vs 1.7, $P = 0.01$). There were no group differences in bowel motion consistency, duration of crying, ease of settling, or frequency of adverse events.

Conclusion: Growth of infants fed GMF is not different to that of infants-fed CMF.

Key words: bottle-feeding; goat milk; growth; infant formula; infant nutrition; milk; randomized control trials.

Abbreviations: CMF, cow milk infant formula; GMF, goat milk infant formula.

Goat milk is widely consumed in Mediterranean and Middle East countries. Like cow milk, goat milk is not suitable for infant use unless modified and fortified to meet infant formula regulations. Goat milk infant formula (GMF), while unknown in many countries, has an established history of use in excess of 10 years in a number of countries including New Zealand, Australia and Taiwan. In New Zealand and Australia, GMF is available at similar cost to soy formulas, both these types of formula being typically 20–50% more expensive than standard cow milk-based formulas. In New Zealand, the use of GMF now exceeds the use of soy-based formulas and comprises approximately 5% of infant formula purchased.

The scientific literature on the use of GMF is scant. In the one published randomized controlled study from Madagascar, 30 malnourished children aged 1–5 years were treated for 15 days with high energy formulations made from powdered goat milk or cow milk.[1] Weight gain did not differ in the two groups. The energy densities of the formulations used were approximately 40% higher than the energy density of standard infant formulas. Thus, although encouraging, additional data on growth in well children fed a formula of normal energy density are required in order to know if goat milk-based formulas are appropriate for infants.

The aims of this study were to determine if growth differed significantly for infants fed goat milk formula compared with infants-fed cow milk formula, and to compare the two formulas with respect to tolerability and safety. We hypothesized that the growth of infants-fed GMF would not differ significantly from that of infants fed cow milk infant formula (CMF).

METHODS

This was a single centre, prospective, double-blind, randomized, controlled comparison of two commercially available infant formulas: GMF (Dairy Goat Co-operative (N.Z.) Ltd, Hamilton, New Zealand) and S-26 CMF (Wyeth Health; Madison, New Jersey, USA). The two infant milk formulas did not differ in the amount of protein, fat or carbohydrate. Energy density differed slightly being 290 kJ per 100 mL for GMF and 274 kJ per 100 mL for CMF.

The study was conducted in Auckland, New Zealand, an ethnically diverse city of approximately 1 million people.[2] Only pregnant women, who had notified their lead maternity caregiver of their decision not to breast-feed, were invited to participate. These women were identified in the latter stages of pregnancy and the immediate post-partum period. An infant was not randomized until their mother had confirmed, after delivery, that they did not want to breast-feed.

Infants were not enrolled if an illness likely to affect growth was diagnosed (e.g. congenital heart disease), if a multiple birth was expected, gestation was less than 37 weeks or birthweight less than 2.5 kg, or the infant's parents planned to move from Auckland in the next 6 months.

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Randomization was performed by the Clinical Trials Research Unit, University of Auckland. A mixed block size was used. Randomization was stratified by gender. Infants were randomized within 72 h of birth.

From the randomization list, a unique identifying code was created for each enrolled infant and used to label all the formulas for that infant. The Clinical Trials Research Unit sent these codes to the formula-packaging company, instructing the packing company on which unique codes were to be applied to boxes of GMF and CMF. Each enrolled infant, therefore, had an individually coded supply of infant formula. The two investigators (BR and CG), who were the only people who allocated boxes of formula powder to each infant, were kept blinded with respect to which infant codes were for either GMF or CMF. The code linking each infant's identifying number with milk formula type was not broken until after the last infant had completed the study.

The infant formula powder was packed as boxes containing single serve sachets, with each sachet containing enough powder to make a 250 mL feed bottle at the feeding concentration according to the manufacturers mixing instructions. The mothers were given verbal and written instructions on the preparation of the formula, including that any infant formula remaining at the end of each feed was to be discarded. In order to estimate the volume of formula consumed, mothers were provided with a diary and asked to keep a daily record of how much of each 250 mL bottle of formula was discarded. The infants were fed the study formula from the commencement of the trial, at age 1–3 days, until 168 days of age. No other formula was to be given from randomization until 168 days of age. Feeding instructions were provided that delivered 150–200 mL of formula/kg per day.[3] Caregivers were permitted to introduce weaning foods after 112 days.

Infant weight, length and head circumference were measured in triplicate using dedicated equipment. Weight was measured to the nearest 10 g using MT 30 modified scales (supplied by Advasco Scales, Auckland, New Zealand). The scales were calibrated before weighing the baby at each visit. Length was measured to the nearest millimetre using a Harpenden Neonatometer stadiometer, calibrated to conform to ISO 9002 standards (manufactured by Holtain, Crymych, UK). Two people were involved in positioning the infant for the length measurements. Head circumference was measured to the nearest millimetre using Teaching-Aids at Low Cost (TALC) insertion circumference tapes made of plasticized paper (TALC, St. Albans, UK). For reporting and analysis, the mean of the triplicate measures was used.

Infant and maternal demographics were described using a structured, predominantly closed-ended questionnaire completed at enrolment. Data were collected on infant formula intake, and on adverse events using a diary, completed by the mother and reviewed at each study visit.

The study nurse visited the infant within 72 h of birth, and at 14, 28, 56, 84, 112, 140 and 168 days of age. At each visit, infant formula was provided, adherence with the study requirements determined, the infant measured, the diary reviewed and the number of unused sachets recorded. Adverse events, other foods and drinks consumed, the infant's typical bowel motions, usual sleeping and crying patterns and prescribed medicines were recorded.

An adverse event included any illness, sign, symptom, or clinically significant laboratory test abnormality that appeared during the course of the trial, irrespective of any potential relationship this event may have had with the trial formulas. Infants experiencing adverse events that caused discontinuation of the study formula received follow up. With the mother's permission, the subsequent scheduled visits were completed and measurements made of weight, length and head circumference.

A serious adverse event was defined as any untoward medical occurrence that resulted in death, life-threatening illness, hospitalization, serious disability, congenital anomaly, or required intervention to prevent permanent impairment or damage. Serious adverse events were reported immediately to the project manager, the principal investigator and the sponsor and were notified to the Data Safety and the Ethics Committee.

A Data Safety Committee received unblinded data from the trial at monthly intervals. They reviewed the non-serious and serious adverse events and made recommendations on study continuation to the principal investigator.

The study personnel remained blinded until the last infant completed the study. Mothers were unblinded after the last study visit, after which time they had no further contact with study personnel. The unblinding of mothers was performed by a designated independent person.

As no local reference data on growth variance were available, sample size requirements were estimated based upon published contemporary growth studies of infants-fed milk formula.[4] A sample size of 60, 30 in each group, was expected to provide 80% power (with $\alpha = 0.05$) to detect a 4 g/day difference between the GMF and CMF groups in bodyweight increase from birth to 112 days of age and a 0.08 mm/day difference between the GMF and CMF groups in bodylength increase during the same period.

The dataset was created and stored within the University of Auckland and analysed independently of the sponsors. Analyses were performed on an intention to treat basis using the statistical analysis package, SAS version 8 (SAS Institute, Cary, NC, USA). All tests of significance were two-tailed. The comparisons between the GMF and CMF groups used univariate and multivariate methods, including repeated measures ANOVA using SAS proc mixed.

Ethical approval was obtained from the Auckland Ethics Committee of the New Zealand Ministry of Health. Written informed consent was obtained from the mothers of all enrolled infants. An external auditor audited the study.

RESULTS

From April 2001 to February 2002, 77 infants were registered, with 72 of these infants randomized (36 each to GMF and CMF groups). Ten of the randomized infants discontinued the intervention before study completion, six from the GMF group and four from the CMF group. Growth measurements were obtained from eight of these 10 infants. The details of enrolment and study completion are shown in Figure 1. Ninety-four per cent of the visits at which the growth measurements were taken occurred within ±2 days of the planned 14, 28, 56, 84, 112, 140 and 168 days of age.

There were no differences between the GMF and CMF groups in infant and maternal demographics and maternal health history (Table 1). The ethnic proportions of the sample was not different from that of the Auckland population aged less than 5 years (European/other 59%, Maori 18% and Pacific 23%).[2]

At enrolment the average weight of infants in the GMF group (mean ± SD) was 3.33 ± 0.43 kg and in the CMF group 3.43 ± 0.47 kg; and at study completion 8.07 ± 0.90 kg (GMF) and 7.87 ± 0.99 kg (CMF). In the repeated measures analysis, after adjustment for age and gender, the difference in average weight gain over the 168-day study period for the GMF group versus the CMF group was not significant (+309 g; 95%

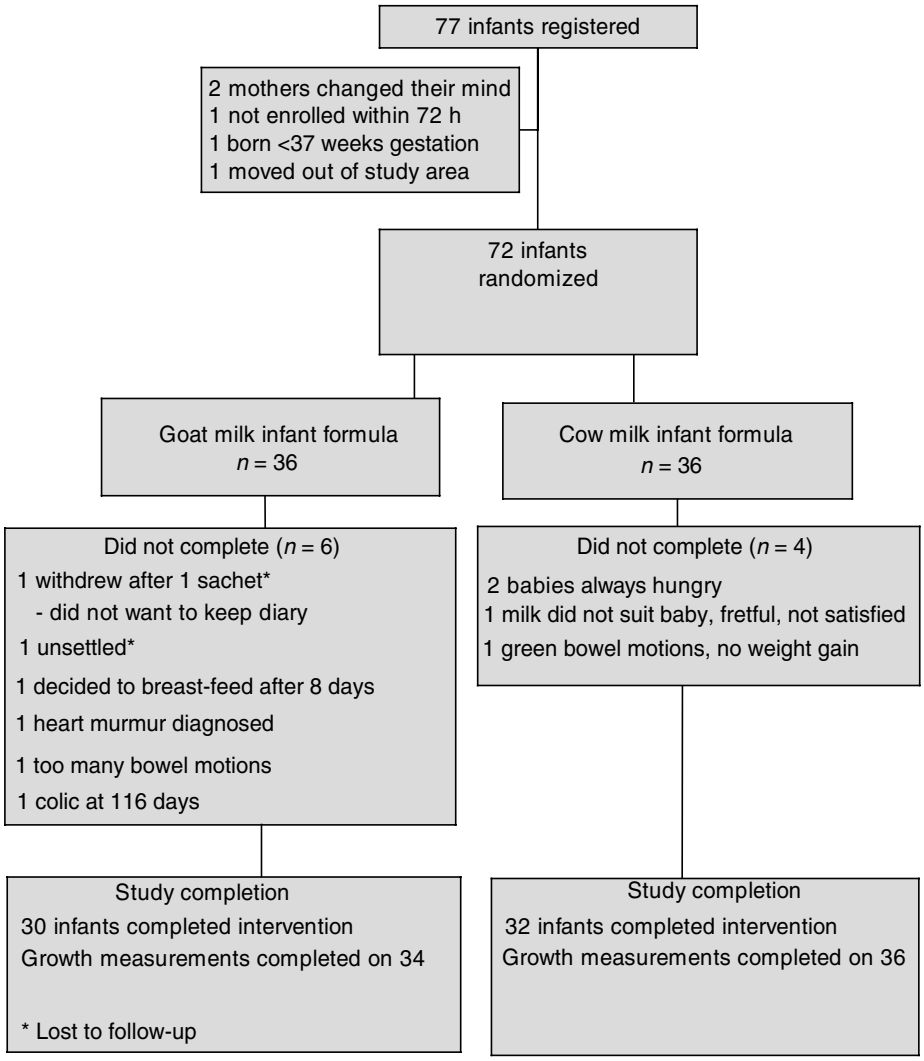

Fig. 1 Study enrolment, randomization and completion.

CI = −49 to +668, $P = 0.09$). There was no significant gender difference although male infants were initially 97 g heavier than female infants ($P = 0.37$ for gender comparison of weight increase).

At enrolment the average length of infants in the GMF group was 50.0 ± 2.2 cm and in the CMF group 50.5 ± 2.1 cm; and at study completion 67.8 ± 3.0 cm (GMF) and 67.0 ± 2.7 cm (CMF). After adjustment for age and gender, the difference in average increase in length over the 168-day study period for the GMF group versus the CMF group was not significant (0.8 cm; 95% CI = −0.2 to +1.8, $P = 0.09$). Unlike the measurement of weight, there was a significant gender difference with male infants, on average 1 cm longer than female infants ($P = 0.03$).

At enrolment the average head circumference of infants in the GMF group was 35.1 ± 1.5 cm and in the CMF group 35.3 ± 1.2 cm; and at study completion 43.6 ± 1.1 cm (GMF) and 43.6 ± 1.4 cm (CMF). After adjustment for age and gender, the difference in average increase in head circumference over the 168-day study period for the GMF group versus the CMF group was not significant (+0.3 cm; 95% CI = −0.2 to +0.8, $P = 0.23$). As with length there was a significant gender difference. Male infants had a head circumference on average 0.6 cm larger than female infants ($P = 0.02$).

Based upon the diary record of how much study formula was discarded from each 250 mL bottle, an estimate was made of the volume of milk consumed by each infant. These analyses did not include the 10 infants who withdrew from the study before completion. The average daily intake of formula (mean, SD) consumed did not differ significantly for infants randomized to GMF (820, 133 mL) compared to CMF (865, 125 mL) ($P = 0.18$).

Weaning foods were introduced before age 112 days for nine (25%) of the infants randomized to GMF and 11 (31%) of the infants randomized to CMF ($P = 0.28$). By age 140 days 85% of infants and by age 168 days 100% of infants, in both groups, were receiving weaning foods.

Bowel motion frequency and consistency, duration of crying and ease of settling were monitored at each visit. Summary data based upon the average overall visits are shown in Table 2. The median number of bowel motions per day was significantly greater for the GMF group compared with the CMF group ($P = 0.01$). There was no difference between groups in bowel motion consistency, duration of crying or ease of settling.

Table 1 Comparison of maternal and infant demographics and maternal health history for infants randomized to goat milk infant formula (GMF) and cow milk infant formula (CMF)

Characteristic	*n* (%)		*P*-value
	GMF group ($n = 36$)	CMF group ($n = 36$)	
Maternal age in years (mean ± SD)	30.6 ± 5.8	28.4 ± 6.4	0.13
Maternal ethnicity			0.84
European/other	21 (58)	19 (53)	
Maori	9 (25)	9 (25)	
Pacific	6 (17)	8 (22)	
Household income <$30 000 per annum†	18 (50)	18 (50)	1.00
Marital status			0.68
Married	20 (56)	19 (53)	
Permanent relationship	8 (22)	11 (30)	
Single	8 (22)	6 (17)	
History of gestational diabetes	5 (14)	2 (6)	0.43
History of pre-eclampsia	3 (8)	4 (11)	1.00‡
Mother current smoker	19 (54)	19 (54)	1.00
Median gestation in weeks (5th, 95th centiles)	40 (37, 42)	40 (38, 41)	0.95
Birthweight in kg (mean ± SD)	3.39 ± 0.43	3.48 ± 0.48	0.38
Male gender	21 (58)	20 (56)	0.81
Infant fed breast milk during first 2 days	6 (17)	5 (14)	0.74
Infant fed milk formula during first 2 days	35 (97)	34 (94)	0.38

†Median family income in 1996 for New Zealand families where youngest child less than 5 years old was NZ $33 500.[10]
‡Fisher's exact test.

The proportions of infants with adverse events reported at each visit did not differ between the two groups. The adverse events reported were all events that would be expected to occur during infancy. Comparisons of the frequency of specific adverse events (colds, coughing illnesses, ear infections, thrush, chest infections, vomiting, diarrhoea, rashes, constipation, food refusal and screaming) did not differ between the GMF and CMF groups.

Twelve infants experienced serious adverse events during the study. Five occurred in infants in the GMF group and seven in infants in the CMF group. The five serious adverse events in the GMF group were high fever and cough in one, bronchiolitis in two, cough in one and viral meningitis in one. The seven serious adverse events in the CMF group were a blood nose in one, pneumonia in one, pallor with fast heart rate in one, cough and fever in one, a febrile illness in one, a strangulated hernia in one and one infant was accidentally dropped on the ground.

At the last visit the mothers were asked to guess which of the two trial formulas their infant had received. The mothers of 15 (46%) infants randomized to GMF guessed correctly compared with mothers of 8 (24%) infants randomized to CMF ($\chi^1_2 = 3.27$, $P = 0.07$).

DISCUSSION

In the repeated measures analysis after adjustment for age and gender, infants in the GMF group, who were on average 93 g lighter at enrolment, gained on average 309 g more weight than infants in the CMF group over the 168-day study period. This difference was not significant, although it was equivalent to approximately 4% of the average infant weight at study completion. When converted to centiles for age using WHO/CDC reference data and calculated using EpiInfo 2000 (CDC, Atlanta, GA, USA), the average (95% CI) centile at study completion for the GMF group was 67th (52nd, 80th) and for the CMF group 62nd (42nd, 78th). These centile differences are not clinically significant.

A breast milk-fed group was not included in this trial. Following trial completion, we compared the average weight of infants randomized to each of the two infant formulas to the average weight at similar ages for a random sample of New Zealand infants, 67% of whom were exclusively breast-fed to age 3 months and 92% who were either fully or partially breast-fed.[5] This comparison group consisted of 503 infants randomly selected from all births in New Zealand as a control group for a case–control study of sudden infant death syndrome. Forty-eight per cent of the infants were male. Their median age was 4 months. The weight of the infants randomized to either GMF or CMF did not differ from this reference data (Fig. 2).

Gender differences in growth were evident, being statistically significant for the comparisons of length and head circumference. These gender differences are consistent with those reported by others and confirm the importance of stratification of randomization by gender.[6,7]

Table 2 Comparison of bowel motion frequency and consistency for infants randomized to goat milk infant formula (GMF) versus cow milk infant formula (CMF)

	n (%)		*P*-value
	GMF group ($n = 34$)	CMF group ($n = 36$)	
No. bowel motions per day (median, 5th, 95th centiles)	2.4 (1.1, 4.0)	1.7 (1.0, 4.4)	0.01
Had runny bowel motions at any visit	5 (15)	6 (17)	0.82
Had hard bowel motions at any visit	4 (12)	2 (6)	0.35
Cried for 3–6 h per day at any visit	3 (9)	7 (19)	0.19
Always or most of the time easy to settle at all visits	17 (50)	15 (42)	0.48

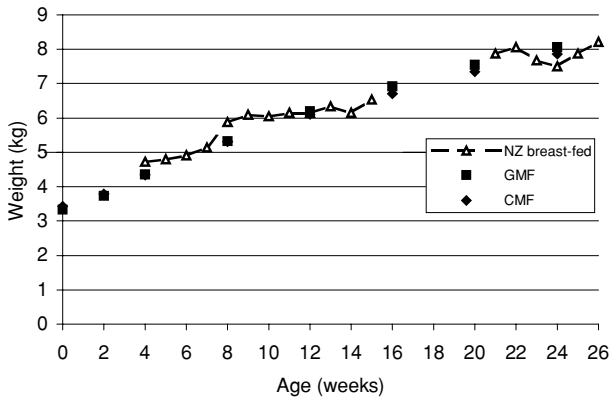

Fig. 2 Weight gain of infants randomized to goat milk infant formula (GMF) or cow milk infant formula (CMF) compared with weight of a random sample of predominantly breast-fed New Zealand infants (NZ breast-fed).[5]

Although greater than the CMF group, the frequency of bowel motions in the GMF group was not excessive and was not associated with any significant difference in consistency. The reasons for the difference in bowel motion frequency are unclear. Lactose is the only carbohydrate in both formulas. In cow milk formula, the fat of cow milk is entirely replaced by vegetable oils. In contrast, the fat of GMF is comprised of goat milk fat and vegetable oils. Therefore, intrinsic factors in goat milk fat may play a role. It is possible that the differences in bowel motion frequency are related to differences in digestibility between the two formulas. Following acidification, goat milk produces a softer curd than cow milk.[8]

No differences were noted between the two groups in infant behaviours or in the frequency of adverse events such as vomiting, diarrhoea, constipation, food refusal or screaming, any of which would imply a difference in the infants' ability to tolerate the two formulas. Therefore, the tolerability and safety of GMF appeared not to differ from that of CMF.

It must be noted that this study was not designed to determine differences in allergenicity between GMF and CMF. Children with proven immunoglobulin E (IgE)-mediated CMF allergy are also at increased risk of allergy to GMF.[9] In such children, GMF would be inappropriate. However, in healthy non-allergic children, the data from this study indicate that GMF is a suitable alternative to CMF.

No blood or urine samples were collected from enrolled infants. We were concerned in this initial study that the inclusion of such testing would have an adverse effect on study retention thus reducing the high quality growth data that was obtained from the repeated measures on almost all of the enrolled infants. From our prior experience in the use of GMF, which has been available in New Zealand for over 15 years, we were confident that the nutrient composition of the GMF was sufficiently similar to CMF that such testing was not required to ensure the infants safety. Specifically, the folate concentration of GMF was similar to that of CMF.

The growth and safety data from this initial GMF study adds to the knowledge obtained from the only other study to date of GMF in children.[1] In particular, this study shows that adequate growth is sustained over the first half of infancy when GMF is the predominant source of nutrition. Breast milk remains the food of choice for infants, but for infants who cannot be breast-fed, this study shows GMF is an appropriate alternative.

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