Trial of ready-to-use supplemental food and corn-soy blend in pregnant Malawian women with moderate malnutrition: a randomized controlled clinical trial

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ABSTRACT

Background: Malnutrition during pregnancy in sub-Saharan Africa is associated with poor birth outcomes.

Objective: This study compared maternal and offspring anthropometry for moderately malnourished pregnant women receiving ready-to-use supplemental food (RUSF), a fortified corn-soy blend (CSB+) with a daily multiple micronutrient antenatal supplement [United Nations International Multiple Micronutrient Preparation (UNIMMAP)], or standard of care comprising CSB+ and iron and folic acid (IFA).

Design: A single-blind randomized controlled clinical trial was conducted in southern Malawi among 1828 pregnant women with moderate malnutrition, defined as a midupper arm circumference (MUAC) ≥20.6 and ≤23.0 cm. Women received 1 of 3 dietary treatment regimens that provided ∼900 kcal/d and 33–36 g protein/d. Maternal and infant anthropometry were followed until the child was 3 mo old.

Results: Newborns had a mean length-for-age *z* score of −1.3 ± 1.2 and 22% were stunted at birth. Mothers receiving RUSF had the highest weight gain during supplementation (3.4 ± 2.6, 3.0 ± 2.2, and 3.2 ± 2.4 kg for the RUSF, CSB+ with UNIMMAP, and CSB+ with IFA groups, respectively; $P = 0.03$). Newborn birth weights and lengths were similar across intervention groups, but the incidence of newborns with a birth weight <2.4 kg (weight-for-age *z* score <−2) was higher in the CSB+ with UNIMMAP group than the other groups (17%, 18%, and 24% for the CSB+ with IFA, RUSF, and CSB+ with UNIMMAP groups, respectively; $P = 0.02$). At birth, HIV-exposed newborns had a similar length and weight as newborns without HIV exposure, but their head circumference was smaller (34.0 ± 1.5 and 34.3 ± 1.6 cm, respectively; $P = 0.02$). At 3 mo of age, HIV-exposed infants had smaller weights, lengths, and head and arm circumferences than infants without HIV exposure.

Conclusions: RUSF improved maternal weight gain compared with CSB+ with UNIMMAP. The large amount of food given and the modest effect on linear growth in newborns suggests that stunting in utero is unlikely to be reduced by supplemental food alone. This trial was registered at clinicaltrials.gov as NCT02120599. *Am J Clin Nutr* 2017;106:1062–9.

Keywords: maternal malnutrition, pregnancy, Malawi, dietary supplementation, RUSF

INTRODUCTION

Malnutrition during pregnancy is common among poor women in the developing world and may well be attributable to inadequate dietary intake in the face of increased nutrient requirements. Among women of reproductive age in Malawi, 8.8% have a BMI (in kg/m^2) <18.5 and 28.0% are anemic (1). Given the preconception nutritional status of Malawian women, it is estimated that malnutrition adversely affects ∼15% of pregnancies (2). Malnourished pregnant women are at an increased risk of maternal mortality, disability, and poor birth outcomes; to our knowledge, the benefits of treating moderately malnourished pregnant women in an attempt to decrease these adverse outcomes have not been thoroughly explored (3). In theory, food supplements consumed during pregnancy should lessen a woman's malnutrition and improve infant birth outcomes.

In Malawi, as in other resource-limited settings, fortified corn-soy blend (CSB+) flour is recommended for adults with malnutrition (4). The WHO recommends that pregnant women in

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Supplemental Figure 1 and Supplemental Tables 1–4 are available from the "Online Supporting Material" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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Abbreviations used: CSB, fortified corn-soy blend; FH, fundal height; IFA, iron and folic acid; LNS, lipid nutrient supplement; MUAC, midupper arm circumference; RUSF, ready-to-use supplemental food; SGA, small-for-gestational-age; UNIMMAP, UN International Multiple Micronutrient Preparation.

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regions with high rates of iron deficiency should receive an iron and folic acid (IFA) supplement (5). A recent Cochrane review showed that daily supplementation with a multiple micronutrient antenatal supplement, such as the UN International Multiple Micronutrient Preparation (UNIMMAP), resulted in fewer low-birth-weight and small-for-gestational-age (SGA) babies than supplementation with IFA (6). Food supplementation for pregnant women with moderate malnutrition is the prescribed standard of care in Malawi, although it is not commonly given. Although the use of lipid nutrient supplements (LNSs) has been studied in pregnant women without malnutrition, there is little published evidence about their use as a treatment specifically for malnourished pregnant women (7, 8).

This study tested the hypothesis that a lipid-based ready-to-use supplemental food (RUSF) designed specifically for pregnant women with malnutrition or a CSB+ with a daily UNIMMAP would improve maternal recovery from malnutrition and increase infant birth weight and length and would secondarily improve infant anthropometry and survival at 6 wk and 3 mo, compared with the standard of care (CSB+ with daily IFA).

METHODS

Study design

This assessor-blinded randomized controlled clinical trial was conducted in southern Malawi and compared maternal and newborn outcomes when one of 3 supplementation regimens was given to moderately malnourished pregnant women. Moderate malnutrition was defined as a midupper arm circumference (MUAC) $\geq$20.6 and $\leq$23.0 cm (9).

The primary outcomes at study onset were as follows: *1*) proportion of women who reached an MUAC $\geq$23.1 cm for 2 consecutive visits, *2*) change in MUAC, *3*) newborn birth weight, *4*) newborn birth length, and *5*) proportion of infants born prematurely. Secondary outcomes were as follows: *1*) change in maternal weight from treatment onset until the final weight measurement, *2*) change in maternal hemoglobin concentration from treatment onset until 10 wk later, *3*) duration of treatment, and *4*) infant anthropometry and survival at 6 and 12 wk.

The sample size goal was estimated to be 1800 moderately malnourished pregnant women, divided equally among the 2 treatment groups (RUSF and CSB+ with UNIMMAP) and the control group (CSB+ with IFA). This size allowed for 15% attrition, yielding a final sample size of 1530 (n = 510/group) With a 2-tailed significance of 0.05, there was 80% power to detect a difference of 50 g in birth weight between groups, a mean difference of 0.1 cm in maternal MUAC between groups, a mean difference in 0.3 cm in newborn birth length, an 8% difference in the proportion of women reaching an MUAC $>$23 cm, and a 5% difference in the proportion of children born prematurely.

All participants were randomly assigned to receive RUSF, CSB+ with UNIMMAP, or CSB+ with IFA using a random number generator that prospectively assigned participant identification numbers to a treatment group in blocks of 60. Women chose a sealed envelope that contained a study number that was linked to the previously randomly assigned treatment. Because the supplements were visually distinct, the study subjects were not blinded. To minimize study personnel awareness of a mother's assigned treatment regimen, the study aide who dispensed the food looked up each participant's study number, selected the assigned food, and placed the food in an opaque bucket. Data entry and analysis was conducted completely blinded to intervention group.

Subjects

Pregnant women $>$18 y of age presenting at 15 antenatal clinics in southern Malawi with moderate malnutrition (defined as an MUAC $\geq$20.6 and $\leq$23.0 cm) were recruited between March 2014 and December 2015. Enrollment criteria were as follows: a fundal height (FH) $<$35 cm, willingness to attend the antenatal clinic every 2 wk during pregnancy, and plans to remain in the area for delivery and until 3 mo postpartum. Women who had pregnancy complications, such as severe malnutrition (MUAC $<$20.6 cm), gestational diabetes, preeclampsia, hypertension, or severe anemia (blood hemoglobin concentration $<$70 g/L) at enrollment, were excluded from the study but were provided the standard of care nutritional treatment and were referred to a health facility clinician for medical management. After 296 women were enrolled, the enrollment criteria were expanded to include female individuals 16 or 17 y of age to extend participation to a substantial number of otherwise eligible subjects.

Most of the subjects were subsistence farmers, who grew corn, tubers, and legumes on small plots of land, resided in mud huts without electricity, and collected water from boreholes or wells.

This trial was registered at clinicaltrials.gov as NCT02120599 and was approved by the Institutional Review Boards of Washington University in St. Louis, California Polytechnic State University, San Luis Obispo, and the University of Malawi College of Medicine. Participants gave verbal and written informed consent to be in the study for themselves and their infants.

Participation

On enrollment, participants were interviewed and demographic and health information was recorded. Participants also completed the Household Food Insecurity Access Scale (10) to identify the level of household food insecurity. Participants' HIV status was recorded for those who had testing results available. For participants not already tested, HIV status was established by a rapid test after routine counseling by clinic voluntary counseling and testing counselors. Participants' weight, height, MUAC, and triceps skinfold thickness were measured. Weight was measured with a Seca 803 Precision for Health scale. Height was measured with a Seca stadiometer. MUAC was measured twice on the left arm in centimeters to the nearest 10th of a centimeter with a flexible measuring tape (TALC), according to standard procedures; if the measurements differed by $>$1 mm, a third measurement was taken and the 2 closest measurements were recorded and averaged. FH was measured in the supine position with a nonelastic tape, measured to the nearest 0.5 cm (11). Study nurses were trained by a certified nurse trainer to measure FH, and inter-rater reliability was within 1.0 cm.

Enrolled women returned to the clinic every 2 wk for anthropometric measurements (weight, MUAC, and triceps skinfold thickness) and health checks (blood pressure, interim illness questions, and FH measurement) and to receive their 2-wk supply of treatment food or supplements. When their MUAC reached

≥23.1 cm for 2 consecutive visits, the treatment food was no longer provided and the women "graduated" from the study; however, IFA supplements were continued for the remainder of their pregnancy. After graduation, women were asked to visit the clinic every 4 wk and were assessed for relapse of malnutrition. If a relapse (MUAC ≤23.0 cm) occurred, mothers resumed consumption of their assigned treatment food or supplements.

A trained, dedicated birth anthropometry team frequently communicated with women for whom delivery was thought to occur within the next 2 wk. A team was dispatched to measure the infant within a few hours of being notified of delivery. Recumbent length was measured (Seca 417 length board) in triplicate to the nearest millimeter and averaged for analysis. Birth weight was measured in duplicate (MTB20 digital scale; Adam Equipment) to the nearest 10 g and averaged. If the 2 measurements differed by >10 g, a third measurement was taken and the outlier was eliminated. Head circumference was measured (Seca head circumference measuring band 212) to the nearest millimeter in duplicate and averaged. Efforts were made to minimize interobserver bias by periodic interobserver comparison and standardized training and techniques.

At the 6-wk and 3-mo postpartum visits, maternal weight and MUAC were measured and the participants' health history was taken. Infant weight, length, head circumference, and MUAC were also measured. In addition, infant hemoglobin was measured at the 3-mo visit.

Study foods

Two interventions (RUSF and CSB+ with UNIMMAP) were compared with the standard of care, which consisted of CSB+ with IFA. The food supplements were provided in biweekly rations of ten 250-g bottles of RUSF or 5 kg of CSB+. The RUSF provided 920 kcal/d, 36 g of protein/d, and ~200% of the Recommended Dietary Allowance for most micronutrients during pregnancy. The RUSF energy content was designed to provide 450 kcal/d to support the increased energy needs during the third trimester of pregnancy plus an additional 470 kcal/d to support recovery from moderate malnutrition. The CSB+ with UNIMMAP treatment ration had amounts of energy, protein, and micronutrients similar to the RUSF treatment (**Table 1**). The antenatal UNIMMAP micronutrient tablet contained 15 micronutrients (**Supplemental Table 1**). The CSB+ with IFA treatment provided the same quantity of CSB+ as the CSB+ with UNIMMAP ration, but with a daily iron (60 mg) and folic acid (400 μg) tablet instead of a daily UNIMMAP tablet. The CSB+ formulation was "super cereal: CSB with sugar" (12).

TABLE 1
Nutrient content of supplemental foods[1]

				Pregnant women 19–30 y of age	
Nutrient	RUSF[2]	CSB+ with UNIMMAP[3]	CSB+ with IFA[4]	RDA	UL
Energy, kcal	920 (NA)	893 (NA)	893 (NA)	NA	NA
Protein, g	36 (NA)	33 (NA)	33 (NA)	NA	NA
α-Linolenic acid (18:3n–3) (ω-3), g	2.3 (161)	0.0 (0)	0.0 (0)	1.4	NA
Linoleic acid (18:2n–6) (ω-6), g	14.0 (107)	0.0 (0)	0.0 (0)	13	NA
DHA (22:6n–3), g	211 (NA)	0 (NA)	0 (NA)	NA	NA
EPA (20:5n–3), g	43 (NA)	0 (NA)	0 (NA)	NA	NA
Vitamin A, μg	2628 (341)	3210 (417)	2410 (312)	770	3000
Vitamin B-1 (thiamine), mg	3.2 (228)	1.7 (121.5)	0.3 (20)	1.4	NA
Vitamin B-2 (riboflavin), mg	3.8 (270)	4.7 (335)	3.3 (235)	1.4	NA
Vitamin B-3 (niacin), mg	35.0 (194)	36.8 (204)	18.8 (104)	18	35
Vitamin B-6, mg	4.0 (210)	5.9 (198)	4.0 (210)	1.9	100
Vitamin B-12, μg	5.5 (262)	7.3 (253)	4.7 (181)	2.6	NA
Folic acid, μg	574 (143)	659 (165)	659 (163)	400	1000
Vitamin C, mg	170 (200)	281 (331)	211 (249)	85	2000
Vitamin D, μg	30 (200)	31 (206)	25 (169)	15	100
Vitamin E, mg	39 (261)	30 (197)	20 (130)	15	1000
Vitamin K, μg	192 (213)	71 (78)	71 (78)	90	NA
Iodine, μg	300 (136)	244 (170)	94 (43)	220	1100
Copper, mg	2.4 (240)	2 (200)	0 (0)	1.0	10.0
Iron, mg	45 (170)	45 (181)	79 (292)	27	45
Zinc, mg	24.6 (223)	26.8 (243)	11.8 (107)	11	40
Magnesium, mg	327 (93)	400 (114)	400 (114)	350	350
Calcium, mg	1830 (183)	851 (85)	851 (85)	1000	2500
Selenium, μg	123 (205)	65 (108)	0 (0)	60	400

[1] Values are expressed as amounts (% RDA). CSB+, fortified corn-soy blend; IFA, iron and folic acid; NA, not applicable; RDA, Recommended Dietary Allowance; RUSF, ready-to-use supplemental food; UL, tolerable upper limit; UNIMMAP, UN International Multiple Micronutrient Preparation.

[2] Assumes a daily portion of 175 g of RUSF.

[3] Assumes a daily portion of 235 g of CSB+ with UNIMMAP.

[4] Assumes a daily portion of 235 g of CSB+ plus iron (60 mg) and folic acid (400 μg).

Statistical analyses

Data were double entered and discrepancies were resolved after examination of the data collection cards. Characteristics and outcomes were tabulated. Women for whom newborn outcomes were not collected were considered to have defaulted. Data were analyzed with JMP Pro software (version 12.1.0; SAS Institute). Anthropometric *z* scores were calculated with the WHO R macro (WHO Anthro, version 3.2.2, January 2011; http://www.who.int/childgrowth/software/en/). Only singleton pregnancies were included in the newborn comparisons.

An intention-to-treat analysis was performed to compare all outcomes using ANOVA for continuous parameters and a chi-square test for categorical outcomes. Wilcoxon's rank-sum tests were performed if the normality requirement was not met, and a Fisher's exact test was used if the expected cell count was <5 for categorical outcomes. For pairwise comparisons, connecting letter plots were created using Tukey-Kramer honestly significance difference tests.

Some women delivered before receiving their second treatment ration, raising the concern that they had not been treated long enough to observe a clinical effect. In a second analysis, the intention-to-treat analysis was repeated with these women excluded. Women who delivered before receiving their second ration were also compared as a group to women who received ≥2 treatment rations.

In addition, a subgroup analysis was conducted for women with HIV who were treated with 1 of the 3 treatment regimens, and another analysis was conducted to compare women with HIV to women without HIV.

The effect of the different treatment regimens or duration of treatment on total maternal weight gain was analyzed with multivariable linear regression. We centered the numeric predictor (length of treatment) to reduce collinearity in the model. A generalized linear model with binomial error and logit link and the same predictor parameterization was used to determine whether duration of treatment or treatment group influenced the categorical response (stunting at birth). Partial F tests or likelihood ratio tests (chi-square tests) were first calculated to determine whether treatment group or duration of treatment had any association with the response variable through either the main effect or the interaction term. Statistical significance was set at $P < 0.05$, and all statistical tests were 2 sided.

RESULTS

A total of 2284 pregnant women with an MUAC ≤23.0 cm were screened and evaluated for study enrollment, and 1828 women met the study inclusion criteria and were enrolled (**Supplemental Figure 1**). Maternal characteristics at enrollment were similar across intervention groups (**Table 2**). At enrollment, study

TABLE 2
Nutritional and demographic characteristics of malnourished Malawian pregnant women enrolled in a supplemental feeding trial, by treatment group[1]

Characteristic	RUSF, n = 613	CSB+ with UNIMMAP, n = 605	CSB+ with IFA, n = 610	P[2]
Age, y	21.5 ± 5.4	21.3 ± 5.0	21.9 ± 5.5	0.21
First pregnancy	300 (49)	285 (47)	268 (44)	0.20
Household food insecurity[3]				0.14
Secure	25 (4)	29 (5)	33 (5)	
Mild	23 (4)	25 (4)	29 (5)	
Moderate	115 (19)	123 (20)	132 (22)	
Severe	450 (73)	427 (71)	416 (68)	
Clean water source used				
Borehole	430 (70)	425 (70)	438 (72)	0.78
Tap	73 (12)	69 (11)	68 (11)	0.91
Education, y				0.89
None	64 (10)	61 (10)	71 (12)	
1–3	94 (15)	102 (17)	89 (15)	
4–6	224 (37)	218 (36)	231 (38)	
7–8	148 (24)	158 (26)	147 (24)	
Secondary	79 (13)	63 (10)	69 (11)	
Tertiary	4 (1)	3 (1)	2 (0.3)	
BMI, kg/m^2	19.6 ± 1.4	19.8 ± 1.3	19.7 ± 1.3	0.35
MUAC, cm	22.3 ± 0.6	22.3 ± 0.6	22.3 ± 0.6	0.56
Height, cm	154.3 ± 5.5	154.0 ± 5.9	154.3 ± 5.7	0.47
Stature, height <145 cm	28 (5)	38 (6)	25 (4)	0.19
Triceps skinfold, mm	9.3 ± 2.3	9.4 ± 2.3	9.2 ± 2.3	0.24
Fundal height, cm	22.3 ± 5.7	22.6 ± 5.3	22.8 ± 5.4	0.21
HIV infection	64 (10)	60 (10)	70 (11)	0.67

[1] Values are expressed as means ± SDs or n (%). CSB+, fortified corn-soy blend; IFA, iron and folic acid (standard of care); MUAC, midupper arm circumference; RUSF, ready-to-use supplemental food; UNIMMAP, UN International Multiple Micronutrient Preparation.

[2] P values were calculated with one-factor ANOVA (continuous measures) and the chi-square test (categorical measures).

[3] The Household Food Insecurity Access Scale was used to categorize participants by level of household food insecurity.

participants had a mean age of 21.5 y and this was the first pregnancy for nearly half of the participants. Most women had completed 1–6 y of primary education, and 10% had no formal education. Approximately 71% of women were classified as severely food insecure.

Women enrolled in the study had a mean FH of 22.6 cm, a BMI of 19.7, and an MUAC of 22.3 cm. Approximately 5% of women were of short stature, with a height of <145 cm. Approximately 10% of women had HIV.

Women received a mean 5.0 rations of the food intervention over a period of 11.4 wk from enrollment until delivery. Women in the RUSF group had the highest mean weight gain during treatment until the final weight measurement (3.4, 3.0, and 3.2 kg in the RUSF, CSB+ with UNIMMAP, and CSB+ with IFA groups, respectively; $P = 0.03$). Among the participants, 75% had low weekly weight gain during treatment until the final weight measurement, defined as <454 g/wk (13). The mean final MUAC was 22.2 cm and did not differ by treatment group ($P = 0.11$). The change in MUAC was close to 0 for all intervention groups and the variance was 4–10 times greater than the mean change (**Table 3**). The RUSF group had the greatest number of participants (35%) who attained an MUAC >23.0 cm before delivery, followed by CSB+ with IFA (33%) and CSB+ with UNIMMAP (29%), but there were no differences between groups ($P = 0.12$).

There were 1467 live singleton births and 18 live twin pairs and there was 1 set of triplets. Among singleton births, 94% were measured within 24 h and 98% were measured within 48 h. An estimate of extreme prematurity is delivery with FH <28 cm (14). Approximately 5% of deliveries occurred in women with FH <28 cm, and there were no differences by intervention group.

No differences in birth weight, length, or head circumference were found by treatment group. Approximately 20% of all infants measured were born underweight (weight-for-age z score < -2 or birth weight <2.4 kg); the CSB+ with IFA group had the lowest incidence of underweight infants at birth (18%, 24%, and 17% in the RUSF, CSB+ with UNIMMAP, and CSB+ with IFA groups, respectively; $P = 0.02$) (**Table 4**). At 6 and 12 wk after birth, no differences in infant anthropometry or hemoglobin were found among intervention groups.

Regression analyses showed evidence of a treatment effect and an effect of duration of treatment on maternal weight gain up until the final weight measurement. The only difference in mean weight gain was found between the RUSF and CSB+ with UNIMMAP treatment groups. Women who received the CSB+ with UNIMMAP treatment gained less than those who received RUSF, 0.14 kg (95% CI: 0.10, 0.70 kg). Regression analyses revealed an association between the duration of feeding and birth length ($P = 0.03$) and weight gain ($P < 0.0001$). Regardless of the treatment group, each additional week of treatment was associated with 0.21 kg of additional weight gain (95% CI: 0.20, 0.23 kg). The regression analyses showed no evidence of a treatment effect on the likelihood that a mother would have an infant who was not stunted at birth. There was evidence of an effect of the duration of treatment. The model showed that the odds of an infant being stunted at birth decreased 3.9% with each additional week the woman received a treatment (OR: 1.03; 95% CI: 1.02, 1.06), and the odds of not having a stunted infant birth for women who received the longest amount of treatment were 2.9 times the odds of women with the shortest duration of treatment (OR: 2.99; 95% CI: 1.6, 5.8).

TABLE 3
Maternal outcomes of a supplemental feeding trial in pregnancy, by treatment group[1]

	RUSF		CSB+ with UNIMMAP		CSB+ with IFA		
Outcome	*n*	Value	*n*	Value	*n*	Value	P[2]
Weight gain from enrollment to final measurement,[3] kg	547	3.4 ± 2.6	540	3.0 ± 2.2	559	3.2 ± 2.4	0.03[4]
Time from enrollment to delivery, wk	572	11.7 ± 6.6	580	11.1 ± 6.4	590	11.4 ± 6.3	0.26
Treatment rations received	572	4.9 ± 2.9	580	4.9 ± 2.8	590	5.0 ± 2.8	0.73
Delivery before receiving second treatment ration	572	32 (6)	580	40 (7)	590	31 (5)	0.53
Weight gain[3] <454 g/wk	547	403 (74)	540	424 (79)	559	408 (71)	0.42
Change in MUAC	572	0.0 ± 0.09	580	0.2 ± 0.8	590	0.1 ± 0.8	0.11
Final MUAC, cm	572	22.2 ± 1.0	580	22.1 ± 0.9	590	22.2 ± 0.9	0.11
Graduated from trial	572	199 (35)	580	168 (29)	590	192 (33)	0.12
Final fundal height, cm	572	31.2 ± 2.6	580	31.0 ± 2.6	590	31.4 ± 2.2	0.12
Final fundal height <28 cm	572	33 (6)	580	39 (6)	590	20 (3)	0.06
Type of pregnancy loss							
Miscarriage	613	5 (0.8)	605	6 (1.0)	610	6 (1.0)	0.94
Stillbirth	613	4 (0.7)	605	11 (1.8)	610	4 (0.7)	0.07
Lost to follow-up	613	26 (4)	605	27 (5)	610	27 (4)	0.99

[1] Values are expressed as means ± SDs or *n* (%). CSB+, fortified corn-soy blend; IFA, iron and folic acid (standard of care); MUAC, midupper arm circumference; RUSF, ready-to-use supplemental food; UNIMMAP, UN International Multiple Micronutrient Preparation.

[2] P values were calculated using one-factor ANOVA (continuous measures) and the chi-square test (categorical measures).

[3] Weight gain analysis includes only women receiving treatment for ≥14 d; 103 women with only 1 visit who had singleton births and were not lost to follow-up were excluded from this analysis.

[4] RUSF was significantly different from CSB+ with UNIMMAP with one-factor ANOVA, which was confirmed by Tukey-Kramer post hoc testing.

TABLE 4
Infant outcomes at birth and at follow-up at 6 and 12 wk, by treatment group[1]

	RUSF		CSB+ with UNIMMAP		CSB+ with IFA		
Outcome	*n*	Value	*n*	Value	*n*	Value	P^2
Birth							
Length, cm	487	47.1 ± 2.2	485	47.0 ± 2.3	495	47.1 ± 2.2	0.75
Weight, kg	487	2.8 ± 0.4	485	2.7 ± 0.4	495	2.7 ± 0.4	0.86
Head circumference, cm	487	34.3 ± 1.6	485	34.1 ± 1.5	495	34.3 ± 1.6	0.13
MUAC, cm	487	9.6 ± 0.9	485	9.5 ± 0.9	495	9.6 ± 0.8	0.12
WFA, *z* score	487	−1.2 ± 1.0	417	−1.3 ± 1.0	495	−1.2 ± 0.9	0.29
LFA, *z* score	487	−1.3 ± 1.2	485	−1.3 ± 1.2	495	−1.3 ± 1.2	0.66
WFL, *z* score[3]	424	−0.4 ± 1.0	485	−0.5 ± 1.1	438	−0.5 ± 1.0	0.33
HCFA, *z* score	487	0.1 ± 1.3	485	−0.5 ± 1.2	495	−0.1 ± 1.3	0.10
Underweight at birth, WFA <−2	487	89 (18)	485	110 (24)	495	81 (17)	0.02[4]
Stunted at birth, LFA <−2	487	107 (23)	485	116 (25)	495	101 (21)	0.32
6 wk of age							
Length, cm	481	53.8 ± 2.3	456	53.6 ± 2.6	485	53.9 ± 2.4	0.13
Weight, kg	481	4.4 ± 0.6	456	4.4 ± 0.7	485	4.4 ± 0.6	0.70
Head circumference, cm	481	38.1 ± 1.4	456	38.0 ± 1.5	485	38.0 ± 1.4	0.60
MUAC, cm	481	11.9 ± 1.0	456	11.8 ± 1.1	485	11.9 ± 1.1	0.67
12 wk of age							
Length, cm	443	58.2 ± 2.5	444	58.2 ± 2.6	456	54.4 ± 2.5	0.67
Weight, kg	443	5.5 ± 0.7	444	5.6 ± 0.8	456	5.5 ± 0.8	0.62
Head circumference, cm	443	40.4 ± 1.6	444	40.3 ± 1.4	456	40.3 ± 1.5	0.35
MUAC, cm	443	13.0 ± 1.1	444	13.1 ± 1.1	456	13.0 ± 1.2	0.63
Infant deaths[5]	443	29 (4.6)	444	23 (4.3)	456	19 (3.1)	0.71

[1] Values are expressed as means ± SDs or *n* (%). CSB+, fortified corn-soy blend; HCFA, head-circumference-for-age; IFA, iron and folic acid (standard of care); LFA, length-for-age; MUAC, midupper arm circumference; RUSF, ready-to-use supplemental food; UNIMMAP, UN International Multiple Micronutrient Preparation; WFA, weight-for-age; WFL, weight-for-length.

[2] *P* values were calculated with one-factor ANOVA (continuous measures) and the chi-square test (categorical measures).

[3] For WFL *z* scores, 188 infants were excluded because they were too short (<45.00 cm).

[4] CSB+ with UNIMMAP was significantly different from CSB+ with IFA.

[5] Infant death was defined as death reported by the mother or local health workers before 12 wk of age.

There were 161 women who delivered before their return for their first follow-up visit and thus received only one ration of food. An analysis comparing women who received <14 d of treatment with women who received ≥14 d of treatment was completed. Women who did not receive a second treatment ration were less food insecure and had a higher BMI and FH (**Supplemental Table 2**). Infants born to women receiving only one ration had a lower length by 0.4 cm ($P = 0.01$) and lower birth weight by 100 g ($P = 0.02$) (**Table 5**). The differences in weight and length seen at birth were also apparent at 3 mo of life.

Pregnancy outcomes were compared for the 194 women with HIV and for those without HIV. Women with HIV were older and were less likely to be primigravid. These women also had a lower BMI and smaller triceps skinfold thickness and were more likely to be taking medications in the 14 d before enrollment (**Supplemental Table 3**). No significant differences between participants with and without HIV were observed for maternal outcomes (**Supplemental Table 4**). Birth length and weight were not affected by maternal HIV status, but head circumference at birth was smaller in HIV-exposed infants. At 12 wk, HIV-exposed infants were shorter, weighed less, had a smaller head circumference, and had a smaller MUAC (**Table 6**).

DISCUSSION

In this randomized controlled supplemental feeding trial of pregnant women with moderate malnutrition in Malawi, women given RUSF gained more weight from the initiation of treatment until their final clinic visit than women given CSB+ with UNIMMAP, but there were no significant differences in weight gain between the standard of care (CSB+ with IFA) group and the RUSF or and the CSB+ with UNIMMAP group. In all groups, maternal rates of weight gain were very low: 75% of participants who received a second treatment ration had an average weight gain of <454 g/wk from the time of treatment initiation until the final weight measurement.

Mean birth weights and lengths were not affected by the type of dietary treatment provided to women during pregnancy and the mean length-for-age *z* score at birth was −1.3, which is well below what might be expected in a well-nourished population. The duration of treatment was associated with a reduction in the likelihood that a woman would have a stunted infant at birth. The duration of feeding ranged from 1 to 28.6 wk but was 9.4 wk on average.

This study is limited in that no true control group was included. National guidelines in Malawi prescribe that moderately malnourished pregnant women should receive supplemental food,

TABLE 5
Infant outcomes comparing pooled treatment groups treated ≥14 d to pooled treatment groups treated <14 d[1]

Outcome	Received treatment ≥14 d		Received treatment <14 d		P^2
	n	Value	*n*	Value	
Birth					
Length, cm	1376	47.1 ± 2.2	91	46.7 ± 2.3	0.01
Weight, kg	1376	2.7 ± 0.4	91	2.6 ± 0.4	0.02
WFA, *z* score <−2	1376	259 (19)	91	21 (23)	0.44
Head circumference, cm	1376	34.2 ± 1.6	91	34.0 ± 1.5	0.18
MUAC, cm	1376	9.6 ± 0.8	91	9.5 ± 0.9	0.29
6 wk of age					
Length, cm	1359	53.8 ± 2.4	63	53.4 ± 2.9	0.28
Weight, kg	1359	4.4 ± 0.6	63	4.3 ± 0.7	0.20
Head circumference, cm	1359	38.0 ± 1.4	63	38.0 ± 1.7	0.83
MUAC, cm	1359	11.9 ± 1.1	63	11.7 ± 1.4	0.16
12 wk of age					
Length, cm	1273	58.3 ± 2.5	70	57.6 ± 2.8	0.03
Weight, kg	1273	5.6 ± 0.7	70	5.3 ± 0.8	0.01
Head circumference, cm	1273	40.3 ± 1.5	70	40.2 ± 1.6	0.10
MUAC, cm	1273	13.1 ± 1.1	70	12.8 ± 1.2	0.36

[1] Values are expressed as means ± SDs or *n* (%). MUAC, midupper arm circumference; WFA, weight-for-age.

[2] *P* values were calculated with Student's *t* test (continuous measures) and Fisher's exact test (categorical measures).

TABLE 6
Infant outcomes from malnourished pregnant women comparing pooled treatment groups with women with HIV to pooled treatment groups with women without HIV[1]

Outcome	Women with HIV		Women without HIV		P^2
	n	Value	*n*	Value	
Birth					
Length, cm	164	46.8 ± 2.2	1303	47.1 ± 2.3	0.09
Weight, kg	164	2.7 ± 0.4	1303	2.7 ± 0.4	0.73
WFA, *z* score <−2	164	33 (21)	1303	247 (19)	0.86
Head circumference, cm	164	34.0 ± 1.5	1303	34.3 ± 1.6	0.02
MUAC, cm	164	9.6 ± 0.9	1303	9.6 ± 0.8	0.87
6 wk of age					
Length, cm	165	53.5 ± 2.5	1257	53.8 ± 2.4	0.13
Weight, kg	165	4.2 ± 0.6	1257	4.4 ± 0.6	<0.01
Head circumference, cm	165	37.6 ± 1.3	1257	38.1 ± 1.5	<0.01
MUAC, cm	165	11.6 ± 1.0	1257	11.9 ± 1.1	<0.0.
12 wk of age					
Length, cm	157	57.6 ± 2.5	1186	58.0 ± 2.5	<0.01
Weight, kg	157	5.3 ± 0.8	1186	5.6 ± 0.7	<0.01
Head circumference, cm	157	39.8 ± 1.5	1186	40.4 ± 1.5	<0.01
MUAC, cm	157	12.8 ± 1.3	1186	13.1 ± 1.1	<0.01

[1] Values are expressed as means ± SDs or *n* (%). MUAC, midupper arm circumference; WFA, weight-for-age.

[2] *P* values were calculated with Student's *t* test (continuous measures) and Fisher's exact test (categorical measures).

although this is rarely done in practice. Thus, it would be unethical not to offer these women some supplemental food; therefore, these data do not inform us about birth outcomes in untreated moderately malnourished pregnant women. In addition, data regarding gestational age may have been strengthened if ultrasonography had been employed; therefore, this trial does inform of what effects dietary interventions might have when initiated at gestational age points during pregnancy. Use of ultrasonography is not routine in Malawi or in most rural clinics in Africa. Our goal in this study was to work within the context of current antenatal care in rural Malawi and to design a research study that could be implemented at a programmatic level in the future; thus, we did not include ultrasonographic evaluation in this study.

The 161 women who delivered before receiving their second treatment ration represent women who were later in their pregnancies and those who delivered prematurely. Outcomes observed among these women were what might be expected, in that their infants were smaller at birth than women who received more treatment rations, but infant weights and lengths at 3 mo were similar. A small effect of 0.4 cm was observed for birth length when women who received food for >14 d were compared with those who received treatment for <14 d; however, no effect between groups was observed when analyzed by food group.

For women with HIV, there was no observed effect of any one of the intervention groups compared with another, but the sample size of 189 women is quite small to detect such differences. Women with HIV were more likely to have regular health care visits and take medication, given their HIV status. The birth anthropometry of infants born to women with HIV was similar to that of infants born to women without HIV; however, we observed that HIV-exposed infants had a 0.3-cm smaller head circumference at birth. It is also notable that growth faltering was observed in HIV-exposed infants after birth.

In the past 50 y, both observational and experimental studies have been conducted to assess the effect of food supplementation or dietary intake on neonatal outcomes (15). Multiple micronutrient supplementation in pregnancy was shown to decrease SGA births by 11–13% (15). In a pooled analysis of 15 trials, Kawai et al. (16) found that maternal multiple micronutrient supplementation increased birth weight (pooled mean difference: 44 g; 95% CI: 28, 60 g) and reduced the number of low-birth-weight infants (pooled RR: 0.86; 95% CI: 0.79, 0.93) compared with IFA supplementation. Although multiple micronutrient supplementation led to larger babies, it showed no effect on preterm delivery (pooled RR: 0.99; 95% CI: 0.95, 1.03). A multiple micronutrient supplementation trial in rural Bangladesh, however, showed a significant reduction in risk for preterm birth (RR: 0.85; 95% CI: 0.80, 0.91; $P = 0.001$) and low birth weight (RR: 0.88; 95% CI: 0.85, 0.91; $P < 0.001$) compared with IFA (17).

Balanced protein-energy supplements have shown the most persuasive evidence for the prevention of adverse neonatal outcomes, reducing the rate of SGA births by 44% and the prevalence of low birth weight by 32% (18). A recent review by Papathakis et al. (19) showed that protein-energy supplements increased birth weight by ~74 g, comparable to the 73 g (95% CI: 30, 117 g) reported in the review by Imdad and Bhutta (18). Two studies that evaluated the effects of supplemental with prenatal LNSs showed that LNSs increased birth weight by 85 g on average ($P = 0.04$) in Ghanaian infants (7) but had a more modest effect in Bangladeshi infants, increasing mean birth weight by only 46 g ($P < 0.01$) (20). Effects on birth length were less significant. Imdad and Bhutta (18) reported a mean difference of 0.16 cm (95% CI: 0.02, 0.31 cm), which is smaller than the mean difference of 0.20 cm ($P < 0.01$) reported in

Bangladeshi infants (20). No significant effect for length was found in the Ghana study (7).

In our study, only about one-third of women increased their MUAC to >23.0 cm and ~52% of their MUAC stayed >23.0 cm despite receiving a generous ration of supplemental food and micronutrients. Change in MUAC also did not correlate well with maternal weight gain. A review of outcomes associated with anthropometric measurements during pregnancy, a MUAC of <23.0 cm was associated with intrauterine growth restriction and LWB but is limited, because the research included mostly adult pregnancies and varied for at what time point MUAC measured (9). The small change in MUAC in addition to high relapse rates suggests that MUAC may be most appropriately used as an identification measurement for malnutrition rather than a criterion on which to stop feeding during treatment. Evidence has also suggested that low weight gain for even brief periods during pregnancy increases the risk of fetal stunting (21). Consequently, the lack of continuity of feeding throughout the second and third trimesters attributable to this recovery criterion could have contributed the limited treatment effects seen in this study.

Maternal undernutrition, especially during the second and third trimesters, is associated with reduced birth weight and length (15). The mean birth weight and mean birth length in this study were equivalent to <15th percentile of the WHO weight- and length-for-age growth standards, with 22% of infants stunted at birth and 19% of infants underweight at birth. Compared with the national statistics of 37% of children <5 of age being stunting in Malawi, it appears that >50% of stunting begins in utero and is evident at birth (22).

In this study, the size of the supplemental ration was substantial and there were no indications that compliance was poor, yet 22% of newborns were stunted at birth. It seems clear that food and micronutrient supplementation alone was not enough in the rural Malawian context to affect better growth in utero. The relatively modest benefits seen from these treatment regimens alone should prompt a renewed focus on the paradigm that a multitude of domains, such as diet, inflammation, gut health, and epigenetics, affect growth in utero (23). Research on some of these domains has been conducted in pregnant women (most notably, malaria and other interventions against infectious diseases); although these studies have helped reduce the risk of prematurity, fetal growth stunting, and SGA birth, their impact has also been modest (24). Interventions that include a combination of both nutrition-specific and nutrition-sensitive interventions to affect multiple domains may be necessary to improve growth in utero (25). Trials exploring this issue should be given high priority in the future.

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