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Goat Milk Based Infant Formula in Newborns: A Double-Blind Randomized Controlled Trial on Growth and Safety.

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ABSTRACT

Objectives: We aimed to determine the growth and safety parameters in newborns fed a goat milk based infant formula (GMF) using a randomized double-blind trial, in which a cow milk formula (CMF) served as a control and a breast fed (BF) group as a reference.

Methods: Healthy term infants (n = 218) aged up to 14 days were recruited from 25 European study centers and randomized to GMF or CMF. Weight, length, head circumference were measured at baseline, and at 14, 28, 56, 84, and 112 days at the study clinics. Adverse events were recorded and stool characteristics, reflux, fussiness, colic, and flatulence were self-reported by parents in 3-day diaries. Anthropometric measurements were transformed to WHO standardized age- and sex-adjusted *z*-scores. Analyses of covariance and linear mixed modeling were used to statistically analyze growth, while adjusting for potential confounders when studying the breast-fed group (n = 86).

Results: Comparing the GMF to the CMF group, weight gain [mean difference 227.8 g (95% CI −16.6 to −439.0)] and z-scores for anthropometric measurements were similar after 112 days intervention. Infant formula groups showed greater mean (SD) weight z-scores than the BF group from 84 days onwards (GMF: 0.28 (0.84), CMF: 0.12 (0.88), BF −0.19 (1.02), $P < 0.05$), whereas length and head circumference z-scores were similar. Incidences of serious adverse events and reflux, fussiness, colic, and flatulence were similar among the three groups.

Conclusion: Our data demonstrate that GMF provides adequate growth, has a good tolerability, and is safe to use in infants.

Key Words: goat milk protein, growth, infant formula, stool characteristics, tolerability symptoms, weight gain

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What is known:

- Results from four studies suggest that goat milk based infant formula consumption results in adequate growth in infants
- There is need to study nutritional suitability, safety and tolerability of goat milk based infant formula in well-designed studies

What is new:

- Growth and tolerability were demonstrated to be adequate in infants fed goat milk based infant formula
- Occurrence of adverse events in goat milk infant formula group was similar to cow milk infant formula group, but lower than for breast-fed group
- Blood stained stools did not occur throughout the intervention.

Optimal early life nutrition is pivotal for early and later life health outcomes. Human milk is considered the best source of nutrition for infants (1), whereas infant formula (IF) is the recommended alternative when human milk is unavailable. Goat milk based infant formula (GMF) is a relatively unknown alternative of infant formula, but has been approved by European Food Safety Authority and WHO/FAO (2,3).

Data on nutritional suitability, safety and tolerability of GMF has been reported previously in four studies. A prospective observational study in infants fed exclusively breast milk (BM, n = 659), a GMF (n = 32) or a cow milk based infant formula

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(CMF; n = 159), or a combination of BF with GMF (n = 40) or with CMF (n = 86) displayed similar weight gain after 12 months of age. Stool characteristics of infants fed GMF resembled those of infants fed BM (4). In a double-blind randomized controlled trial for 168 days comparing a CMF and a GMF in 72 infants, no significant differences in weight gain, stool consistency, duration of crying, ease of settling, or frequency of adverse events (AE) were observed (5). A study in infants who were randomized to receive a GMF (n = 101) or a CMF (n = 99) exclusively for at least four months, and thereafter in addition to complementary food until 12 months, did not show significant differences in z-scores for weight, length, head circumference or weight for length. There were no differences in the occurrence of serious adverse events (SAE), general health, and incidence of dermatitis or medically diagnosed food allergy (6). Similar outcomes were observed in another double-blind randomized controlled trial in 79 infants fed either exclusively GMF or CMF for 6 months (7).

However, these studies have their limitations: either the study was observational (4) or considered underpowered (5,8), or included non-exclusive feeding of the GMF (5,7). The study from Zhou et al (6). provides the most reliable clinical data so far and needs replication for a better understanding of the nutritional adequacy and safety of GMF. In addition, incidences of blood stained stools were observed in this study in the GMF group, which requires further investigation. To address the ability of GMF to support healthy growth, as well as its safety and tolerability, we designed a well-powered randomized double-blind controlled trial in newborns exclusively fed either GMF or CMF. We hypothesized that GMF-fed infants do not show nutritionally relevant lower weight gain (a difference of ≥3 g/day in weight gain has been suggested by the American Academy of Pediatrics as a relevant nutritional difference between groups (9)) after 112 days intervention as compared to CMF-fed infants. In addition, exclusively breast-fed infants were studied as references.

METHODS

Study Design and Participants

We designed a multi-center prospective double-blind randomized controlled trial comparing two IFs with a reference arm of exclusively BF-fed infants. Parents of infants were recruited from 25 hospitals or pediatric practices in Germany, Croatia, Austria, and Spain. Recruitment period was between July 2015 and May 2018. Infants were eligible for inclusion in the study if the following criteria were met: a gestational age between 37 and 42 weeks; an APGAR score at 10 minutes after birth of ≥9; a birth weight between 2.500 and 4.500 g; aged between 1 and 14 days; and parent's willingness to exclusively feed their infant the allocated IF or BF throughout the study period. Exclusion criteria were any congenital anomalies, gastrointestinal disorder or malformation, hospitalization for longer than 3 days, and participation in another trial. For safety reasons, infants with suspected or known allergies to cow or goat milk proteins or parents or siblings with food allergies were excluded from participation in the randomized groups. The study protocol was reviewed by the ethics committee of all study centers and written informed parental consent was obtained for each infant prior to start of the study.

Allocation and Blinding

Treatment allocation of GMF and CMF was done according to a generated randomization schedule performed by an independent statistician using the procedure PLAN in SAS version 9.4 (SAS Institute Inc., Cary, NC). Randomization schedule was stratified by sex and study site to ensure equal (1:1) distribution of intervention formula and sex among the study sites. The list of randomization codes was kept concealed to the investigational sites and randomized participants. Sealed envelopes were kept at the study sites containing allocation information in case of emergencies that required unblinding.

Investigational Products

The GMF (Kabrita®, Ausnutria B.V., the Netherlands) and CMF (Mead Johnson & company, USA) were intended for infants aged 0 to 12 months and complied to WHO/FAO (2) and FDA (10) regulations. Packaging and labeling of the two formulas were identical. The formulas were similar in nutritional content and details can be found in Table 1, Supplemental Digital Content, *http://links.lww.com/MPG/C823*. The label of the IFs contained feeding recommendations and the advice to consult a health care professional before use.

Intervention

From enrollment on, the infants were fed the allocated infant formula or BM exclusively for 112 days. No other food or drinks other than water, medication, and mineral/vitamin supplements were allowed during the intervention period.

Anthropometric measurements were performed in duplicate at baseline, at day 14 (visit 2), 28 (visit 3), 56 (visit 4), 84 (visit 5), and 112 (visit 6) by trained research nurses following a standardized protocol. Weight was measured using calibrated weighing scales to the nearest 5 grams with clothing and diaper removed. Crown-to-heel-length was measured to the nearest 0.1 cm using a neonatometer. Head circumference was measured using a non-flexible measuring tape to the nearest 0.1 cm. Stool characteristics and tolerability symptoms (i.e. reflux, colic, flatulence, and fussiness), and IF consumption were self-reported by the parents using a 3-day diary prior to each study visit. Stool consistency and color were assessed using the infant stool form scale (11), where lower scores indicated more watery stools. Occurrence of AE and medical treatments were orally discussed and assessed during the study visits. AE and diseases were coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 20.1). AE was defined as any untoward medical occurrence in a subject during the study period. An AE could be any unfavorable sign including an abnormal laboratory finding, symptom, or disease temporally associated with the use of a product, whether or not it is considered related to that product. An SAE was any AE that was a life-threatening AE, or results in death, hospitalization or prolongation of existing hospitalization, persistent or significant disability or incapacity, or was an important medical event.

Study Outcomes

The primary outcome was weight gain in grams from enrollment to 112 days of intervention. Weight gain was analyzed by using weight at each time point as dependent variable and body weight at baseline (visit 1 value) as one of the covariates. Secondary outcomes included weight gain at intermediate time points (day 14, 28, 56, and 84) and gain in length, head circumference, and WHO age- and sex-standardized *z*-scores for weight, length, head circumference, and weight-for-length, and safety and tolerability as assessed by stool characteristics, tolerability symptoms, medication use and AE after 112 days and at intermediate time points.

Formula intake was estimated using differences between provided and returned IF. Treatment compliance was evaluated by comparing the estimated formula intake to the recommended intake. Full compliance was defined as consuming at least 80% of the estimated age-appropriate IF volume.

Sample Size Calculation

To detect a nutritionally significant lower weight gain of 336 g after 112 days intervention in infants fed GMF as compared to infants fed CMF, 64 subjects per arm were required assuming a mean weight SD of 660 g for boys and girls combined (12,13), an alpha of 2.5% and a beta of 80% (nQuery Advisor 7.0). Accounting for a drop-out rate of 25%, a total of 86 subjects were planned to be enrolled for each formula group. Drop-outs beyond the expected 25% were replaced. For the BF group, 86 subjects were aimed to be enrolled, resulting in a total of 258 participants.

Statistical Analyses

Prior to unblinding of study, the statistical analyses plan and coding for statistical analyses were finalized. Assessment of protocol deviations for allocation to intention-to-treat (ITT) or per-protocol (PP) analyses sets was performed completely in blind. No interim analyses were carried out.

To draw reliable conclusions on the nutritional efficacy of GMF, both the ITT and PP should result in the same conclusion (14). The ITT analyses set was defined as all participants that agreed to start the trial and received at least one allocated feed or BF, those who completed the intervention according to the protocol were also included in the PP set. Age- and sex-adjusted *z*-scores were computed for weight, length, head circumference and weight-for-length using the WHO child-growth standards (13). Analysis of covariance was used to examine the anthropometric measurements among the three groups after 112 days and at intermediate time points. Multivariate linear mixed model for repeated measures were used to explore the time course of the *z*-scores of anthropometrics including all study visits.

All models were adjusted for site, sex, and the baseline value. For comparison with BF, we additionally adjusted the model for potential confounding from age (day) and weight (gram) at enrollment, maternal educational level (no graduation, graduation, apprenticeship, university degree, academic title, other), and smoking during pregnancy (y/n). Tolerability symptoms (i.e. reflux, colic, flatulence, and fussiness) and AE and SAE were summarized by descriptive statistics, relative risk ratios (RR) and their respective 95% confidence intervals (CI).

Statistical significance for the primary outcome was set at $P < 0.025$, whereas significance for the secondary outcomes was considered at $P < 0.05$. All data analyses were performed using SAS software version 9.4 (SAS Institute inc., Cary, NC).

RESULTS

Baseline Characteristics

ITT analyses included 108 GMF-fed infants, 102 CMF-fed infants, and 86 BF infants that received at least one feeding of either human milk or allocated formula (Fig. 1). A total of 74 infants completed the study in the GMF and 79 infants in the CMF group. The PP analysis set consisted of 65 GMF-fed, 65 CMF-fed, and 65 BF infants who completed the study without major protocol deviations. Most often reported protocol deviations included: weight measurement were outside time window of ±3 days or were not complete for each visit; formula intake was <80% of the recommended volume; BF infants received >12 days formula feeding; and unblinding of treatment regimen.

At baseline, characteristics of the infants fed GMF or CMF were comparable, except for a slightly higher proportion of German infants allocated to receive GMF (37.0% vs 30.4%) (Table 1). Mothers who BF were likely to be higher educated, and to have smoked less before or during pregnancy as compared to the mothers in the formula groups. BF-infants were older at enrollment in the study than their formula-fed counterparts. Finally, a relatively larger fraction of BF infants were enrolled in Germany.

Compliance and Formula Consumption

Mean treatment compliance, calculated by comparing the estimated formula intake to the recommended intake, was 134.9%

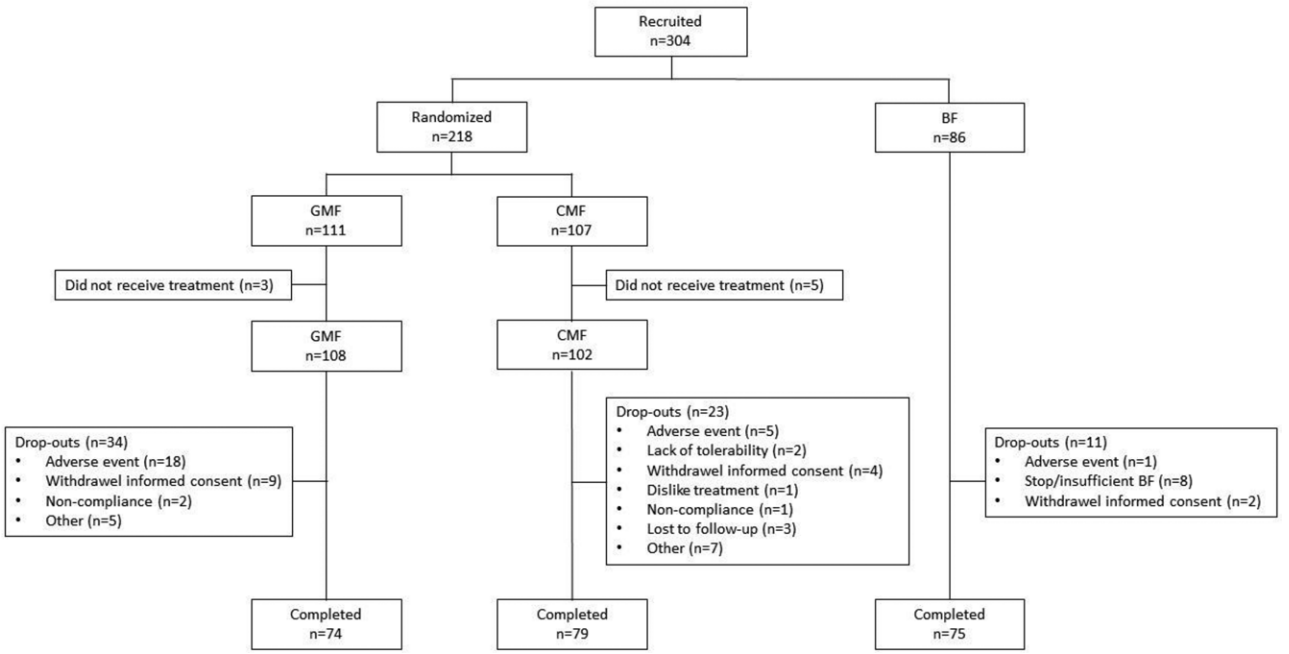

FIGURE 1. Flow chart of the infants under study. CMF = cow milk based infant formula; BF = breast-fed; GMF = goat milk based infant formula.

TABLE 1. Maternal and offspring characteristics for the 296 participants under study.

	GMF	CMF	BF
	(n = 108)	(n = 102)	(n = 86)
Maternal characteristics			
Caucasian ethnicity	107 (99.1%)	99 (97.1%)	79 (91.9%)
Education			
None/secondary	58 (53.7%)	50 (49.0%)	19 (22.1%)
Higher national diploma	19 (17.6%)	20 (19.6%)	32 (37.2%)
Degree and higher	28 (25.9%)	30 (29.4%)	29 (33.7%)
Missing	3 (2.7%)	2 (2.0%)	6 (7.0%)
Smoking			
Before pregnancy	38 (35.2%)	29 (28.4%)	10 (11.6%)
During pregnancy	27 (25.0%)	16 (15.7%)	7 (8.1%)
Infant characteristics			
Sex – male	53 (49.1%)	48 (47.1%)	42 (48.8%)
Gestational age (wk)	39.1 ± 1.2	39.1 ± 1.2	39.2 ± 1.2
Birth weight (g)	3307 ± 406	3370 ± 433	3409 ± 416
Characteristics at enrolment:			
Age(d)	7.3 ± 4.0	7.2 ± 4.2	8.9 ± 3.5
Weight(g)	3273 ± 418	3349 ± 451	3405 ± 438
Length(cm)	50.4 ± 1.9	51.9 ± 2.2	50.9 ± 2.1
Head circumference (cm)	34.8 ± 1.2	35.2 ± 1.2	35.5 ± 1.3
Country of birth:			
Germany	40 (37.0%)	31 (30.4%)	68 (79.1%)
Croatia	26 (24.1%)	26 (25.5%)	13 (15.1%)
Spain	41 (38.0%)	45 (44.1%)	4 (4.7%)
Austria	1 (0.9%)	0 (0%)	1 (1.1%)
Prior medication and therapies*	87 (80.6%)	83 (81.4%)	84 (97.7%)

Results are presented in n (%) or mean ± SD. BF = breast-fed; CMF = cow milk based infant formula; GMF = goat milk based infant formula
*Prior medication and therapies, any medication taken and treatment performed prior to the date of visit 1, including vaccines and vitamins.

for GMF and 135.0% for CMF in the ITT study sample. The mean (SD) IF volume in the GMF group increased from 765.8 ml (225.2) at visit 2 to 953.8 ml (257.1) at visit 6, whereas this was 781.4 ml (157.2) to 985.5 ml (242.5) for the CMF group. The mean caloric intake was similar between the two formula groups at all time points ($P > 0.3$).

Primary Outcome

After 16-wk intervention, the mean (SE) weight was 7009.0 g (96.1) for GMF, 6781.2 g (99.5) for CMF and 6449.3 g (139.9) for BF infants (Table 2, Supplemental Digital Content, *http://links.lww.com/MPG/C823*). Infants fed GMF showed a 227.8 g (95% CI 16.6–439.0) higher mean weight than infants fed CMF for the ITT set and a 206.6 g (95% CI -21.8-435.1) higher mean weight for the PP set. For both ITT and PP, when analyzed with weight at baseline as one of the covariates, the 95% CI of the mean weight difference between GMF and CMF was higher than the hypothesized -336 g margin ($P < 0.001$), indicating that the weight gain of the GMF group was significantly not lower than that of the CMF group.

Secondary Outcomes

The mean z-scores of anthropometrics are shown in Table 3, Supplemental Digital Content, *http://links.lww.com/MPG/C823*. As compared to the BF infants, weight z-scores of infants fed GMF and CMF were significantly higher from visit 3 onwards and from visit 5 onwards, respectively. As compared to the BF group, the GMF group showed significantly lower length and head circumference z-scores at baseline, whereas the weight-for-length z-scores were greater from visit 4 onwards. The GMF group showed significantly lower head circumference-for-age z-scores than the CMF group at baseline. All the mean z-scores of anthropometrics were within "1 SD" of the WHO growth standards.

Over the 16-wk intervention, the overall SAE incidence was low for BF (n = 4), GMF (n = 5), and CMF (n = 12). The risk of SAE was lower in the GMF group as compared to the CMF group, but the difference did not reach statistical significance [RR 0.39 (95% CI 0.14–1.08) Table 2]. The causality was considered unlikely attributable to the type of feeding in the majority of the cases (GMF: 80%, CMF: 83.3%). The GMF had a significantly lower risk of AE as compared to the BF group [RR 0.81 (95% CI 0.67-0.98)], whereas the risk was similar between the GMF and the CMF group. The majority of the reported AE was considered "unlikely" causally related to the intervention (GMF: 62.1 %, CMF: 73.0%). An "assured" relatedness was considered in 6.1% of the GMF and 1.6% of the CMF group. The severity of the AE (i.e. slight, moderate, or severe) was similar between GMF and CMF. The top three of AE was identical among the three groups, namely gastro-intestinal disorders, infections and infestations, and skin and subcutaneous tissue disorders.

No differences in incidence rates between the GMF group and CMF group were seen for the tolerability symptoms (Table 2). The GMF group, as compared to the BF group, reported significantly lower incidence rates for reflux, colic, fussiness, and flatulence, however, these associations disappeared when using those infants who completed the intervention period (n = 75; Table 4, Supplemental Digital Content, *http://links.lww.com/MPG/C823*). No incidences of bloody stools were reported throughout the intervention period in all groups. The mean (SD) stool consistency was generally indicated as soft stools. The scores for stool consistency were higher for GMF as compared to CMF [2.2 (0.6) vs 2.0 (SD 0.4); $P < 0.001$] and higher as compared to the BF group [2.2 (0.6) vs 1.8 (SD 0.5); $P < 0.001$]. Similar stool consistency scores were observed for the individual study visits.

DISCUSSION

In this 16-wk multi-center double-blind randomized controlled trial, we observed that infants fed exclusively GMF, as compared to infants fed exclusively CMF, showed similar gain in weight, length, and head circumference. Also, standardized weight, length, and head circumferences; WHO z-scores; and incidence rates of AE were similar between the GMF and CMF groups. Toward the end of the 16 week trial, the BF infants showed lower weight z-scores than the formula-fed infants. All the mean z-scores of anthropometrics in the formula-fed and BF groups were within "1 SD" of the WHO growth standards. Tolerability symptoms were also similar between the GMF and CMF groups, except for a lower likelihood of watery stools and a higher likelihood of hard stools in infants fed GMF. In comparison to the BF group, the GMF and CMF had a similar and low risk of SAE, a significantly lower risk of AE, as well as lower incidence rates for reflux, colic, fussiness, and flatulence. Finally, the higher risk for blood-stained stools in GMF-fed infants reported by Zhou et al (6). was not observed in our study. Our study confirms the findings of previous studies concluding that GMF supports adequate growth and is safe for use in infants (4–7).

The weight z-score of formula-fed infants was significantly higher than those of the BF group from visit 5 onwards. An increased

TABLE 2. Relative risk and 95% CI of the AE and tolerability symptoms over the 16-wk intervention period in the intention-to-treat analysis set (n = 296)

	GMF (n = 108)	CMF (n = 102)	BF (n = 86)	GMF vs CMF	GMF vs BF
	n (%)	n (%)	n (%)	RR (95% CI)	RR (95% CI)
Safety*					
SAE	5 (4.6)	12 (11.8)	4 (4.7)	0.39 (0.14–1.08)	1.00 (0.28–3.59)
Infections and infestations	2 (1.9)	6 (5.9)	1 (1.2)		
Gastro-intestinal disorders	1 (0.9)	2 (2.0)	1 (1.2)		
Metabolism and nutrition disorders	1 (0.9)	–	–		
AE	66 (61.1)	63 (61.8)	65 (75.6)	0.99 (0.80–1.12)	0.81 (0.67–0.98)
Gastro-intestinal disorders	42 (38.9)	36 (35.3)	28 (32.6)		
Infections and infestations	32 (29.6)	33 (32.4)	42 (48.8)		
Skin and subcutaneous tissue disorders	18 (16.7)	15 (14.7)	16 (18.6)		
Tolerability symptoms					
Bloody stools	0 (0)	0 (0)	0 (0)	–	–
Reflux	86 (79.6)	87 (85.3)	68 (79.6)	0.93 (0.82–1.05)	0.81 (0.79–0.89)
Colic	82 (75.9)	84 (82.4)	83 (96.5)	0.92 (0.80–1.06)	0.79 (0.70–0.88)
Fussiness	85 (78.7)	86 (84.3)	85 (98.8)	0.94 (0.82–1.06)	0.80 (0.72–0.88)
Flatulence	84 (77.8)	86 (84.3)	84 (97.7)	0.92 (0.81–1.05)	0.79 (0.72–0.86)

BF = breast-fed; CMF = cow milk based infant formula; GMF = goat milk based infant formula. *Multiple responses possible.

weight gain in formula-fed infants compared to BF infants has often been shown in literature, possibly due to differences in self-regulation resulting in lower levels of energy intake of BF infants (15). Another theory is the "early protein hypothesis," stating that higher protein content in formula as compared to human milk causes an endocrine and hormone disbalance and consequently an increased energy intake and weight gain (16,17). Nonetheless, Patro-golab et al concluded in 2 reviews of high quality studies that the "early protein hypothesis" lacks convincing evidence to assess the long-term effects on obesity and body composition (18,19).

The incidence of SAE was low and similar among the three groups and similar to previously reported (5–7). The incidence of AE in the GMF was similar to CMF, but lower as compared to the BF group. These data suggest that the GMF under study is safe for use in infants. Although, the number of drop-outs due to an AE was higher in the GMF group as compared to the CMF and BF groups. A third of the total AE in the GMF group emerged in the first week of intervention. Although, most early emerging AE were of transient duration, the reason for these early emerging AE is unclear and needs attention in future studies.

The parental reported mean stool consistency was generally indicated as soft. Infants fed GMF showed higher consistency scores throughout the intervention, due to the higher incidence of "hard" (n = 26) and lower incidence of "watery" (n = 57) stools as compared to the infants fed CMF (n = 9, n = 57 respectively). This finding is inconsistent with previous findings that reported no significant differences in watery stool frequencies between GMF and CMF groups (4–6). The most prominent differences in ingredients between GMF and CFM under study cannot directly explain the higher incidence of hard stools. The addition of β-palmitate in GMF has been associated with lower fecal calcium excretion and consequently softer stools (20–23). The higher levels of iron in the CMF (1.22 mg/100 ml IF vs 0.80 mg/100 ml IF) was previously shown to be unrelated to stool characteristics (24). Most importantly, however, the incidence of constipation reported as an AE was similar between GMF (n = 10) and CMF (n = 8), which suggests that these results may not be clinically relevant.

There are a few potential limitations in the present study. Due to logistic issues of a multi-center study that were of random nature (i.e. due to lower enrolment rate and shelf life of the infant formula), not all random blocks were completed. This theoretically could have jeopardized randomization. However, the reasons were completely random and the baseline characteristics between the infants fed GMF and CMF showed no noteworthy differences. Therefore, we argue that this has not affected our main conclusions. Furthermore, the duration of the current trial was 16 weeks, which is adequate to show potential short-term growth differences (9). Future studies may consider evaluating long-term GMF exposure into childhood and its respective growth and body composition.

A strength of this study was the inclusion of a local breast-fed reference group for comparison of the formula groups. Furthermore, the study was well-powered, as assured by a post-study power analysis for the PP analyses (β = 0.95) and ITT analyses (β = 0.98).

CONCLUSIONS

In conclusion, in this well-powered randomized double-blind controlled trial, we observed similar increments in weight, length, and head circumference, and incidences of tolerability parameters and (S)AE between infants fed exclusively GMF and CMF for 16 weeks. We conclude that GMF provides adequate growth and is safe and suitable for use in infants.

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