Prenatal food supplementation fortified with multiple micronutrients increases birth length: a randomized controlled trial in rural Burkina Faso[1–4]

Lieven Huybregts, Dominique Roberfroid, Hermann Lanou, Joris Menten, Nicolas Meda, John Van Camp, and Patrick Kolsteren for the MISAME Study Group

ABSTRACT

Background: Prenatal multiple micronutrient (MMN) or balanced energy and protein supplementation has a limited effect on birth size of the offspring.

Objective: The objective was to determine whether a prenatal MMN-fortified food supplement (FFS) improves anthropometric measures at birth compared with supplementation with an MMN pill alone.

Design: We conducted a nonblinded, individually randomized controlled trial in 1296 pregnant women in 2 villages in rural Burkina Faso. Supplements were provided on a daily basis, and compliance was closely verified by using a community-based network of home visitors.

Results: Anthropometric measures at birth were available for analysis for 87% of the 1175 live singleton deliveries enrolled. After adjustment for gestational age at birth, the FFS group had a significantly higher birth length (+4.6 mm; $P = 0.001$). FFS supplementation resulted in a modestly higher birth weight (+31 g; $P = 0.197$). Subgroup analyses showed clinically important treatment effects on birth length (+12.0 mm; $P = 0.005$) and on birth weight (+111 g; $P = 0.133$) for underweight [body mass index (in kg/m^2) <18.5] pregnant women. Women with early pregnancy anemia who received FFS gave birth to longer newborns (+7.3 mm; $P = 0.002$) than did those who received MMN supplementation.

Conclusions: The provision of FFS to pregnant women resulted in higher birth length than did MMN supplementation. For women with a suboptimal prepregnancy nutritional status, MMN supplementation should be complemented with a balanced energy and protein supplement to produce a clinical effect on birth size. The trial was registered at clinicaltrials.gov as NCT00909974. *Am J Clin Nutr* 2009;90:1593–600.

INTRODUCTION

Infants born with a low birth weight (LBW; birth weight $<$ 2500 g) are at higher risk of neonatal morbidity and mortality (1) and adverse health outcomes in adulthood (2, 3). Additionally, newborns with LBW have a greater risk of lower cognitive capacity (4) and behavioral problems during infancy and childhood (4, 5). Because the prevalence of LBW in Sub-Saharan African is estimated to be as high as 14% (6), improving the nutritional status of newborn children is a high priority on the public health agenda.

LBW is an indicator of both premature delivery and poor fetal growth in countries where the estimation of gestational age is challenging. Intrauterine growth retardation (IUGR) due to suboptimal maternal nutrition is considered the main cause of LBW in developing countries (7). However, the relation between maternal nutrition status and fetal growth is complex (7, 8), and various types of interventions to improve maternal nutrition have yielded modest and conflicting results on LBW (9). Whereas high-protein supplements seem to lead to a higher risk of smaller and thinner newborns (10), balanced protein and energy supplementation appears to have only a modest effect on birth weight, excepted in one study in The Gambia (11), which showed a significant increase in birth weight (by 136 g) after energy-dense biscuits were provided (4.25 MJ/d) during pregnancy.

During the past decade, the hypothesis that multiple micronutrient (MMN) deficiencies could hamper fetal growth was put forward and tested in several randomized controlled trials. Recently, we showed that daily MMN supplementation resulted in a modestly higher birth weight (52 g; $P = 0.035$) and birth length (3.6 mm; $P = 0.012$) than did daily iron and folic acid supplementation (12). These outcomes were confirmed by a recent meta-analysis combining well-designed MMN intervention studies in several countries (13). A striking conclusion in most of these studies was that effects of MMN on birth weight were greater in mothers with a higher body mass index (BMI; in kg/m^2) (14).

[1] From the Department of Food Safety and Food Quality, Ghent University, Ghent, Belgium (LH, HL, JVC, and PK); the Child Health and Nutrition Unit, Department of Public Health, Institute of Tropical Medicine, Antwerp, Belgium (DR, JM, and PK); the Centre Muraz, Ministry of Health, Bobo-Dioulasso, Burkina Faso (NM); and IRSS, Ouagadougou, Burkina Faso (HL).

[2] None of the sponsors had any role in the study design, data collection, data analysis, or writing of the report.

[3] Supported by Flemish University Council, Nutrition Third World, and the Belgian Ministry of Development. The multiple micronutrient premix was donated by Nutriset, France.

[4] Address correspondence to P Kolsteren, Child Health and Nutrition Unit, Department of Public Health, Institute of Tropical Medicine, 155, Nationalestraat, 2000 Antwerp, Belgium. E-mail: pkolsteren@itg.be.

Received June 17, 2009. Accepted for publication September 1, 2009.
First published online October 7, 2009; doi: 10.3945/ajcn.2009.28253.

A possible explanation for the modest and sometimes conflicting results on birth size observed in food or MMN supplementation studies could be that they addressed only partially the additional nutritional needs during pregnancy. We hypothesized that providing a daily prenatal balanced energy/protein (<25% of the energy from protein) dietary supplement enriched with MMN would result in a higher birth weight and birth length than would a daily MMN supplementation alone. To our knowledge this is the first study that directly compared the effect of providing extra FFS with MMN supplementation in a developing country.

SUBJECTS AND METHODS

Study site and population

The study was performed in Burkina Faso, a country characterized by 16% LBW prevalence (6) and multiple MMN deficiencies. A previous study in the same health district reported that in a community-based sample of 2999 pregnant women, 63.1% (1892/2999) suffered from anemia (hemoglobin < 11.0 g/dL); in a subsample, 69.4% (218/314) of the pregnant women had serum retinol concentrations <20 μmol/dL (15). Additionally, the usual energy intake from fat in this rural community was found to be low (16); therefore, ideally, a food supplement should contain a reasonable amount of fat. The study was conducted from March 2006 to July 2008 in the catchment area of 2 rural health centers (total inhabitants ≈12,000) of the health district of Houndé, Tuy Province, in the midwest area of the country, after the termination of our previous intervention study (12). The climate is Sudano-Sahelian, with one rainy season between May and September–October. The staple food is mainly maize, which is consumed with a complement of leafy vegetables (16). The region is malaria endemic. A community-based network of 30 home visitors visited all women of childbearing age monthly at their homes to screen for amenorrhea. In case of a suspected pregnancy, women were referred to the health center for a formal pregnancy test. No exclusion criteria were used except that participants planning to leave the study area within the next 2 y were not eligible.

Supplements

The fortified food supplement (FFS) intervention group was given a fortified spread consisting of 33% peanut butter, 32% soy flour, 15% vegetable oil, 20% sugar, and an MMN cocktail providing the Recommended Daily Allowance for pregnant women. This allowance was based on previous studies that showed that the energy intake during the different trimesters of gestation did not differ from that of women who were not pregnant (16). The composition of the MMN cocktail was equal to that of the UNICEF/WHO/UNU International Multiple Micronutrient Preparation (UNIMMAP) (17) and was made available by Nutriset (Malauny, France). A daily FFS dose of 72 g provided 1.56 MJ (372 kcal) and 14.7 g protein. The complete nutritional composition of both supplements is given in **Table 1**. The MMN intervention received UNIMMAP daily in the form of a tablet manufactured by Scanpharm (Copenhagen, Denmark). The MMN was the same as used in the study by Roberfroid et al (12).

TABLE 1
Nutritional composition of a single dose (72 g) of fortified food supplement (FFS) and an International Multiple Micronutrient Preparation (UNIMMAP) multiple micronutrient (MMN) tablet[1]

Nutrient	FFS	MMN
Energy (MJ)	1.56	—
Energy from protein (%)	15.8	—
Energy from fat (%)	67.0	—
Carbohydrates (g)	15.9	—
Protein (g)	14.7	—
Fat (g)	27.6	—
SFA (g)	8,1	—
MUFA (g)	12.1	—
PUFA (g)	7.3	—
ω-3 Fatty acids (g)	0.4	—
ω-6 Fatty acids (g)	7.0	—
Total dietary fiber (g)	9.1	—
Vitamin A (RE)	881	800
Vitamin D (IU)	200	200
Vitamin E (mg)	13	10
Thiamine (mg)	1.6	1.4
Riboflavin (mg)	1.6	1.4
Niacin (mg)	21	18
Vitamin B-6 (mg)	2.0	1.9
Folate (μg)	461	400
Vitamin B-12 (μg)	2.6	2.6
Vitamin C (mg)	71	70
Zinc (mg)	17	15
Iron (mg)	35	30
Copper (mg)	2.7	2.0
Selenium (μg)	65	65
Iodine (μg)	150	150
Calcium (mg)	90	—

[1] SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids; RE, retinol equivalents.

The spread consisted of a powder-in-fat mixture, which has been shown to have good oxidative and microbiological stability (18). The FFS was pretested during a pilot phase, and the most acceptable recipe for the FFS was determined by an acceptability study evaluating 10 different recipes of FFS by using a convenience sample of 160 pregnant women. The supplement was produced by a local women's association, and the micronutrients were dosed by a laboratory technician. The homogeneity of the FFS was verified by analyzing iron and zinc levels of 10 subsamples per batch produced. To ensure the food safety of the food supplement, peanut butter samples were analyzed for aflatoxin B1 and total aflatoxin with liquid chromatography–tandem mass spectrometry by using an in-house validated method. All of 10 samples had aflatoxin B1 and total aflatoxin concentrations that were significantly lower than the European upper levels of 2 and 4 μg/kg, respectively (19).

Study allocation and design

A randomization scheme was generated by a computer program in permuted blocks of 4. Randomization numbers were sealed in opaque envelopes by administrative staff. After identifying an eligible subject, the consulting physician in the field opened the next sealed envelope. For allocations to the MMN group, he transmitted the randomization number to a pharmacist packaging the MMN in individual plastic zip sachets containing

31 tablets. For allocation to the FFS group, project staff prepared a plastic bag containing 31 FFS sachets. Each sachet of MMN or FFS was labeled with the woman's name, geographic location, and identification number. Home visitors kept both the MMN and FFS with them and visited 10–20 participants per day to provide and directly observe the supplement intake. Home visitors recorded on a daily basis gestational morbidity and monitored miscarriage and still births. Additionally, as part of a different study on malaria prevention, women were also randomly assigned to receive either a double dose or a triple dose of combined sulfadoxine-pyriméthamine in the second and third trimesters. The results of the malaria study will be presented elsewhere.

In case of malaria infection, quinine (300 mg, 3 times/d) was used. Severely anemic (hemoglobin $<$ 7 g/dL) participants were given iron (200 mg) and folic acid (250 μg) tablets twice daily for 3 mo. During the second and third trimesters, all participants received albendazole (400 mg) as a deworming agent.

After the aims and modalities of the study were explained in the local languages, written consent was sought and obtained from all participants. The study was approved by the ethical committees of the Center Muraz, Bobo-Dioulasso, Burkina Faso, and the Institute of Tropical Medicine, Antwerp, Belgium.

Measurements

All measurements and quality control were organized as described by Roberfroid et al (12). Moreover, placental weight was recorded by a digital weighing scale (TEFAL, Fleurus, Belgium) to the nearest 1 g. Placentas were weighed untrimmed without removing the cord. The weighing scales were calibrated daily.

Statistical analyses

The primary outcomes of the study were birth weight, birth length, and Rohrer's ponderal index [weight/length^3 (g/cm^3)]. Birth length and ponderal index were measured to distinguish between short and thin newborns. The secondary outcomes included the percentage of LBW infants ($<$2500 g); the percentage of small-for-gestational age (SGA) infants, defined as birth weight lower than the 10th percentile of a well-nourished reference population (20); the percentage of large-for-gestational age (LGA) infants, defined as birth weight higher than the 90th percentile of our cohort population; thoracic circumference, head circumference, and midupper arm circumference at birth; placental weight (recorded because of its specific mediating role in nourishing the fetus) (21); cord hemoglobin concentration; the percentage of preterm births (born $<$37wk); the percentage of miscarriages (defined as fetal loss before 28 wk of gestation); the percentage of stillbirths (delivery of an infant showing no sign of life after 28 wk of gestation); and the percentage of perinatal deaths (stillbirth or death of a live born infant in the first 7 d after birth) and neonatal death (death within the first 28 d of life). The compliance rate was calculated by dividing the total number of supplements effectively taken under direct observation by the theoretical number of supplements allowed, ie, the number of days between inclusion and censorship. Loss to follow-up was defined as a period of nonparticipation $>$2 wk.

All analyses were performed on an intention-to-treat basis. Data are presented as means ± SDs. Only singleton pregnancies were included in the analysis. The necessary sample size was set at 1260 women to detect a 90-g difference in birth weight between both groups, with an SD of 450 g (12), a statistical power of 90%, a type I error of 5%, and a 20% anticipated drop-out level. This sample size allowed the detection of a difference in birth length of 5 mm between the control and intervention groups.

To estimate the influence of missing outcome data, outcome analysis was repeated after imputation of missing birth weights, birth lengths, and placental weights under the "missing at random" assumption. For this purpose the STATA command MICE for chained equations (22) with 50 imputations was used. Predictors for the regression model for imputation were maternal age, height, gravidity, malaria prevention, place of delivery (home/health center), gestational age at delivery, and maternal weight gain during pregnancy. Maternal weight (intercept) and maternal weight increases during pregnancy (slope) were estimated from a random-effects model of the maternal weights during the pregnancy: 155 (13.2%) birth weights, 156 (13.3%) birth lengths, and 185 (24.3%) placental weights were imputed.

The effect of the intervention on the outcomes was analyzed by using linear regression (continuous variables) or logistical regression (binary variables). All analyses were adjusted for health center catchment and malaria prevention regimen to account for the study design. Additional tests to estimate the effect of the intervention on IUGR, regardless of premature delivery, were performed with adjustment for gestational age. The interaction between gestational age at delivery and intervention group on each of the outcomes was evaluated by adding the interaction term (gestational age $\times$ intervention group) in the regression models. Statistical significance was set at $P < 0.05$, and all statistical tests were 2-sided. A Pearson's correlation test was used to evaluate the association between parametric continuous variables.

Exploratory analyses were performed to evaluate the differences between FFS and MMN on 3 relevant sets of subgroups defined by maternal BMI at inclusion, maternal hemoglobin concentration at inclusion, and primigravidae. Mothers who enter pregnancy underweight (BMI $<$ 18.5) or anemic (hemoglobin $<$ 11 g/dL) (23–26) and primigravid mothers (23, 24) are known to have a higher risk of having LBW offspring. A subgroup analysis according to anemia status was redone restricting the analysis to women enrolled during the first trimester of gestation. The latter was done to avoid the influence of plasma expansion on hemoglobin concentration, which is believed to start taking effect from 10 to 12 wk of gestation (27). Interactions between intervention group and subgroups were considered significant at $P < 0.1$. All analyses were done with STATA 10.0 (StataCorp, College Station, TX).

RESULTS

From March 2006 to December 2007, 1296 mothers were enrolled in the study (**Figure 1**). Outcome data were available for 1020 of 1296 pregnant women. Overall, baseline characteristics were balanced over the study groups, except that women allocated to the FFS group were smaller ($-$0.62 cm; P = 0.062) and less anemic (41.6% compared with 48.8%; P = 0.013) (**Table 2**). The main reason for missing birth weights was delivery at home. Baseline characteristics for missing birth

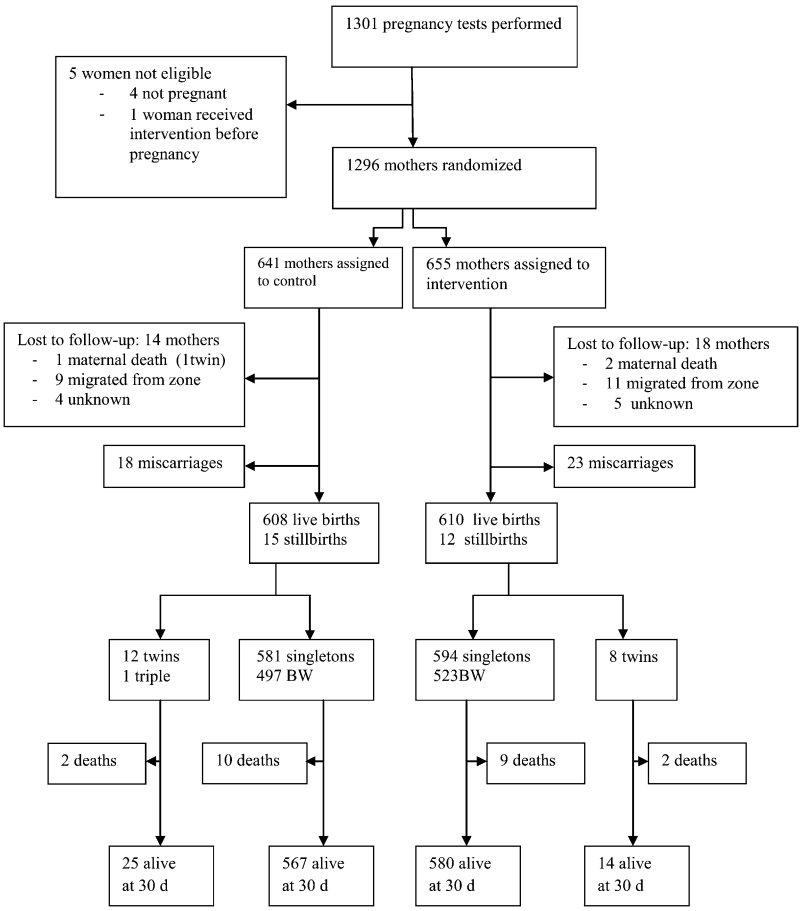

FIGURE 1. Trial profile of the study. BW, birth weight.

weights were not significantly different between the FFS and MMN group.

Compliance was slightly unbalanced between study groups: 75.4% for the FFS group and 77.1% for the MMN group (P = 0.183). Five women in the FFS group refused the supplement, mainly because of its sweet taste, whereas none of the MMN group participants refused the supplement.

After adjustment for gestational age at delivery, birth weight did not differ significantly between groups (**Table 3**). However, birth length was 4.6 mm (95% CI: 1.8, 7.3; P = 0.001) higher on average in the FFS group. However, multiple regression models including treatment (FFS compared with MMN), gestational age at delivery, and birth length as covariates showed that FFS did not result in thinner (ponderal index: −0.018 g/cm^3; 95% CI: −0.054, 0.017; P = 0.308) or lighter newborns (birth weight: −16.9 g; 95% CI: −53.8, 20.0; P = 0.370).

Placental weight was 15.6 g (95% CI: 0.4, 30.7; P = 0.044) higher, on average, for newborns in the FFS group. No significant interaction between gestational age at delivery and intervention group on any of the outcomes was found. The analyses were carried out again with adjustment for apparent baseline imbalances in maternal height and anemia prevalence and after the imputation of missing outcome data. In both cases, the results were very similar to those of the initial analysis (data not shown).

There were no significant difference in stillbirth or neonatal mortality rates (**Table 4**). Two cesarean sections were performed in mothers in the FFS group and 4 in mothers in the MMN group. The effect of FFS on birth length was modified by maternal BMI (P for interaction = 0.102) and maternal anemia (P for interaction = 0.053) at inclusion, and the effect on placental weight was modified by gravidity (P for interaction = 0.029) and maternal BMI at inclusion (P for interaction = 0.100) (**Table 5**).

FFS appeared to have more of an effect on placental weight (+55.5 g; 95% CI: 17.2, 93.9; P = 0.005) for primigravidae than for multigravidae. On the other hand, it is noteworthy to report that FFS was only efficacious for birth length in multigravid women. FFS was more efficacious for birth length (+12.0 mm; 95% CI: 3.7, 20.2; P = 0.005), placental weight (+54.6 g; 95% CI: 10.0, 99.2; P = 0.017), and birth weight (+111 g; 95% CI: −34, 256; P = 0.133) in mothers who were underweight at enrollment. In addition, the mean birth length was 7.3 mm (95% CI: 2.7, 11.8; P = 0.002) higher in the FFS mothers who were anemic at enrollment. No treatment effect on birth weight and length was noticed in nonanemic mothers. The hemoglobin concentration and BMI at study inclusion showed only a weak correlation (r = 0.039, P = 0.107).

We repeated the analyses excluding mothers who were not enrolled during the first trimester to avoid the influence of plasma expansion on hemoglobin concentration. Birth weight was higher by 143.8 g (95% CI: −5.8, 293.4; P = 0.059), birth length was higher by 8.4 mm (95% CI: −0.3, 17.2; P = 0.058), and placental weight was higher by 35.2 g (95% CI: −16.2, 86.7; P = 0.177) in the anemic group, which was given FFS. No differences in the effects were found in the nonanemic group.

TABLE 2
Characteristics at study enrollment for 1296 participants according to study group[1]

Characteristics	MMN (n = 641)	FFS (n = 655)
Gestational age (wk)	16.1 ± 6.7[2]	16.2 ± 6.9
Trimester [n (%)]		
First	251 (39.2)	255 (38.9)
Second	356 (55.5)	346 (52.8)
Third	34 (5.3)	54 (8.2)
Maternal age (y)	24.5 ± 6.3	24.6 ± 6.2
School attendance [n (%)]		
No	568 (88.6)	576 (84.8)
Primary	46 (7.2)	67 (10.2)
Secondary	14 (2.2)	15 (2.3)
Gravidity [n (%)]		
0	133 (20.7)	132 (20.2)
1–2	226 (35.3)	231 (35.3)
≥3	282 (44.0)	292 (44.6)
At least one previous fetal death [n (%)]	133 (20.7)	111 (16.9)
No. of previous child deaths [n (%)]		
0	187 (36.8)	215 (41.1)
1–2	252 (49.6)	244 (46.7)
≥3	69 (13.6)	64 (12.2)
BMI (kg/m^2)	21.0 ± 2.2	20.8 ± 2.2
BMI <18.5 kg/m^2 [n (%)]	80 (12.5)	87 (13.3)
Maternal height (cm)	163.0 ± 5.8	162.3 ± 6.1
Maternal MUAC (cm)	26.0 ± 2.2	25.8 ± 2.2
Hemoglobin at enrollment (g/dL)[3]	11.0 ± 1.6	11.2 ± 1.6
<7 g/dL [n (%)]	4 (0.6)	4 (0.6)
<11 g/dL [n (%)]	287 (44.8)	251 (38.3)
≥11 g/dL [n %)]	301 (47.0)	352 (53.7)

[1] MMN, multiple micronutrient tablet; FFS, fortified food supplement; MUAC, midupper arm circumference.
[2] Mean ± SD (all such values).
[3] Values at enrollment were not available for 105 participants (n = 53 for the MMN group and 52 for the FFS group).

DISCUSSION

The results of our study showed that daily supplementation with FFS resulted in a higher birth length than did daily MMN supplementation, whereas only a slightly, but insignificantly, higher birth weight was detected. FFS did not lead to lower incidences of LBW and SGA.

This study had many limitations. First, it was impossible to blind participants or project collaborators for the intervention allocation. However, care was taken to blind staff who performed the anthropometric measurements at delivery; measurement bias was therefore unlikely. Second, compliance with the intervention was lower than expected. The main reason was that some participants left the study area from time to time for weekly field labor. In such cases, supplements for 1 wk were provided but their intake was not directly observed and thus not recorded. Last, despite our active home-visitors network, the proportion of women included early in pregnancy was lower than expected. This was mainly due to culturally defined practices surrounding pregnancy disclosure, particularly in the Mossi population.

The lack of effect of FFS on birth weight has several possible explanations. First, contrary to the study in The Gambia, which reported a major positive effect on birth weight, our reference group was given MMN, which is also known to increase birth weight. Second, the daily amount of supplemented energy (1.56 MJ/d) was lower than that in the study in The Gambia (4.25 MJ/d) (11). Because we did not target the supplementation on undernourished mothers only, a more modest amount of energy was provided but under strict control of compliance. Third, the treatment effect could be flawed by diet substitution. However, the latter is considered less likely because of the small portion size of the FFS (72 g). Additionally, from a dietary assessment substudy in 257 pregnant women, which used three 24-h dietary recalls, we found higher energy (+1716 kJ; $P < 0.001$), protein (+16.4 g; $P < 0.001$), and fat (+24.8 g; $P < 0.001$) intakes in participants from the FFS group than in participants from the MMN group (Huybregts et al, unpublished observations, 2006).

The significant effect of FFS on birth length was unexpected, but is of major public health importance in the prevention of early life stunting (28). On the basis of a meta-analysis of 6 studies, Kramer and Kakuma (29) calculated an insignificantly higher birth length by 0.10 cm (95% CI: −0.06, 0.26) with a balanced energy and protein supplementation. A study in Chile compared the effect of a milk-based supplement containing MMN and ω-3 (n−3 fatty acids) with a milk-based supplement and found taller (+3.7 mm; $P = 0.019$) and heavier (+65.4 g; $P = 0.034$) infants (30). Previously, we found that the mean birth length in the MMN group was 3.6 mm higher than in the iron and folic acid intervention group (12). From the results presented herein, it appeared that incorporation of the MMN in a fat-rich food supplement would add to this effect.

The mechanism by which FFS could lead to a higher birth length remains unknown, but it is noteworthy that the FFS provided energy mainly from fat, whereas the dietary energy intake from fat in these pregnant women is known to be well below the minimal recommended intake of 20% (16, 31). An observational study from India suggested that mothers who consumed more fat, independently of energy intake, at weeks 18 and 25 of gestation, gave birth to newborns with a higher neonatal length (32). On the other hand, the negative effect of micronutrient interactions (eg, zinc-iron) on absorption appears less pronounced in fortified food matrices than in concentrated pharmacologic formulas (33).

Primigravidity is a well-established but not fully understood risk factor for poor birth outcome (23, 24). From our earlier intervention study (12), MMN was only effective on birth weight and birth length in multigravid women. Although the interaction test was not statistically significant, the results from this study consistently showed that FFS resulted in a higher birth length only in multigravid women, with no differential effect on birth weight. Two hypotheses are put forward for this: the nutritional supplementation is either insufficient because of the possibly higher nutritional requirements of, typically younger, primigravid women or poor birth outcome related to first pregnancies is not nutritionally mediated. Primigravid women had lower hemoglobin concentrations, but similar BMIs, at study inclusion compared with multigravid women. The pronounced effect of FFS on mean placental weight in primigravid women was somewhat surprising, especially in the absence of a treatment effect on mean birth weight. Some authors proposed placental development as a "nutritional indicator" related to birth weight (21, 34). However, the importance of placental weight as an index, independent of birth weight, for later child development and health is poorly documented, and most of the nutritional intervention studies did not report placental weight as an outcome.

TABLE 3
Primary and secondary outcome data for the study groups[1]

	MMN		FFS					
Outcome	*n*	Values	*n*	Values	Difference/OR (95% CI)[2]	*P*	Difference/OR (95% CI)[3]	*P*
Birth weight (g)	497	2931 ± 433[4]	523	2943 ± 456	12 (−43, 67)	0.666	31 (−16, 78)	0.197
LBW [*n* (%)]	497	67 (13.5)	523	67 (12.8)	0.94 (0.65, 1.35)	0.746	0.79 (0.52, 1.19)	0.259
SGA [*n* (%)]	494	177 (35.8)	518	167 (32.2)	0.85 (0.65, 1.10)	0.218	—	—
LGA [*n* (%)]	497	44 (8.9)	523	60 (11.5)	1.34 (0.89, 2.02)	0.167	1.40 (0.92, 2.13)	0.119
Birth length (mm)	497	476 ± 24	522	480 ± 26	3.7 (0.6, 6.7)	0.020	4.6 (1.8, 7.3)	0.001
Arm circumference (mm)	493	102.5 ± 9.2	518	103.0 ± 9.5	0.51 (−0.64, 1.67)	0.384	0.76 (−0.32, 1.85)	0.167
Head circumference (mm)	497	334.7 ± 15.8	522	334.3 ± 17.7	−0.45 (−2.52, 1.61)	0.668	0.10 (−1.79, 2.00)	0.914
Ponderal index (g/cm^3)[5]	497	2.7 ± 0.3	522	2.7 ± 0.3	−0.053 (−0.092, −0.012)	0.010	−0.048 (−0.088, −0.009)	0.017
Placental weight (g)	432	564 ± 115	455	579 ± 118	14.8 (−0.7, 30.2)	0.060	15.6 (0.4, 30.7)	0.044
Gestational age (wk)	567	39.1 ± 2.5	576	38.9 ± 3.0	−0.23 (−0.55, 0.08)	0.148	—	—
Preterm, <37 wk [*n* (%)]	567	79 (13.9)	576	92 (16.0)	1.17 (0.84, 1.62)	0.343	—	—
Hemoglobin in cord blood (g/dL)	477	15.2 ± 2.4	505	15.2 ± 2.5	−0.003 (−0.314, 0.307)	0.983	0.001 (−0.309, 0.312)	0.994

[1] LBW, low birth weight; SGA, small-for-gestational-age; LGA, large-for-gestational-age; OR, odds ratio; MMN, multiple micronutrient tablet; FFS, fortified food supplement.
[2] Differences calculated by multiple linear regression. ORs calculated by multiple logistical regression. All analyses adjusted for health center and malaria prevention.
[3] Differences calculated by multiple linear regression. ORs calculated by multiple logistical regression. All analyses adjusted for health center, malaria prevention, and gestational age at delivery.
[4] Mean ± SD (all such values).
[5] Ponderal index (birth weight/ birth length^3).

We previously reported that MMN supplementation, compared with iron and folic acid supplementation, increased the mean birth weight (+119 g; $P = 0.012$) of infants only for mothers that entered pregnancy with an optimal nutritional status (BMI > 22), which questions the public health efficacy of such supplementation (12). In the present study, we reported a larger effect of FFS on birth length (+12.0 mm) and placental weight (+54.6 g) for the group of underweight mothers. Also, birth weight increased by 111 g with FFS in this subgroup, albeit not statistically significant.

The meta-analysis by Kramer and Kukuma reported that the effect of balanced energy and protein supplementation on birth weight in underweight mothers was not significantly larger than in well-nourished mothers (9, 29), but many of the included studies did not present data on compliance and diet substitution. In addition, most of the food supplements used in those studies were not enriched in multiple micronutrients. On the other hand, a study in Guatemala reported a greater effect on birth weight of a high-energy supplement when mothers had a low prepregnancy weight (35). On a program level, Ortolano et al (36) noticed that prenatal food supplementation and intensified prenatal care for undernourished mothers resulted in the same mean birth weights as for well-nourished mothers.

The FFS increased birth length significantly and showed a tendency to increase birth weight more in infants of anemic mothers than of their nonanemic peers. Anemia is often associated with other micronutrient deficiencies (37, 38), but also with a suboptimal nutritional status (37, 39). Anemic mothers are known to be more likely to give birth to LBW infants (25, 26), so the apparent increase in birth weight and the significant increase in birth length are important public health findings for this target group.

Supplementation of women who were underweight or anemic at enrollment with FFS resulted in mean birth lengths and placental weights that were similar to their well-nourished peers. However this was not the case for birth weight, which was in line with the main findings of the study.

In conclusion, FFS significantly increased the mean birth length of infants of all participating mothers, which was

TABLE 4
Stillbirth and perinatal and neonatal mortality outcomes for the study groups[1]

	MMN		FFS			
	Total *n*	No. of cases (%)	Total *n*	No. of cases (%)	OR (95% CI)[2]	*P*
Births	596		606[3]			
Stillbirths	596	15 (2.5)	606	12 (2.0)	0.78 (0.36, 1.68)	0.52
Neonatal deaths	581	10 (1.7)	594	9 (1.5)	0.88 (0.35, 2.17)	0.78
Early neonatal	581	4 (0.7)	594	4 (0.7)	0.96 (0.24, 3.90)	0.96
Late neonatal	581	6 (1.0)	594	5 (0.8)	0.82 (0.25, 2.71)	0.75
Perinatal deaths	596	19 (3.2)	606	16 (2.6)	0.82 (0.42, 1.60)	0.56

[1] MMN, multiple micronutrient tablet; FFS, fortified food supplement; OR, odds ratio.
[2] ORs calculated by multiple logistical regression, adjusted for health center and malaria prevention.
[3] Excludes one maternal death.

TABLE 5
Subgroup analysis for birth weight, birth length, and placental weight according to primigravidity, maternal BMI, and maternal hemoglobin concentration at enrollment[1]

	MMN		FFS					
Outcome	*n*	Mean ± SD	*n*	Mean ± SD	Difference (95% CI)[2]	*P*	Difference (95% CI)[3]	*P*
Gravidity								
Birth weight (g)						0.699[4]		0.307[4]
Primigravidae	100	2646 ± 453	104	2656 ± 517	10 (−126, 147)	0.882	54 (−55, 163)	0.333
Multigravidae	397	3003 ± 398	419	3014 ± 410	11 (−44, 67)	0.692	25 (−25, 74)	0.327
Birth length (mm)						0.307[4]		0.347[4]
Primigravidae	100	466 ± 28	104	467 ± 33	0.4 (8.1, 8.8)	0.933	2.8 (4.3, 9.9)	0.441
Multigravidae	397	479 ± 22	418	483 ± 23	4.4 (1.3, 7.5)	0.006	5.0 (2.1, 7.9)	0.001
Placental weight (g)						0.024[4]		0.029[4]
Primigravidae	87	533 ± 119	88	584 ± 133	52.2 (13.8, 90.6)	0.008	52.6 (14.6, 90.6)	0.007
Multigravidae	345	573 ± 113	367	578 ± 115	5.7 (−11.1, 22.5)	0.507	7.1 (−9.4, 23.5)	0.400
Maternal nutritional status								
Birth weight (g)						0.194[4]		0.183[4]
BMI <18.5 kg/m^2	54	2810 ± 480	64	2916 ± 408	99 (−62, 261)	0.227	111 (−34, 256)	0.133
BMI ≥18.5 kg/m^2	439	2947 ± 425	457	2945 ± 463	−2 (−60, 58)	0.957	19 (−31, 69)	0.455
Birth length (mm)						0.110[4]		0.102[4]
BMI <18.5 kg/m^2	54	469 ± 25	64	480 ± 24	11.4 (2.5, 20.3)	0.013	12.0 (3.7, 20.2)	0.005
BMI ≥18.5 kg/m^2	439	477 ± 23	456	480 ± 27	2.7 (−0.6, 6.0)	0.105	3.7 (0.8, 6.6)	0.014
Placental weight (g)						0.085[4]		0.100[4]
BMI <18.5 kg/m^2	48	526 ± 96	54	579 ± 124	54.7 (10.2, 99.2)	0.016	54.6 (10.0, 99.2)	0.017
BMI ≥18.5 kg/m^2	382	570 ± 116	399	579 ± 118	9.4 (−7.1, 25.9)	0.264	10.7 (−5.5, 26.8)	0.196
Maternal hemoglobin								
Birth weight (g)						0.581[4]		0.337[4]
Hemoglobin <11.0 g/dL	217	2914 ± 431	198	2940 ± 451	24 (−61, 108)	0.584	49 (−24, 123)	0.186
Hemoglobin ≥11.0 g/dL	239	2961 ± 447	293	2949 ± 467	−14 (−93, 65)	0.733	3 (−64, 70)	0.929
Birth length (mm)						0.137[4]		0.053[4]
Hemoglobin <11.0 g/dL	217	475 ± 25	198	481 ± 27	6.0 (1.1, 11.0)	0.017	7.3 (2.7, 11.8)	0.002
Hemoglobin ≥11.0 g/dL	239	477 ± 24	292	479 ± 27	0.8 (−3.5, 5.1)	0.712	1.6 (−2.1, 5.4)	0.397
Placental weight (g)						0.681[4]		0.778[4]
Hemoglobin <11.0 g/dL	189	564 ± 118	173	580 ± 117	14.8 (−9.6, 39.2)	0.233	16.8 (−7.4, 41.0)	0.172
Hemoglobin ≥11.0 g/dL	213	562 ± 111	256	581 ± 118	22.1 (−1.1, 43.0)	0.039	22.7 (2.3, 43.2)	0.030

[1] MMN, multiple micronutrient tablet; FFS, fortified food supplement.
[2] Difference calculated by multiple linear regression adjusted for health center and malaria prevention.
[3] Difference calculated by multiple linear regression adjusted for health center, malaria prevention, and gestational age at delivery.
[4] *P* for interaction.

accompanied by an insignificant increase in birth weight. FFS had more of an effect on birth size for mothers who entered pregnancy anemic or undernourished. The results of both intervention studies that we performed in Burkina Faso indicate that a targeted approach is desirable. Prenatal MMN supplementation appears to be more beneficial on birth outcomes for mothers that enter pregnancy adequately nourished. For mothers with a suboptimal prepregnancy nutritional status, MMN supplementation should be accompanied by a balanced energy and protein supplement to have any clinical effect on birth size.

The MISAME (Micronutriments et Santé de la Mère et de l'Enfant) Study Group thanks the families of Karaba and Koho who participated in the study, the health staff of the Houndé district, Noufou Sankara (district directors), and the staff of Center Muraz for their logistical and administrative support. Nutriset (France) is acknowledged for the development and manufacture of the MMN premix. The authors thank Carl Lachat for text editing and Ak'Ingabe Guyon for language revision.

The MISAME Study Group consisted of a Field Investigator Team (J-P Ki and V Koudougbo, sociologists; L Toe and H Lanou, physicians; E Da, obstetrician-gynecologist; G Lougue, pharmacist; B Negalo and O Guebe, nurses; and B Hien, laboratory technician), a Logistic Team (S Ouattara, coordinator; B Bicaba; C Kouakou Yameogo; N Diallo; M Sanou; and A Hien, pharmacist), and a Scientific Committee (Jane Kusin, Amsterdam University, Netherlands; Francis Delpeuch, head of the Tropical Nutrition Unit in IRD, Montpellier, France; John Van Camp, Food Safety and Food Quality, faculty of Bioscience Engineering, Ghent University, Belgium; Pierre Bourdoux, Pediatric Laboratory, Université Libre de Bruxelles, Belgium; Serge Diagbouga, Center Muraz, Burkina Faso; Sylvestre Tapsoba, National Director For Nutrition, Ministry of Public Health, Burkina Faso; Mete Boncoungou, regional Director for Health, Ministry of Public Health, Haut-Bassin, Burkina Faso; and Philippe Nikiema, biochemist, University of Ouagadougou, Burkina Faso.

The authors' responsibilities were as follows—PK, LH, JVC, NM, and DR: designed the study and the protocol; DR and LH: implemented the study; LH: analyzed and interpreted the data and drafted the manuscript; PK, JVC, NM, and DR: coordinated the implementation of the study and helped analyze and interpret the data and write the manuscript; HL: coordinated the field investigations; and JM: helped with the data analysis. All authors contributed substantially to the manuscript and approved the final version. None of the authors had any potential conflicts of interest.

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The American Journal of Clinical Nutrition