Effects of maternal multiple micronutrient supplementation on fetal growth: a double-blind randomized controlled trial in rural Burkina Faso[1–3]

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ABSTRACT

Background: Intrauterine growth retardation is a major predictor of child health in developing countries.

Objective: We tested whether providing pregnant women with the UNICEF/WHO/UNU international multiple micronutrient preparation (UNIMMAP), rather than iron and folic acid alone, improved fetal growth and its correlates.

Design: An intention-to-treat, double-blind, randomized controlled trial including 1426 pregnancies was carried out in rural Burkina Faso. Tablet intake was directly observed.

Results: Pregnancy outcome was known in 96.3% of the participants. After adjustment for gestational age at delivery, both birth weight (52 g; 95% CI: 4, 100; $P = 0.035$) and birth length (3.6 mm; 95% CI: 0.8, 6.3; $P = 0.012$) were significantly higher in the UNIMMAP group. UNIMMAP had a differential effect by percentiles of birth weight and length distributions: the risk of large-for-gestational-age infants was higher in the UNIMMAP group (OR: 1.58; 95% CI: 1.04, 2.38; $P = 0.03$), although the risk of low birth weight remained unchanged. The effect of UNIMMAP on birth size was modified by maternal body mass index at enrollment and could be more important in multiparous women and women taking sulfadoxine-pyrimethamine. Unexpectedly, the risk of perinatal death was marginally significantly increased in the UNIMMAP group (OR: 1.78; 95% CI: 0.95, 3.32; $P = 0.07$), and this seemed to affect mainly primiparous women (OR: 3.44; 95% CI: 1.1, 10.7; P for interaction $= 0.11$).

Conclusions: Maternal UNIMMAP modestly but significantly increased fetal growth. The resulting benefit on infant growth and survival needs to be assessed. The possible lack of benefit and potential harm in primiparous women should be further investigated. This trial was registered at clinicaltrials.gov as NCT00642408. *Am J Clin Nutr* 2008;88:1330–40.

INTRODUCTION

Low birth weight (LBW; birth weight <2500 g) is an important predictor of mortality and morbidity in the neonatal period (1, 2), of early postnatal growth (3, 4), and growth during childhood (5, 6). It also has negative effects on cognitive and behavioral development in the first years of life (7, 8), health status during childhood (1, 4, 9), and adult health (10–12). Moreover, women born with LBW are more likely to give birth to infants with LBW, contributing to the trans-generational cycle of malnutrition and poverty (13). As much as 16% of all live births worldwide are LBW, >90% being in low-income countries (14). Rates are particularly high in Asia and sub-Saharan countries (13). In Burkina Faso, it is estimated that 19% of all live births in 1999–2005 were LBW (15).

In developing countries, most cases of LBW are attributed to intrauterine growth retardation (IUGR) rather than to preterm delivery (16, 17). Although numerous factors interact with and affect fetal development (18, 19), maternal malnutrition, particularly micronutrient deficiencies, is assumed to be a major determinant of IUGR. Dietary surveys have consistently shown that multiple micronutrient deficiencies, rather than single deficiencies, are common (20–22). It is therefore expected that providing multiple micronutrients, rather than iron and folic acid (IFA) alone, as currently recommended, could have an effect of public health importance on fetal growth and its correlates (21, 23). Apart from its soundness on scientific grounds, this new strategy is attractive in terms of policy planning: multiple micronutrient supplementation is inexpensive and only minor adjustments to policy would be needed to implement it. Therefore the UNICEF/WHO/UNU designed a new multiple micronutrient supplement for pregnant and lactating women—the UNICEF/WHO/UNU international multiple micronutrient preparation (UNIMMAP)—that provides the Recommended Dietary Allowance (RDA) of 15 vitamins and minerals (24). However, additional evidence is needed to establish the effects of maternal multiple micronutrient supplements on infant and maternal health (25).

In a noteworthy initiative to generate high-quality evidence, a network of research teams was invited to test the UNIMMAP

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supplement under various field conditions (24). The study described here is part of a series of efficacy studies on the effect of the UNIMMAP supplements on pregnancy outcomes (26). To date, only 3 trials have been carried out in Africa, 2 of which were conducted in urban settings. Both of them experienced the significant problem of missing data (27, 28). The third study, in Niger (29), was not designed to assess the impact of prematurity on birth weight, nor to differentiate symmetrical and asymmetrical IUGR (13). This article presents the results of a trial of UNIMMAP in a rural area of Burkina Faso, where LBW is a significant public health problem.

SUBJECTS AND METHODS

Study setting

The study took place from March 2004 to October 2006 in the Houndé health district (southwest of Burkina Faso) in the area covered by 2 health centers (12 000 inhabitants). The climate is Sudano-Sahelian, with a dry season from October to March. The diet is essentially cereal-based (30). In 2004 and 2006, food consumption surveys estimated the average caloric intake during pregnancy at 8.6 and 8.1 MJ during the postharvest and preharvest season, respectively (data not shown). Malaria transmission is perennial, with seasonal variations. In 2002, the HIV prevalence among pregnant women in the district was estimated at 2%. The incidence of LBW in term infants was ≈17% at the District Hospital in 2000–2001 (31).

Selection of subjects

The recruitment of participants was community-based. During a preliminary census, houses in the study area were mapped and numbered, and a unique identification code was allocated to every woman of childbearing age. Twenty-five locally trained home visitors visited every compound monthly to detect pregnancy early, and possible cases were referred to the health center for pregnancy testing. Once pregnancy was confirmed, the study purpose and procedures were explained in the local language: Bwamu, Moré, or Dioula, and a signed informed consent was sought. There were no exclusion criteria, other the plan to leave the area within the next 2 y.

Study design and intervention

The study was a factorial, double-blind, randomized controlled trial, with directly observed supplement intake. Pregnant women were randomly assigned to receive either IFA or UNIMMAP daily until 3 mo after delivery (**Table 1**). UNIMMAP contained less iron than IFA because vitamin C, vitamin A, and riboflavin were expected to enhance iron absorption and/or utilization (24). Intervention and control micronutrient tablets were identical in appearance and manufactured by Scanpharm (Copenhagen, Denmark) in containers with a letter code (A/B) by intervention group. This code was kept secret from study participants and staff until completion of preliminary data analysis. Micronutrients were kept in a cool room until allocation. Vitamin C concentrations, the most labile component in UNIMMAP, were monitored once a year by HPLC and found to be remarkably constant through the trial (100% in 2005; 96% in 2006).

Participants were also randomly assigned to receive either the malaria chemoprophylaxis recommended by health authorities (300 mg chloroquine/wk) or intermittent preventive treatment (1500 mg sulfadoxine and 75 mg pyrimethamine once in the second and third trimester) (32, 33). Results of the malaria intervention will be presented elsewhere.

TABLE 1
Composition of the UNICEF/WHO/UNU international multiple micronutrient preparation (UNIMMAP) and the iron and folic acid (IFA) supplement[1]

Nutrient	Form	IFA concentration	UNIMMAP concentration	Unit
Vitamin A	Retinol equivalent	—	800	μg
Vitamin D	Cholecalciferol	—	200	IU
Vitamin E	Tocopherol	—	10	mg
Vitamin B-1	Thiamine HCL	—	1.4	mg
Vitamin B-2	Riboflavin	—	1.4	mg
Niacin	Nicotinamide	—	18	mg
Folic acid	—	400	400	μg
Vitamin B-6	Pyridoxine	—	1.9	mg
Vitamin B-12	Cyanocobalamin	—	2.6	μg
Vitamin C	Ascorbic acid	—	70	mg
Zinc	Zinc sulfate	—	15	mg
Iron	Ferrous fumarate	60	30	mg
Copper	Copper sulfate	—	2	mg
Selenium	Sodium selenite	—	65	μg
Iodine	Potassium iodide	—	150	μg

[1] UNIMMAP was developed by UNICEF/WHO/UNU for pregnant and lactating women.

The randomization scheme was generated by a computer program in permuted blocks of 4. Randomization numbers were sealed in opaque envelopes. At each inclusion, the consulting physician opened the next sealed envelope and transmitted the randomization number to a pharmacist managing the allocation sequence and the packaging of drugs in Center Muraz. The pharmacist was also blinded to the intervention. Individual plastic zip bags contained 31 tablets each and were labeled with the participant's name, address, and identification numbers only. Home visitors kept the bags and visited 10–25 pregnant women per day to ensure the directly observed intake of tablets. When women had a short scheduled absence from home, tablets were given to the woman in advance. The home visitors updated their visit reporting sheets daily. Tablet intake, pregnancy termination (fetal loss, stillbirth, or live birth), and symptoms such as nausea, fatigue, or abdominal pain were recorded. The home visitors also encouraged pregnant women to attend their scheduled antenatal visits and deliver their infants in health centers and referred them to health services in case of disease. Two supervisors (sociologists) performed a quality assessment of each home visitor's work monthly on a randomly chosen day (34).

In a case of maternal illness, appropriate treatments were provided according to national guidelines. Severely anemic women (hemoglobin < 70 g/L, without dyspnea) received ferrous sulfate (200 mg) + folic acid (0.25 mg) twice daily, for 3 mo, regardless of their allocation group. All participants also received 400 mg albendazole in the second and third trimesters. If malaria occurred despite chemoprophylaxis, quinine (300 mg, 3 times/d) was given for 5 d. Vitamin A (200 000 IU) was given to all women after delivery, in accordance with national recommendations. The study was approved by the ethics committees of the Center Muraz, Bobo-Dioulasso, Burkina Faso, and the Institute of Tropical Medicine, Antwerp, Belgium.

Measurements

At enrollment, we measured maternal height, weight, arm circumference, hemoglobin concentration, urine protein, and sugar in all participants. Malaria infection was assessed through thick blood films. Weight and arm circumference were measured again at each antenatal visit. Hemoglobin concentration was assessed again between 30 and 34 wk of gestation. Maternal height was measured to the nearest 1 cm with a SECA 220 scale (Seca, Hanover, MD) or a wall SECA 206 scale and weight to the nearest 100 g with a SECA 701 scale or a SECA UNISCALE. Maternal midupper arm circumference was measured to the nearest 1 mm with a SECA girth measuring tape or a SECA 212 tape.

A consultant obstetrician performed trans-abdominal ultrasound fetal biometry as soon as possible after inclusion of a subject in the study to assess gestational age (model 500; Aloka, Tokyo, Japan). The fetal ultrasound was repeated between 28 and 32 wk of gestation for obstetrical follow-up. Scan stills were printed and stored in the participant's file. When the results of an ultrasound biometry were unavailable, the gestational age was computed on the basis of the last menstrual period. The hemoglobin concentration in maternal and cord blood was measured by spectrophotometry with a HemoCue device (HemoCue Ltd, Dronfield, United Kingdom); a daily calibration check was made with the use of a HemoCue Control Cuvette.

Newborn length and weight were measured to the nearest 1 mm with a SECA 207 scale and to the nearest 10 g with a SECA 725 scale, respectively. Newborn occipitofrontal head circumference and midupper arm circumference was measured to the nearest 1 mm with a SECA girth measuring tape or a SECA 212 tape. All measurements were made in the health centers. Only measurements taken within the first 24 h after birth were included in the analysis. To ensure reliability, all anthropometric variables were measured twice, once by clinic staff and a second time by an anthropometrist hired by the project. The average of the 2 measures was used for analysis. If there was a large discrepancy between the 2 measures, a consistency check of the file was made by a supervisor. All weighing scales were calibrated daily. The accuracy and precision of measures were established monthly through a standardization session (35).

Cord blood was collected in a dry tube without any preservative (60.610.001; Starstedt, Nümbrecht, Germany) and allowed to clot at 4 °C. The serum resulting from centrifugation at 3000 revolutions/min during 10 min was immediately frozen at −20 C°. Soluble transferrin receptor (sTfR) concentrations in serum were measured in a random sample of 200 sera samples with an immunonephelometric assay (Dade Behring, Marburg, Germany).

Statistical analysis

The primary outcomes we examined were gestational duration, birth weight, birth length, and Rohrer ponderal index at birth [weight (g) × 100/length^3 (cm)]. Birth length and Rohrer index were used to discern short and thin infants. Both patterns result in a lower birth weight but are likely to have different health consequences (13). Secondary outcomes were LBW (<2500 g), small-for-gestational age (SGA; birth weight below the 10th percentile of a reference population) (36), large for gestational age (LGA; birth weight above the 90th percentile of the study population), thoracic circumference, head circumference, midupper arm circumference, hemoglobin concentration in mothers during the third trimester, hemoglobin and sTfR concentrations in cord blood, preterm birth (born at <37 wk of gestation), stillbirth (delivery of an infant showing no sign of life after a gestational age of 28 wk), and perinatal death. Kramer et al's method was used to define SGA because it is a recent reference based on ultrasound measurements (36). However, LGA was computed within our cohort population, because any reference would be inappropriate to detect LGA infants in such a population given the shift to the left of the whole body weight distribution. We defined loss to follow-up as a participant leaving the study area for a period longer than 2 consecutive weeks or delivering their infant in a place outside the study area.

We calculated the sample size to detect a difference of 90 g in birth weight (37) between groups with a power of 90% and a 2-sided significance level of 5%, assuming an SD of 400 g (38) and a 10% loss to follow-up and fetal loss. To assess the importance of supplementation timing on outcomes, the initial randomization scheme had 3 groups: IFA from early pregnancy stage, UNIMMAP from early pregnancy stage, and IFA from inclusion and UNIMMAP beginning at gestational age 5 mo, the median time of first antenatal visit in Burkina Faso (39). However, the pilot phase made it clear that such early detection was culturally difficult, and we decided to randomly assign the subjects to the IFA and UNIMMAP groups, keeping the initially calculated sample size of 1370 as the estimated difference was reported to be smaller than foreseen (38, 40).

Only singleton pregnancies were included in the analysis because fetal loss and anthropometric measures at birth in multiple pregnancies are not primarily nutrition related (41). The effects of micronutrient supplementation were assessed by an intention-to-treat analysis using linear regression models for continuous outcome variables and logistic regression for binary outcome variables, with malaria prevention group and health center as covariates to account for the study design. In addition, we estimated and tested micronutrient supplementation effects adjusted for gestational age at birth (linear effect).

To assess the robustness of the primary analyses to baseline imbalances between treatment groups and missing data, we repeated the analyses adjusting for maternal body mass index (BMI) and hemoglobin at baseline and using multiple imputation of missing data by the MICE system of chained equations (42). Weight (183 observations missing) and height (184 observations missing) were imputed based on a regression model with the following predictors: sex, gestational age (using regression splines) at delivery, primiparity, study site, vitamin supplementation, malaria prevention, place of delivery, maternal weight, and maternal weight increase 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. The Rohrer index was calculated from the imputed data for those with missing weight or height.

As an exploratory analysis, we assessed the treatment effect in 3 preplanned subgroup analyses, with subgroups defined by primiparity, malaria prevention, and maternal nutritional status (43). The subgroup analysis by primiparity was motivated by the fact that newborns of primiparous women are on average lighter and shorter (44–46). Subgroup analyses by malaria prevention were performed because of the factorial design of the study. Lastly, subgroup analyses by maternal nutrition was planned because micronutrients may have a different effect if the mother is herself nutritionally deprived (29, 47). An interaction term was inserted in the models to assess the significance of subgroups

analyses. Moreover, we used the approach of Katz et al (48) to assess whether the treatment effect was constant over percentiles of the weight and length distribution. In this method, differences (and CI) in birth weight and length between treatment and control groups are estimated as a nonlinear smooth function of the percentiles of the birth weight distribution. Statistical significance was set at $P < 0.05$ for all tests, except interaction tests ($P < 0.10$). All analyses were done with Stata 8.0 (StataCorp, College Station, TX).

RESULTS

Of the 4312 women of reproductive age visited monthly, 1426 pregnancies were confirmed by urine testing and were randomly assigned between 15 March 2004 and 6 February 2006. Fifty-two women (3.8%) were randomly assigned twice for consecutive pregnancies.

The participants were predominantly young (mean ± SD: 24.4 ± 6.3 y) illiterate women (80.1%): 19.8% were nulliparous and 8.2% were grand multiparous (parity ≥ 8). The mean (± SD) gestational age at recruitment was 17.3 ± 7.8 wk (range: 5, 36 wk), and 34.6% ($n = 493$) of the participants were recruited in the first trimester of pregnancy. The nutritional status of the participants was suboptimal: 10.4% ($n = 149$) had a BMI (in kg/m^2) <18.5 (13.1% among those enrolled during the first trimester of pregnancy), and 43.3% were anemic (hemoglobin < 11.0 g/dL) (31.0% among those enrolled during first pregnancy trimester). The nutritional status of primigravid women was different from that of the other participants. They were smaller (mean difference: 1.43 cm; 95% CI: 0.63, 2.24), had a smaller arm circumference (mean difference: 7 mm; 95% CI: 5, 10), and had a lower hemoglobin concentration (mean difference: 0.34 g/dL; 95% CI: 0.10, 0.57). The study groups were similar with respect to baseline characteristics (**Table 2**), except for small differences in hemoglobin (0.17 g/dL; $P = 0.06$) and BMI (0.27; $P = 0.02$). Data on birth outcome were available for 1315 (92.2%) pregnancies; 3 women died before delivery and 1 underwent a therapeutic abortion. The other missing cases (107 pregnancies) are explained by women who left the study area and were lost to follow-up by the time of delivery. However, during the postneonatal period, we managed to assess the pregnancy outcome for 59 of those lost to follow-up, so that, in total, the pregnancy outcome was known for 96.3% of the participants. The proportion of women lost to follow-up was not different between randomization groups, and the characteristics of those lost to follow-up did not differ from the remainder, except for gestational age at inclusion (15.9 compared with 18.1 wk; $P = 0.05$).

There was no difference in miscarriage frequency among groups. However, an increased risk of stillbirth (OR: 2.23; 95% CI: 0.97, 5.22; $P = 0.06$) and perinatal death (OR: 2.08; 95% CI: 1.07, 4.07; $P = 0.032$) was observed in the intervention group (**Table 3**). This was an unexpected finding. In a subsequent analysis, we included cases lost to follow-up for whom pregnancy outcome could be assessed in the postneonatal period (**Figure 1**). After these cases were included, the increased risk of stillbirth (OR: 1.74; 95% CI: 0.82, 3.69; $P = 0.15$) and of perinatal death (OR: 1.78, 95% CI: 0.95, 3.32; $P = 0.069$) in the intervention group was no longer significant, although it remained borderline for perinatal death. Interactions with primiparity, maternal BMI, and type of malaria prophylaxis were not significant, although they were borderline for primiparity ($P = 0.11$). Half of the perinatal deaths occurred in preterm newborns.

TABLE 2
Baseline characteristics of the participants by allocation group[1]

Characteristics	Control ($n = 712$)	Intervention ($n = 714$)
Maternal age (y)	24.5 ± 6.2[2]	24.3 ± 6.2
<20 y [*n* (%)]	168 (24.6)	184 (25.8)
Gestational age at enrollment (wk)	17.2 ± 7.5	17.5 ± 8.0
First trimester [*n* (%)]	242 (34.0)	247 (36.2)
Second trimester [*n* (%)]	346 (50.1)	334 (46.8)
Third trimester [*n* (%)]	81 (11.4)	92 (12.9)
Schooling		
None [*n* (%)]	567 (79.6)	556 (77.9)
Primary [*n* (%)]	55 (7.7)	76 (10.6)
Secondary [*n* (%)]	15 (2.1)	16 (2.2)
Ethnicity		
Bwa [*n* (%)]	177 (24.9)	171 (23.9)
Mossi [*n* (%)]	426 (59.8)	436 (61.1)
Peuhl [*n* (%)]	61 (8.6)	51 (7.1)
Other [*n* (%)]	48 (6.7)	56 (7.8)
No. of spouses per husband [*n* (%)]		
1	356 (50.0)	356 (49.9)
2	229 (32.2)	229 (32.1)
≥3	96 (13.5)	92 (12.9)
Parity		
0	131 (18.4)	152 (21.3)
1-2	246 (34.5)	233 (32.6)
≥3	306 (43.0)	300 (42.0)
At least one previous fetal loss [*n* (%)]	132 (18.5)	129 (18.1)
No. of previous child deaths [*n* (%)][3]		
0	282 (48.5)	269 (47.9)
1-2	228 (39.2)	223 (39.1)
>2	42 (7.2)	44 (7.8)
BMI at enrollment (kg/m^2)	20.8 ± 2.0	21.0 ± 2.2
<18.5 kg/m^2 [*n* (%)]	84 (11.8)	65 (9.1)
Height (cm)	162.1 ± 5.9	162.2 ± 6.3
Arm circumference (cm)	25.8 ± 2.1	25.9 ± 2.2
Hemoglobin at enrollment (g/dL)[4]	11.1 ± 1.8	10.9 ± 1.6
<7.0 g/dL [*n* (%)]	5 (0.7)	5 (0.7)
≥7.0 to <11.0 g/dL [*n* (%)]	289 (40.6)	318 (44.5)
≥11.0 g/dL [*n* (%)]	342 (48.6)	316 (44.3)

[1] The intervention group received the United Nations international multiple micronutrient preparation (UNIMMAP), and the control group received an iron and folic acid supplement.
[2] $\bar{x}$ ± SD (all such values).
[3] $n = 1143$ if parity was ≥1.
[4] Baseline hemoglobin measurements were not available for 151 participants.

Of the 1315 pregnancies with known birth outcome, 1260 singleton live births were eligible for the analyses. The mean interval between randomization and delivery was 146 ± 56 d, and the directly observed intake accounted for a mean 81.5% of days of participation (80.8% in the control group and 82.1% in intervention group). Most of the deliveries (79.4%) took place in a health center. No difference in study duration, tablet intake, compliance, or place of delivery between groups was observed. Six cesarean sections were performed: 2 in the control group and 4 in the intervention group.

Gestational duration was similar in the intervention and control groups (**Table 4**). In total, 1044 (86.2%) infants were born at term, and the proportion did not differ between groups. The birth

TABLE 3
Mortality outcomes in singleton pregnancies[1]

	Control group		Intervention group		Treatment effect (adjusted for malaria prevention and health center)			
Outcome	*N*	*n* (%)	*N*	*n* (%)	Odds ratio (95% CI)	*P*	Odds ratio[2] (95% CI)	*P*
Stillbirths	628	8 (1.3)	632	18 (2.8)	2.23 (0.97, 5.22)	0.060	1.74 (0.82, 3.69)	0.15
Neonatal deaths	620	6 (1.0)	614	12 (1.9)	2.11 (0.78, 5.67)	0.139	2.10 (0.78, 5.64)	0.14
Perinatal deaths	628	13 (2.1)	632	27 (4.3)	2.08 (1.07, 4.07)	0.032	1.78 (0.95, 3.32)	0.069
In primigravid mothers	120	4 (3.2)	130	14 (9.7)	3.19 (1.02, 10.00)	0.27[3]	3.44 (1.1, 10.66)	0.11[3]
In mothers with BMI ≥ 22 kg/m^2 at inclusion[4]	481	10 (2.1)	452	21 (4.6)	2.29 (1.07, 4.92)	0.69[3]	2.44 (1.14, 5.20)	0.64[3]
In mothers taking sulfadoxine-pyrimethamine	310	6 (1.9)	310	15 (4.8)	2.49 (0.95, 6.52)	0.58[3]	2.57 (0.98, 6.71)	0.29[3]

[1] The intervention group received the UNICEF/WHO/UNU international multiple micronutrient preparation (UNIMMAP), and the control group received an iron and folic acid supplement. Women and infants with follow-up to the distal time point for each outcome were included. The adjusted odds ratios were computed by logistic regression.
[2] Includes those lost to follow-up for whom the pregnancy outcome could be assessed in the postneonatal period.
[3] *P* for interaction.
[4] BMI was calculated as (weight/height^2); 22 kg/m^2 was the cutoff of the upper quartile of the study population.

weight was not recorded for 184 (14.9%) infants, mainly because the birth occurred at home and the baby was presented too late for regular weighing, ie, >24 h after birth. This was particularly the case during the season of intensive agricultural labor (May to September), when more mothers delivering away from the health centers. The proportion of missing data was not different between groups.

After adjustment for gestational age at delivery, birth weight (52 g; 95% CI: 4, 100; $P = 0.035$), birth length (3.6 mm; 95% CI: 0.8, 6.3; $P = 0.012$), arm circumference (1.2 mm; 95% CI: 0.2, 2.3; $P = 0.020$), and chest circumference (2.8 mm; 95% CI: 0.1, 5.6; $P = 0.041$) were all significantly higher in the UNIMMAP group (Table 4).There was no difference in the Rohrer index and head circumference. Similar results were obtained when the analyses were adjusted for maternal hemoglobin and BMI at enrollment and with multiple imputed data (data not shown). Despite the significant differences in birth weight, there was no difference in risk of LBW or SGA between intervention groups. However, the risk of LGA was higher in the multivitamin group (OR: 1.58; 95% CI: 1.04, 2.38; $P = 0.034$). These findings were consistent with the fact that UNIMMAP had a differential effect by percentiles of birth weight and length distributions, as displayed in **Figure 2** and **Figure 3**. In the lowest percentiles of the distributions, the effect of UNIMMAP is not significantly different from zero. Hemoglobin and sTfR concentrations in cord blood were similar among groups. Maternal hemoglobin during the third trimester of pregnancy ($n = 810$) was also similar in both groups (overall: 10.9 ± 1.6 g/dL; mean difference: 0.03 g/dL; $P = 0.8$), as was the change in hemoglobin between baseline and follow-up measurements.

Subgroup analyses provided additional insights (**Table 5**). The effect of UNIMMAP on birth weight and the Rohrer index was significantly modified by maternal BMI at enrollment, the effect being greater in the upper quartile of maternal BMI. Multivitamin supplementation also appeared to increase birth weight more in multigravid women (71 g; 95% CI: 18, 123) and in mothers taking sulfadoxine-pyrimethamine to prevent malaria (77 g; 95% CI: 7, 146), although the interaction tests were not statistically significant. There was no reduction in the risk of LBW or SGA in any of the subgroups.

As regards birth length, none of the interaction tests were significant. The gain in birth length in multigravid women is however noteworthy. Unexpectedly, infants were thinner with UNIMMAP in women taking chloroquine to prevent malaria (*P* value for interaction = 0.01), and this was mainly due to an increased birth length.

DISCUSSION

UNIMMAP was associated with increased birth size compared with standard IFA. Because UNIMMAP provides half the amount of iron as does IFA (24), we could not determine whether the treatment effect was due to that difference, to the addition of other micronutrients, or to both. On one hand, excess iron could yield adverse pregnancy outcomes through oxidative stress (49, 50). However, the evidence available to date is inconsistent (**Table 6**). Studies in Nepal (40), Zimbabwe (28), or Mexico (51)—using an equal iron dosage in all trial groups—did not detect a treatment effect. However, this was also the case in Guinea-Bissau (27) and Indonesia (47), where the iron dosage was lower in the intervention group. Moreover, 2 other trials found a significant effect on birth size despite an equal iron dosage (60 mg) in both intervention and control groups, which seems to indicate that the additional micronutrients were effective independently of iron concentration (52, 53). On the other hand, IFA might also have improved fetal growth substantially. Although the information on maternal and infant outcomes of IFA during pregnancy is very limited (54), a trial in the United States in iron-replete, nonanemic, pregnant women and one in Nepal showed that iron supplementation led to a significantly higher mean birth weight than did placebo (55) or vitamin A alone (40).

The treatment effect observed in our study is consistent with the results of a number of other studies that used UNIMMAP or a similar supplement (29, 38), but not with all of them (28, 40, 47, 51). The potential explanations for the differences in results across studies have not been fully elucidated, although differences in underlying nutritional status of the population, disease epidemiology, and study design are likely factors. The impact of birth weight increase on infant survival and health will be assessed through our follow-up study. However, evidence pointing to improved survival was recently reported. The postnatal mortality risk was reduced by 18% (RR: 95% CI: 0.70, 0.95) in Indonesia (90 d postpartum) and by 14% (RR: 95% CI: 0.66, 1.13) in Tanzania (60 d postpartum), although in the latter study

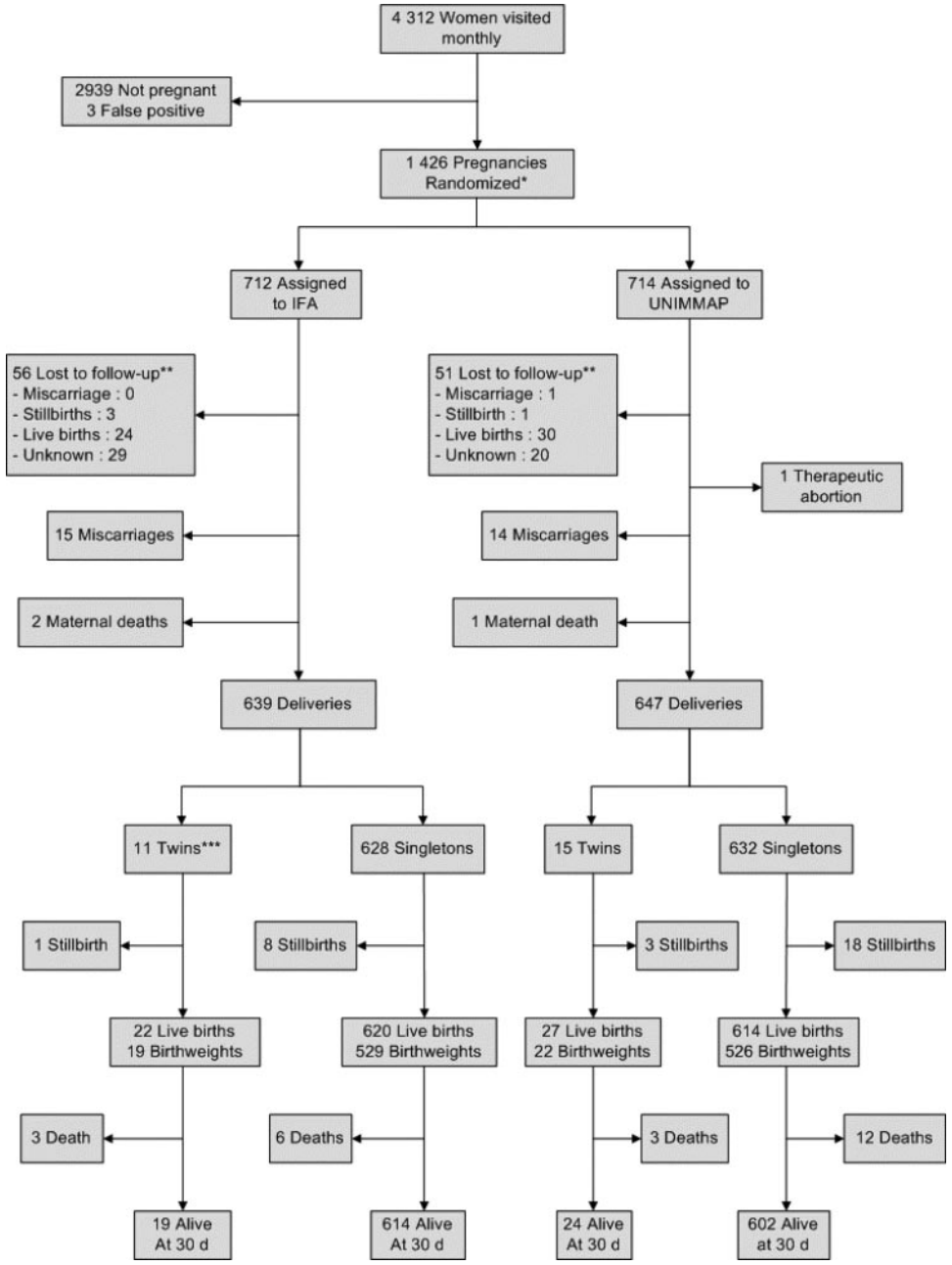

FIGURE 1. Trial profile. *1370 women were randomly assigned once, 52 women were randomly assigned twice, and 2 women were randomly assigned 3 times; **the pregnancy outcome of lost to follow-up was assessed in the postneonatal period; ***1 woman gave births to triplets.

the supplement used was substantially different from UNIMMAP, and no statistical significance was reached (47, 52). In Nepal, a cross-sectional survey conducted 2 y after trial completion showed that the effect of maternal UNIMMAP on fetal weight persisted into childhood (56). The treatment effect on birth weight in those trials was of a similar magnitude as the one observed in our study (21, 67, and 77 g, respectively). The impact of an increased birth length on infant growth and health has been much less studied so far.

Overall, we conclude that, compared with IFA, UNIMMAP supplements improved birth weight modestly. Two explanations are possible. First, the high standard of prenatal care provided in both groups had a positive effect on fetal growth. For instance, the LBW incidence in the control group was substantially lower than estimated in the general population (15.5% compared with 19%) (15) and only 6.5% of newborns had a weight-for-gestational age below −2 SDs of the reference distribution (36). Second, the RDA specification for pregnant women that is based on women in the United States or Canada might be insufficient to improve the micronutrient status of chronically undernourished women. In Guinea-Bissau, the LBW incidence was reduced only when supplements containing twice the RDAs were provided (27). In Tanzania, a substantial increase in the mean birth weight (67 g; 95% CI: 43, 89) was obtained with amounts twice the RDA for vitamin E and 6–10 times for vitamin C and several B vitamins (52). The composition of UNIMMAP is also controversial

TABLE 4
Birth outcomes in singleton live newborns[1]

Outcome	Control group		Intervention group		Treatment effect (adjusted for malaria prevention and health center)[2]		Treatment effect (adjusted for malaria prevention, health center, and gestational age)[2]	
	N	$\bar{x} \pm$ SD or [*n* (%)]	*N*	$\bar{x} \pm$ SD or [*n* (%)]	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*
Gestational age (wk)	604	39.2 ± 2.9	607	39.2 ± 3.1	−0.04 (−0.38, 0.29)	0.79	—	—
Preterm birth	604	81 (13.4)	607	86 (14.2)	1.04 (0.75, 1.45)	0.81	—	—
Birth weight (g)	526	2877 ± 424	526	2914 ± 450	41 (−11, 94)	0.12	52 (4, 100)	0.035
LBW	526	82 (15.6)	526	77 (14.6)	0.91 (0.65, 1.28)	0.59	0.84 (0.58, 1.20)	0.34
SGA	512	213 (41.6)	518	194 (37.4)	0.83 (0.65, 1.07)	0.15	—	—
LGA	526	44 ± 8.4	526	63 ± 12.0	1.53 (1.01, 2.30)	0.043	1.58 (1.04, 2.38)	0.034
Birth length (mm)	524	480.0 ± 24.3	527	482.9 ± 25.0	3.1 (0.09, 6.05)	0.044	3.6 (0.80, 6.33)	0.012
Rohrer index (g/cm^3)	524	2.6 ± 0.3	526	2.6 ± 0.3	−0.01 (−0.05, 0.02)	0.44	−0.01 (−0.05, 0.03)	0.57
Arm circumference (mm)	486	102.5 ± 8.8	487	103.4 ± 8.9	0.9 (−0.2, 2.0)	0.10	1.2 (0.2, 2.3)	0.02
Chest circumference (mm)	525	321.0 ± 22.8	524	323.1 ± 25.2	2.3 (−0.6, 5.2)	0.12	2.8 (0.1, 5.6)	0.041
Head circumference (mm)	526	336.5 ± 15.6	527	337.1 ± 15.8	0.7 (−1.1, 2.6)	0.44	1.0 (−0.7, 2.8)	0.25
Hemoglobin in cord blood (g/dL)	482	15.6 ± 2.7	484	15.4 ± 2.6	−0.2 (−0.53, 0.14)	0.26	−0.19 (−0.53, 0.14)	0.26
sTfR in cord blood (mg/L)	98	2.31	97	2.21	0.10 (−0.09, 0.28)	0.30	−0.9 (−0.27, 0.10)	0.37

[1] SGA, small-for-gestational-age (birth weight less than the 10th percentile of the reference distribution; 41); LGA, large-for-gestational-age (birth weight greater than the 90th percentile of the study distribution); LBW, low birth weight; sTfR, soluble serum transferrin receptor; Rohrer index = (birth weight/ birth length^3).
[2] Difference or odds ratio. Adjusted differences were computed by multiple linear regression. Adjusted odds ratios were computed by logistic regression.

because some potentially important micronutrients, such as magnesium and calcium, are not included. In a trial in India, 14 other micronutrients were added to UNIMMAP, and impressive results on birth size were observed (53). However, other features of that study (eg, hospital-based, restriction to mothers with a BMI < 18.5) make it noncomparable with population-based field studies.

The finding that mean birth weight increased but the proportion of LBW did not decrease with UNIMMAP can be explained by the variable treatment effect across the distribution of birth weight—the effect being more important for the larger infants. Such variation in treatment effect was also observed in Nepal, where IFA increased birth weight for infants smaller than 2800 g,

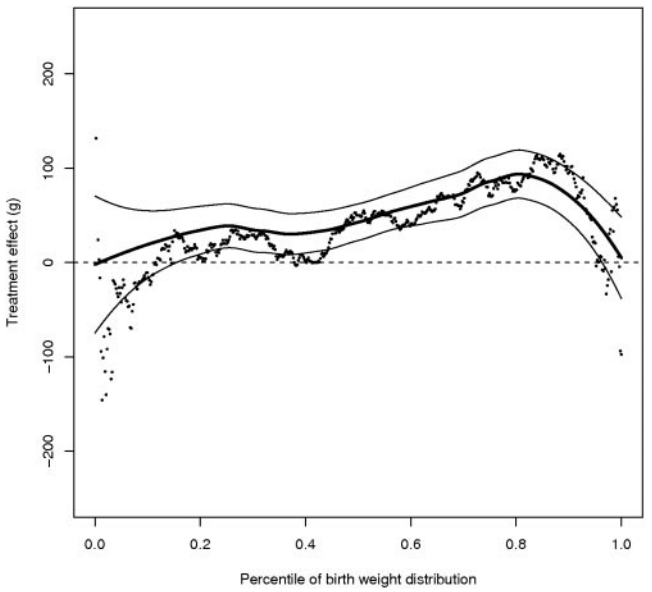

FIGURE 2. Treatment effect across the distribution of birth weight. The estimated difference in birth weight between the women who received the United Nations international multiple micronutrient preparation (UNIMMAP) and those who received iron and folic acid (control group) is shown as a function of the percentiles of birth weights. The zero line indicates no effect of UNIMMAP. The positive *y* values indicate a higher birth weight in the intervention group, and the negative *y* values indicate a lower birth weight. The dashed line represents the observed treatment effects by percentile. The central solid black line represents the smoothed treatment effect, with upper and lower 95% confidence bands, using multiple imputed data.

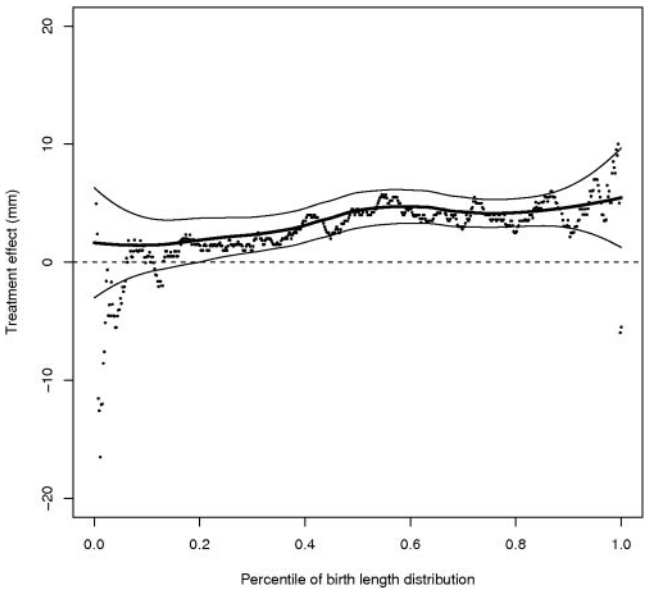

FIGURE 3. Treatment effect across the distribution of birth length. The estimated difference in birth length between the women who received the United Nations international multiple micronutrient preparation (UNIMMAP) and those who received iron and folic acid (control group) as a function of the percentiles of birth lengths. The zero line indicates no effect of UNIMMAP. The positive *y* values indicate a higher birth length in the intervention group, and the negative *y* values indicate a lower length. The dashed line represents the observed treatment effects by percentile. The central solid black line represents the smoothed treatment effect, with upper and lower 95% confidence bands, using multiple imputed data.

TABLE 5
Subgroup analysis of birth weight, birth length, and Rohrer index outcomes in singleton live newborns

	Control group		Intervention group		Treatment effect (adjusted for malaria prevention and health center)[1]		Treatment effect (adjusted for malaria prevention, health center, and gestational age)[1]	
Outcome and subgroup	*n*	$\bar{x} \pm$ SD	*n*	$\bar{x} \pm$ SD	Estimate (95% CI)	*P*	Estimate (95% CI)	*P*
Birth weight (g)								
Mother's parity						0.37[2]		0.48[2]
Primigravida	101	2618 (405)	126	2632 (470)	17 (−98,132)	0.77	38 (−61,137)	0.45
Multigravida	425	2939 (406)	400	3003 (405)	68 (13,124)	0.016	71 (18,123)	0.008
Mother's BMI[3]						0.053[2]		0.078[2]
<22 kg/m^2	402	2852 (429)	376	2855 (449)	7 (−54,69)	0.70	28 (−28,84)	0.40
≥22 kg/m^2	124	2962 (398)	144	3082 (404)	123 (26,220)	0.013	119 (26,212)	0.012
Malaria prevention						0.20[2]		0.37[2]
Chloroquine	259	2886 (408)	274	2894 (452)	8 (−66,81)	0.83	29 (−38,97)	0.39
Sulfadoxine-pyrimethamine	267	2868 (440)	252	2936 (447)	79 (4,154)	0.04	77 (7,146)	0.03
Birth length (mm)								
Mother's parity						0.34[2]		0.36[2]
Primigravida	99	472 (23)	126	473 (28)	0.6 (−6.3,7.5)	0.87	1.2 (−4.9,7.3)	0.70
Multigravida	425	482 (24)	401	486 (23)	4.3 (1.1,7.6)	0.009	4.5 (1.4,7.6)	0.004
Mother's BMI[3]						0.58[2]		0.75[2]
<22 kg/m^2	400	479 (25)	377	481 (26)	2.6 (−0.9,6.2)	0.15	3.4 (0.2,6.7)	0.038
22 kg/m^2	124	483 (22)	144	488 (22)	4.5 (−0.7,9.8)	0.09	4.3 (−0.8,9.5)	0.10
Malaria prevention						0.55[2]		0.25[2]
Chloroquine	257	480 (21)	274	484 (25)	4.0 (0.0,7.9)	0.050	5.0 (1.2,8.7)	0.010
Sulfadoxine-pyrimethamine	267	480 (27)	253	482 (25)	2.3 (−2.1,6.8)	0.30	2.1 (−2.0,6.1)	0.29
Rohrer index (g/cm^3)[4]								
Mother's parity						0.99[2]		0.81[2]
Primigravida	99	2.48 (0.28)	126	2.47 (0.30)	0.00 (−0.08,0.08)	0.84	0.02 (−0.06,0.09)	0.66
Multigravida	425	2.63 (0.29)	400	2.62 (0.31)	−0.01 (−0.05,0.03)	0.71	−0.01 (−0.05,0.033)	0.71
Mother's BMI						0.068[2]		0.09[2]
<22 kg/m^2	400	2.59 (0.30)	376	2.55 (0.30)	−0.04 (−0.08,0.01)	0.077	−0.03 (−0.07,0.01)	0.12
≥22 kg/m^2	124	2.62 (0.28)	144	2.66 (0.32)	0.04 (−0.04,0.11)	0.30	0.04 (−0.04,0.11)	0.30
Malaria prevention						0.008[2]		0.01[2]
Chloroquine	257	2.62 (0.32)	274	2.55 (0.32)	−0.06 (−0.12,−0.01)	0.024	−0.06 (−0.11,0.00)	0.04
Sulfadoxine-pyrimethamine	267	2.58 (0.27)	252	2.62 (0.29)	0.03 (−0.01,0.08)	0.15	0.04 (−0.11,0.09)	0.13

[1] Difference or odds ratio. Adjusted differences were computed by multiple linear regression. Adjusted odds ratios were computed by logistic regression.
[2] *P* for interaction.
[3] BMI was calculated as weight/height^2; 22 kg/m^2 was the cutoff of the upper quartile of the study population.
[4] Rohrer index = weight/length^3.

whereas the multiple micronutrients increased birth weight across the entire distribution of weights (48), resulting in no overall benefit of multiple micronutrients in reducing the incidence of LBW (40). This finding casts doubt on the utility of UNIMMAP supplementation to lower LBW prevalence.

UNIMMAP might also have a differential effect in association with other health variables. Mean birth weight seemed to be increased by UNIMMAP to a greater extent in multigravid women than in primigravid women. This finding was also observed in Nepal (38) and Indonesia (47). In our study, primigravid women were smaller, had a smaller arm circumference, and had a lower hemoglobin concentration. In those young women (18 ± 2 y), nutritional needs of the mother and the fetus accumulate, and this could explain the absence of effect with supplements at the level of the RDA (57). Consistently, UNIMMAP increased birth weight more in women whose BMI at baseline was in the upper quartile. Again, this was also observed in Nepal (38) and Indonesia (47).

UNIMMAP also appears to be more effective in increasing mean birth weight in mothers receiving sulfadoxine-pyrimethamine. Multiple factors have an impact on fetal growth, and it is plausible that UNIMMAP affects fetal growth differently when these other factors are under control, eg, effective malaria prevention (32, 33). Our trial was not powered to assess multiple interactions, but those associations are clinically plausible and some have been replicated in other studies.

It is noteworthy that UNIMMAP resulted in a significant increase in birth length. With the exception of a study in India (53), this finding has not been previously reported. It is unlikely that our finding was due to chance. First, other anthropometric indicators (arm circumference and chest circumference) were also increased, denoting an overall increased fetal growth. Second, it is biologically plausible because micronutrients influence the somatotrophic and insulin axis (58). As for weight, the effect varied by percentiles of the birth length distribution. Indeed, in our study, increased fetal length seemed to be the main contributor to the weight gain observed in the UNIMMAP group, because the Rohrer ponderal index was not different between intervention groups.

The risk of stillbirth and perinatal death increased in the UNIMMAP group with marginal statistical significance, apparently mainly in primiparous women. In an analysis of pooled data from the 2 Nepalese trials, perinatal mortality also increased (59).

TABLE 6
Main characteristics of published receiver operator characteristic studies using the UNICEF/WHO/UNU international multiple micronutrient preparation (UNIMMAP) or a supplement of a similar composition[1]

	Country	*N*	Design[2]	Multiple micronutrients	Controls	BW[3]	Treatment effect	
							BW[4]	LBW[5]
1)	Nepal (38)	1200	Individual randomization; enrollment of singleton pregnancies up to 20 wk; micronutrients given up to delivery; mean BMI at inclusion: 19.8; primigravida: 45%	UNIMMAP	60 mg Fe + 400 μg folic acid	2733 ± 422 g	77 (24, 130) g	0.69 (0.52, 0.93) g
2)	Nepal (40)	1978	Cluster-randomized; 5 groups: vitamin A (1000 μg), folic acid, folic acid–iron, folic acid–iron-zinc, multiple micronutrients up to 12 wk PP; mean BMI at inclusion: 19.0; primigravida: 27%	UNIMMAP except no selenium, no iodine, 30 mg Zn, 60 mg Fe, 100 mg Mg	60 mg Fe + 400 μg folic acid	2659 ± 446 g	7 g	1.03 (0.89, 1.19) g
3)	Indonesia (47)	31290	Cluster-randomized trial; randomization of 262 midwives; strong social marketing; micronutrient up to 90 d PP; primigravida: 35%	UNIMMAP	30 mg Fe + 400 μg folic acid	3176 (3153, 3199) g	21 (−11, 53) g	0.86 (0.73, 1.01) g
4)	Niger (29)	3670	Cluster-randomized trial, 17 health centers, 78 villages; micronutrients given up to delivery; package including malaria prevention and education; mean BMI: 20.4; primigravida: 19.1%	UNIMMAP	60 mg Fe + 400 μg folic acid	3025 ± 205 g	67 (51, 82) g	0.86 (0.66, 1.13) g
5)	Guinea-Bissau (27)	2100	Individual randomization; enrollment until late pregnancy; micronutrients given up to delivery; package including impregnated bed net and chloroquine; 8-wk PP visit; mean BMI: 23.2; primigravida: 30.8%	UNIMMAP (1 RDA); UNIMMAP (2 RDA; except iron, 30 mg/d)	60 mg Fe + 400 μg folic acid	3002 (2952, 3051) g	53 (−19, 125); 95 (24, 166) g	0.86 (0.56, 1.33); 0.69 (0.46, 1.11) g
6)	Zimbabwe (28)	1669	Individual randomization; micronutrients given up to delivery; 33% HIV+; malaria not endemic; mean BMI: 24.8; primigravida: 42%	UNIMMAP except no iodine; 3000 μg vitamin A + 3.5 mg β-carotene	Same iron dosage in both groups	3004 g	49 (−6, 104) g	0.84 (0.59, 1.18) g
7)	Mexico (51)	873	Individual randomization; enrollment up to 13 wk; DOT 6 d/wk; micronutrients given up to delivery; follow-up to 90 d; micronutrients given up to delivery; mean BMI: 24.5; primigravida: 34%	UNIMMAP except no selenium nor copper; 250 mg Mg; 60 mg iron sulfate	60 mg Fe	2977 ± 393 g	4 g	0.94 (0.57, 1.56) g

[1] BW, birth weight; LBW, low birth weight; DOT, directly observed therapy; PP, postpartum; RDA, Recommended Dietary Allowance.
[2] BMI was calculated as weight/height^2.
[3] In the control group. Values are $\bar{x}\pm$ SD or means (95% CIs).
[3-4] Values are means (95% CIs).
[5] Values are risk ratios (95% CIs).

The investigators in those trials raise the possibility that this additional mortality could be due to cephalopelvic disproportion and increased risk of asphyxia in LGA babies (60). However, this explanation is unlikely in our case because half (20 of 40) of the perinatal deaths were premature. Moreover, the apparently lower effectiveness on fetal growth and higher mortality risk in primiparous women is paradoxical in relation to that hypothesis. A potential alternative explanation is that UNIMMAP improved the survival of frail fetuses through pregnancy, but these frail infants are unable to survive the trauma of birth. However, if this was the case, miscarriage risk would be reduced in the UNIMMAP group, which was not observed in our study.

This study provides new data on an issue for which evidence is scarce, ie, the efficacy of UNIMMAP during pregnancy in a rural African setting where malaria is endemic. Our study has many strengths. The use of home visitors permitted early detection of pregnancies, and the rate of assisted deliveries was much higher than reported in the general population (39). Intake of the micronutrients was directly observed, and the follow-up rate was high. Also, care was taken to ensure the accuracy of measurements: an obstetrician assessed gestational age by ultrasound, and all anthropometric indicators were measured twice by an anthropometrist, whose work was checked with monthly quality control. One limitation of the study was the 15% missing data at birth despite the very tight follow-up system. This was mainly due to the women's mobility during the season of intensive agricultural labor. However, a validity check by multiple imputations of missing data confirmed that our results were robust.

In conclusion, UNIMMAP supplements improved fetal growth significantly but modestly, and the benefit on infant health is yet to be demonstrated (25), although improved survival in the Indonesia study raises hope (47). The case of primiparous women, for whom UNIMMAP seemed to provide little benefit and potential harm, should be further investigated through pooled analysis of the results already published, and specific public health approach to this vulnerable group should be designed. Further randomized controlled studies of improvements in both maternal and fetal nutrition in undernourished women through a combination of micro- and macronutrients are also warranted. Harm should be carefully monitored given the potentially increased risk of perinatal mortality. Finally, uncertainties concerning the best composition and dosage of UNIMMAP during pregnancy should be addressed. In particular, there is an urgent need for functional assays to specify the appropriate RDAs for women exposed concomitantly to repeated infectious diseases and chronic and multiple nutritional deficiencies (25, 61).

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The authors' responsibilities were as follows—PK and DR: designed the study and the protocol; DR: implemented the study, analyzed and interpreted the data, and drafted the manuscript; PK: coordinated the implementation of the study and helped analyze and interpret the data and write the manuscript; M-CH: made substantial contributions to the execution and supervision of the study; HL: coordinated the field investigations; JM: helped with the data analysis; NM: contributed to the execution and supervision of the study; and LH: made substantial contributions to the supervision of the field investigations and data management. All authors contributed substantially to the manuscript and approved the final version. No conflicts of interest were declared.

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