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Efficacy of Multiple Micronutrient Supplements during Pregnancy on Zinc Status among Pregnant Women in Ghana: A Randomized Trial

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A B S T R A C T

Background: Multiple micronutrient deficiencies, including zinc deficiency, remain highly prevalent among pregnant women in many low- and middle-income countries and are associated with a multitude of adverse outcomes.

Objectives: The objectives of this analysis were to assess the impacts of prenatal multiple micronutrient supplements (MMS) compared with iron and folic acid (IFA) supplements on maternal zinc status among pregnant women at 36 weeks of gestation and to assess associations with birth outcomes.

Methods: We analyzed plasma zinc concentrations at baseline (<20 weeks of gestation) and late pregnancy (36 weeks of gestation) from a subset of pregnant women randomly assigned to receive either daily MMS (containing 30 mg/d zinc) or IFA supplements ($n = 125$/group) in the iLiNS-DYAD trial in Ghana. Gestational and infant anthropometric outcomes were measured at birth.

Results: At baseline, mean ± standard deviation (SD) plasma zinc concentration was 61.9 ± 13.6 μg/dL, and 16.5% of women were zinc deficient. At 36 weeks of gestation, mean ± SD plasma zinc concentration was lower compared with baseline, but did not differ significantly between groups (IFA: 52.2 ± 8.1 μg/dL compared with MMS: 52.9 ± 9.5 μg/dL; $P = 0.25$). Similarly, there was no difference in the estimated prevalence of zinc deficiency between groups at 36 wk (IFA: 43.0% compared with MMS: 38.4%; $P = 0.24$). There were a few significant associations between maternal plasma zinc concentrations or zinc deficiency and birth outcomes.

Conclusions: Daily MMS supplementation for ≥16 wk during pregnancy did not significantly increase plasma zinc concentrations, and the prevalence of zinc deficiency increased over the course of pregnancy. Other complementary interventions to address both nutritional and underlying nonnutritional causes of zinc deficiency may be necessary to improve zinc status during pregnancy in this and other vulnerable populations.

The trial was registered at clinicaltrials.gov as NCT00970866. https://clinicaltrials.gov/study/NCT00970866

Keywords: zinc deficiency, pregnancy, birth outcomes, multiple micronutrient supplements, plasma zinc concentration, micronutrient supplementation, zinc supplementation, infants

Introduction

Multiple micronutrient deficiencies remain highly prevalent among pregnant women in many low- and middle-income countries (LMICs) and are associated with a multitude of adverse outcomes, including fetal growth restriction, preterm birth, low birth weight, and infant and maternal mortality [1–3]. Although nationally representative biochemical data on micronutrient status among pregnant women are limited, a recent analysis by Stevens et al. [4] estimated that globally, 69% of nonpregnant women of reproductive age (WRA) were deficient in ≥1 of 3 core micronutrients (e.g., iron, zinc, and folate).

Abbreviations: AGP, α-1-acid glycoprotein; BMIZ, BMI z-score; BRINDA, Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia; CRP, C-reactive protein; ICP-OES, inductively coupled plasma ion exchange spectrometry; IFA, iron and folic acid; IZiNCG, International Zinc Nutrition Consultative Group; LMIC, low- and middle-income countries; MMS, multiple micronutrient supplement; RDA, recommended dietary allowance; SQ-LNS, small-quantity lipid-based nutrient supplements; UNIMMAP, United Nations International Multiple Micronutrient Antenatal Preparation; WRA, women of reproductive age.

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Importantly, in 16 of 18 LMICs with available data, the proportion of WRA with low plasma/serum zinc concentrations exceeded 20%, the threshold used to identify a public health problem [5].

Iron and folic acid (IFA) supplementation has been the existing standard of care for pregnant women in LMICs [6]. However, prenatal multiple micronutrient supplements (MMS) have been shown to improve maternal nutritional status and reduce risk of adverse outcomes (e.g., preterm birth, stillbirth, low birthweight, and small for gestational age birth), as compared with IFA [1,7]. Thus, in 2020, the WHO issued a new context-specific recommendation on MMS, indicating that "antenatal multiple micronutrient supplements that include IFA are recommended in the context of rigorous research" [8]. The WHO Guideline Development Group identified a need for more evidence on the efficacy of the dose of iron in MMS, compared with IFA (30 mg compared with 60 mg, respectively) [8], and research has recently been completed to address this knowledge gap [9]. However, there is also remaining uncertainty regarding the optimal dose of zinc in MMS to improve maternal zinc status and prevent risk of preterm birth to the greatest extent possible. In the Women First trial, investigators recently observed that 40% to 70% of pregnant women had low serum zinc concentrations (<50 μg/dL) in the third trimester [10], despite receiving a daily supplement containing 15 mg zinc.

Therefore, this analysis assessed the impacts of prenatal MMS (containing 30 mg zinc) compared with IFA supplements on maternal zinc status (plasma zinc concentrations and the prevalence of zinc deficiency) among pregnant women at 36 weeks of gestation (after ≥16 wk of intervention). As a secondary objective, we assessed associations between maternal zinc status at baseline or at 36 weeks of gestation and birth outcomes (e.g., preterm birth, small-for-gestational age, duration of gestation, etc.).

Methods

Study design, setting, and participants

The current analyses are based on a subsample of pregnant participants enrolled in the iLiNS-DYAD Ghana trial [11,12]. The iLiNS-DYAD Ghana trial was designed as a randomized, partially double-blind, individually randomized controlled trial that compared 3 micronutrient supplements and targeted women during pregnancy (from ≤20 weeks of gestation to delivery) and the first 6 mo postpartum [12]. The supplements provided during pregnancy were: *1*) daily IFA, *2*) daily MMS, and *3*) daily small-quantity lipid-based nutrient supplements (SQ-LNS) [12]; the IFA and MMS study arms were fully blinded. Detailed descriptions of the overall study design and study protocol, as well as the effect of the interventions on multiple outcomes, have been reported previously [11,12]. The present analyses address zinc-related perinatal outcomes of the trial in the IFA and MMS intervention arms only.

The trial was conducted from December 2009 to 2014 in the Yilo Krobo and the Lower Manya Krobo Districts in the Eastern Region of Ghana. Pregnant women were recruited from the antenatal clinics of 4 health care facilities in the study catchment area. Women were invited for screening if they met the following criteria: age ≥18 y, ≤20 weeks of gestation, planned to reside in the study catchment area for the duration of the study, and were willing to accept home visits and consume the study supplements. Women were excluded from the study if they presented with a history of a serious medical condition (i.e., if their antenatal cards indicated HIV infection, tuberculosis, asthma, epilepsy, or any malignancy), had a known milk or peanut allergy, or were participating in another research study.

Eligible women were contacted at home to provide informed consent. Consent materials were presented, both written and orally, in the presence of an impartial witness. Informed consent was obtained from each participant before her recruitment in the study and documented as either a written signature or a fingerprint. Ethical approvals for the study were provided by the Ethical Review Committee of the Ghana Health Services and the Institutional Review Boards of the University of Ghana Noguchi Memorial Institute for Medical Research and the University of California, Davis. The trial was registered as a clinical trial on clinicaltrials.gov (NCT00970866).

Group assignments and blinding

The study statistician at the University of California, Davis, developed group allocations using a computer-generated block randomization scheme (SAS version 9.3; SAS Institute) with block lengths of 9. Allocations were sequentially numbered 1 to 1320, placed in sealed, opaque envelopes, and stacked in numerical order. After completing baseline assessments, recruited women who remained eligible for the study were enrolled; each enrolled participant picked 1 envelope from the 9 topmost envelopes in the stack to reveal her group assignment [12]. Group assignments for IFA and MMS were represented by 6 different color codes (3 for IFA and 3 for MMS), and supplements were color-coded accordingly; investigators, study workers, participants, and data analysts were blinded to the identities of the capsules. Allocation information was kept by the field supervisor and shared with the study statistician. Initial allocation codes were broken after the completion of all preliminary analyses. For the purpose of this analysis, intervention arms were randomly assigned novel blinded group codes, and all analyses were conducted, and interpretation was agreed upon before unblinding group identity.

Intervention products (intervention and comparator), trial supplements

During pregnancy, women randomly assigned to the IFA group received a daily supplement containing 60 mg Fe and 400 μg folic acid; those randomly assigned to the MMS group received a daily MMS containing 1 to 2 recommended dietary allowances (RDA) of 18 vitamins and minerals, including 20 mg iron, 400 μg folic acid, and 30 mg zinc (Table 1). The supplements were produced by DSM South Africa and provided as capsules packaged in blister packs. The formulation of the MMS supplements used in this trial were based on the following: *1*) the United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP) formulation [13]; *2*) a trial in Guinea Bissau, which showed a greater increase in birth weight among infants born to mothers supplemented with MMS containing twice the RDA of 15 micronutrients compared with those supplemented with MMS containing 1 RDA [14]; and *3*) a trial in Australia, which indicated that low-dose iron supplements (20 mg) may be as efficacious in treating anemia in pregnancy as higher-dose supplements, with fewer side effects [15].

TABLE 1
Micronutrient composition of supplements used in the study, with the United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP) multiple micronutrient supplement product specification for comparison

Nutrient	IFA	MMS	UNIMMAP formulation [13]
Vitamin A, μg RE		800	800
Vitamin B-1, mg		2.8	1.4
Vitamin B-2, mg		2.8	1.4
Niacin, mg		36	18
Pantothenic acid, mg		7	
Vitamin B-6, mg		3.8	1.9
Folic acid, μg	400	400	400
Vitamin B-12, μg		5.2	2.6
Vitamin C, mg		100	70
Vitamin D, IU		400	200
Vitamin E, mg		20	10
Vitamin K, μg		45	
Copper, mg		4	2
Iodine, μg		250	150
Iron, mg	60	20	30
Manganese, mg		2.6	
Selenium, μg		130	65
Zinc, mg		30	15

Abbreviations: IFA, iron and folic acid; MMS, multiple micronutrient supplement;.

Procedures

At baseline, information on maternal and household socioeconomic and demographic characteristics was collected via a structured interview. Principal component analysis was used to derive an assets index, constructed based on ownership of a set of assets and household characteristics. Household food insecurity was assessed using the Household Food Insecurity Access Scale [16]. Gestational age was determined by ultrasound biometry (Aloka SSD 500), and anthropometric measurements were collected in duplicate for maternal height (Seca 217; Seca GmbH & Co.), weight (Seca 874), and mid–upper arm circumference (Weigh & Measure, LLC). Venous hemoglobin concentration was determined using a Hemocue model 301 system (Hemocue AG), and venous blood samples (7.5 mL) were collected into trace-element-free polyethylene tubes containing lithium heparin (Sarstedt AG & Co.).

At the end of the baseline visit, women received a 2-wk supply of their assigned supplement and were instructed to consume 1 capsule daily with water after a meal. For the duration of the intervention (during pregnancy), all women were visited biweekly in their homes by a study fieldworker who was responsible for replenishing supplements, assessing adherence, and conducting a systematic symptom-based morbidity recall.

At 36 weeks of gestation, women attended a secondary laboratory visit, where baseline anthropometric and biochemical assessments were repeated. Within 48 h after birth, women were visited in their home or the hospital, and anthropometric measurements of their newborns were completed. Birth weight was measured to the nearest 20 g (Seca 383), and length (Seca 416), head, and mid–upper arm circumferences (Weigh & Measure, LLC) to the nearest 0.1 cm. For infants, weight-for-age, length-for-age, BMI-for-age (BMIZ), and head circumference-for-age *z*-scores were calculated according to the WHO growth standards [17,18]. Weight-for-gestational age, length-for-gestational age, and head circumference-for-gestational age *z*-scores were calculated according to International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) standards [19]. For newborns measured between 3 and 14 d (8.3% of the sample), we back-calculated birth weight, length, and head circumference on the basis of *z*-scores at the time of measurement using the formulas described by the WHO, assuming *z*-scores remained constant [18].

Sample processing and laboratory analyses

Venous blood samples were stored at 4°C until centrifugation, then centrifuged at 1252 × *g* for 15 min, and plasma was aliquoted into microcentrifuge tubes. Plasma samples intended for nutritional biomarker assays were stored in Ghana at −20°C and later shipped on dry ice via air freight to the University of California, Davis, where samples were stored at −70°C until analysis.

Plasma zinc was analyzed by inductively coupled plasma optical emission spectrophotometry (ICP-OES 5900; Agilent Technologies, Inc.) at the University of California, San Francisco MLK Core Facility. Details of the plasma zinc assay by ICP-OES have been described previously [20]. In brief, plasma samples were centrifuged at 4000 × *g* for 15 min and digested overnight at 60°C in trace element grade 70% HNO_3. This solution was then diluted to a final concentration of 5.5% HNO_3 and centrifuged at 3000 × *g* for 10 min before analysis. Each batch of samples run on the ICP-OES was analyzed with Seronorm Trace Elements Serum L-2 (Sero AS) as the reference material. All samples from a particular participant were analyzed in the same analytic run, and 11% of the samples were analyzed in triplicate. The mean (±SD) interrun coefficient of variation for triplicate samples was 5.5% ± 8.4%. C-reactive protein (CRP; mg/L) and α-1-acid glycoprotein (AGP; g/L) concentrations were determined by Cobas Integra 400 plus Automatic Analyzer (Roche Diagnostics Corp.).

Outcome variables

In the present analysis, the outcome variables for the primary intervention effect objective are plasma zinc concentration, adjusted for inflammation [21], and the prevalence of zinc deficiency at 36 weeks of gestation. The outcome variables for the secondary associational objective are duration of gestation (weeks), birth weight (g), and anthropometric z-scores at birth, based on WHO and INTERGROWTH-21st growth standards [17–19].

Sample size

In the present analysis, the main outcome variable was endline plasma zinc concentration. To detect treatment-related differences between intervention groups with an effect size of ≥0.36 SD, a sample size of 125 participants per study intervention group was necessary ($\alpha = 0.05$, $\beta = 0.20$). Samples for the present analysis were randomly selected if they met the following criteria: *1*) participant correctly received the assigned supplement for the entire intervention period [12], and *2*) baseline and 36-wk biospecimen samples were collected, previously analyzed for acute phase protein concentrations (CRP and AGP), and had a plasma aliquot with sufficient volume archived at the University of California, Davis.

Data analysis

A detailed statistical analysis plan was developed before analysis and is available online [22]. All analyses were completed using a complete-case intention-to-treat approach [23]. Descriptive statistics were calculated for all variables. Model assumptions were assessed (e.g., with Shapiro-Wilk tests for normality and assessments of linearity).

Plasma zinc concentrations were adjusted for elevated acute phase proteins, using a regression approach adapted from the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia project [21]. Specifically, if CRP and/or AGP were negatively associated with the outcome ($P < 0.05$) at a given time point, an adjustment by internal regression correction was applied using the inflammation biomarker(s) that showed a significant association with the outcome. Zinc deficiency was defined as plasma zinc concentrations (adjusted for inflammation) <56 μg/dL in the first trimester and <50 μg/dL in the second and third trimesters [21,24].

To assess the effect of the intervention, we followed the pre–post study design, analyzing continuous outcomes using analysis of covariance models to estimate mean differences and binary outcomes using modified Poisson models with robust estimation of SEs to estimate prevalence ratios controlling for baseline plasma zinc concentration in minimally adjusted models [25]. To increase statistical power, we explored secondary analyses fitting adjusted models controlling for baseline covariates associated with the outcome at $P < 0.10$. Potential adjustment variables included baseline BMI, gestational age at enrollment, maternal age, maternal education, assets index, household food insecurity index, primiparity, season at enrollment, hemoglobin concentration at baseline, hemolysis of blood sample, time of day of blood collection, sample processing time, and study duration. Exploratory effect modification was assessed for maternal age, primiparity, baseline plasma zinc status, gestational age at enrollment, and compliance with supplementation. This was conducted by including an interaction term in minimally adjusted models, and significant interactions ($P < 0.10$) were further examined with post hoc stratified analyses and/or regions of significance analyses [25].

The analysis of the secondary objective quantifying the associations between baseline or 36-wk plasma zinc concentration and birth outcomes used multivariable linear regression for continuous outcomes and modified Poisson regression for binary outcomes. All models controlled for the intervention arm and the baseline covariates listed above, except baseline plasma zinc concentration. Covariates were selected based on 2 criteria: their potential value as prognostic factors that could explain some of the variation in the outcomes and provide additional statistical power in analyses, or as potential confounders that may be drivers of both zinc status and the outcomes.

All testing was 2-sided and presented with 95% confidence intervals (CIs). Analyses were conducted in Stata v17 (StataCorp, LLC).

Results

Participant characteristics

A total of 250 pregnant women, who provided baseline and 36-wk plasma samples, are included in the present analyses (Figure 1). At baseline, women were 27.3 ± 5.3 y of age; 28% were primiparous, and the mean gestational age was 16.4 ± 3.0 wk (Table 2). Forty percent were anemic (Hb <110 g/L) and 42% presented with subclinical inflammation (CRP >5 mg/L and/or AGP >1 g/L) (Table 2). Baseline, but not endline, plasma zinc concentrations were associated with CRP concentrations (rho = −0.17, $P = 0.007$), and baseline plasma zinc concentrations were adjusted accordingly; plasma zinc concentrations were not associated with AGP at either time point.

At baseline, the mean unadjusted plasma zinc concentration was 56.6 ± 12.5 μg/dL, and 36.6% had low plasma zinc concentrations. After adjusting for inflammation (CRP only), mean plasma zinc concentration was 61.9 ± 13.6 μg/dL, and the prevalence of low plasma zinc concentrations was 16.5% (Table 3).

Effects of the intervention

Over the course of the intervention period in pregnancy (23.3 ± 3.3 wk), reported adherence to IFA and MMS was 75% and 77% of days, respectively, and did not differ by group ($P = 0.77$).

At 36 weeks of gestation, there were no statistically significant differences in mean plasma zinc concentrations between women in the MMS intervention arm compared with the IFA arm (52.9 ± 9.5 μg/dL compared with 52.2 ± 8.1 μg/dL) in the minimally adjusted model (i.e., adjusted for baseline plasma zinc concentration) ($P = 0.26$; Table 3, Supplemental Table 1) or in the adjusted models (Table 3). Similarly, the prevalence of zinc deficiency did not differ between intervention arms at 36 weeks of gestation (MMS compared with IFA, 38.4% compared with 42.6%, respectively, $P = 0.24$). Maternal age, parity, gestational age at enrollment, baseline plasma zinc deficiency, and compliance with the assigned supplement did not modify the effect of the intervention on plasma zinc concentrations or the prevalence of zinc deficiency at endline (Supplemental Table 1).

Association between zinc deficiency and birth outcomes

In general, plasma zinc concentrations and zinc deficiency, at both baseline and 36 weeks of gestation, were not associated with birth outcomes. Of 64 comparisons, 2 were marginally significant (3.1% of comparisons; fewer than the 6.4% that would be expected by chance alone) (Table 4). Women who had zinc deficiency at baseline had, on average, infants with marginally higher BMIZ at birth than women who were not zinc deficient at baseline (−0.26 ± 1.0 compared with −0.55 ± 0.99, $P = 0.067$). In addition, higher plasma zinc concentrations at 36 weeks of gestation were associated with a reduced risk of stunting at birth based on the INTERGROWTH-21st standards (2.9% compared with 6.1%, $P = 0.075$).

Discussion

Overview of the main results

In the present study, conducted among pregnant women in semiurban communities in Ghana, the overall prevalence of low inflammation–adjusted plasma zinc concentrations increased over the course of pregnancy, from 16.5% to 40.5%, as measured at ~16 and 36 weeks of gestation, respectively. This

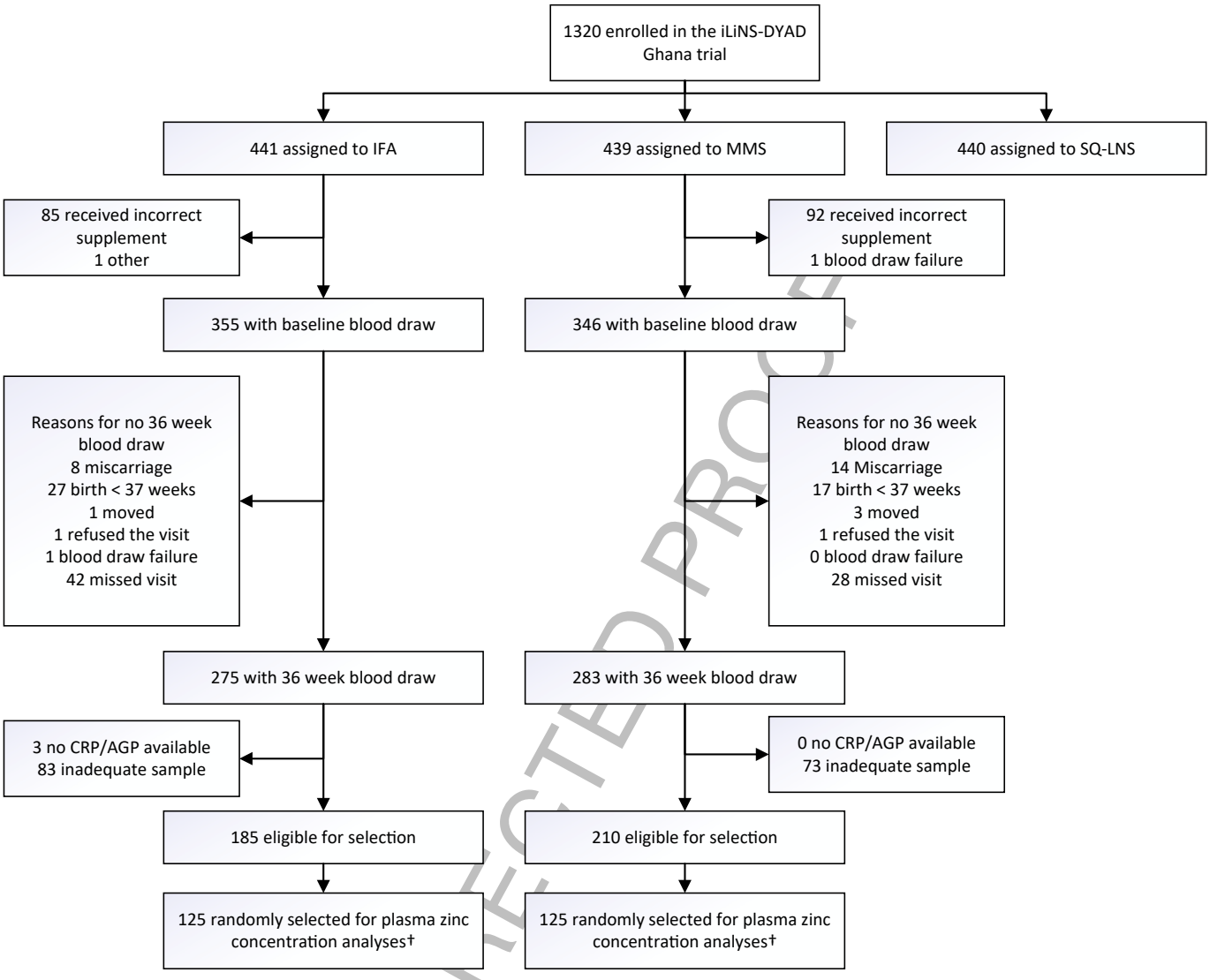

FIGURE 1. Study flow diagram. †Samples for the present analysis were randomly selected from the participants enrolled in the iLiNS-DYAD trial conducted in Ghana if they met the following criteria: *1*) participant received the assigned supplement (IFA or MMS) for the entire intervention period [12], and *2*) baseline and 36-wk biospecimen samples were collected, previously analyzed for acute phase protein concentrations (CRP and AGP), and had a plasma aliquot with sufficient volume archived at the University of California, Davis. AGP, α-1-acid glycoprotein; CRP, C-reactive protein; IFA, iron and folic acid; iLiNS-DYAD, XXX; MMS, multiple micronutrient supplement; SQ-LNS, small-quantity lipid-based nutrient supplement.

suggests a high risk of zinc deficiency in the third trimester of pregnancy and the potential of this population to benefit from zinc supplementation. However, there was no impact of the intervention on plasma zinc concentrations or the prevalence of zinc deficiency in this population. In addition, there were a few significant associations between maternal plasma zinc concentrations or zinc deficiency and birth outcomes.

Effects of the intervention

In the present study, plasma zinc concentrations did not respond to daily zinc supplementation (30 mg/d) provided as part of an MMS. The evidence on the effect of zinc supplementation (provided either alone or as part of an MMS or SQ-LNS product) on zinc status in pregnancy is mixed. Our results are in contrast to a dose–response meta-analysis of zinc supplementation in pregnancy, which reported that for the majority of studies included in the review, zinc supplementation (15–30 mg/d, provided as either zinc alone or MMS) significantly increased serum/plasma zinc status or significantly reduced the number of low serum/plasma values in their participants [26]. For every doubling of zinc intake, there was a significant 3% increase in serum/plasma zinc concentration among pregnant women [26]. However, our results are in line with a later meta-analysis, which reported that although zinc supplementation may have improved maternal serum/plasma zinc concentrations, the effect was not statistically significant (MD = 0.43 μmol/L; 95% CI: −0.04, 0.89; 5 studies), and that studies providing zinc only showed a greater increase (MD: 0.86 μmol/L; 95% CI: 0.67, 1.05; n = 2) than studies that provided additional micronutrients (MD: 0.01 μmol/L; 95% CI: −0.72, 0.72; n = 3) [27]. In addition to the studies included in the aforementioned meta-analyses, several recent trials of zinc supplementation (providing 12–15 mg/d, in either MMS or

TABLE 2
Baseline characteristics of participants

	IFA	MMS
Participants, *n*	125	125
Age, y[1]	27.3 ± 5.2	27.3 ± 5.4
Formal education, y	7.7 ± 3.5	7.2 ± 3.5
Household asset index	0.21 ± 0.96	0.21 ± 0.78
Household moderately or severely food insecure, *n* (%)	34 (27.2)	29 (23.4)
Gestational age at enrollment, wk	16.4 ± 3.1	16.4 ± 2.8
Primiparous, *n* (%)	38 (30.4)	33 (26.4)
BMI[2], kg/m^2	24.5 ± 4.7	23.7 ± 5.8
Underweight (<18.5 kg/m^2), *n* (%)	6 (4.9)	9 (7.4)
Normal (18.5-25 kg/m^2), *n* (%)	71 (58.2)	78 (63.9)
Overweight or obese (>25 kg/m^2), *n* (%)	45 (36.9)	35 (28.7)
Hemoglobin, g/L	112 ± 13	111 ± 11
Anemia (< 110 g/L), *n* (%)	50 (40.0)	50 (40.0)
Elevated CRP (> 5 mg/L), *n* (%)	55 (44.0)	49 (39.2)
Elevated AGP (> 1 g/L), *n* (%)	11 (8.8)	5 (4.0)
Plasma zinc, μg/dL[3]	63.8 ± 14.3	60.1 ± 12.6
Zinc deficiency, *n* (%)[4]	17 (14.1%)	24 (19.2%)

Abbreviations: AGP, α-1-acid glycoprotein; CRP, C-reactive protein; IFA, iron and folic acid; MMS, multiple micronutrient supplement.
[1] Values are means ± SD or *n* (%), unless otherwise specified.
[2] We estimated weight back to the 9th weeks of gestation using a restricted cubic spline model regressing baseline weight on gestational age at enrollment with 4 knots based on quintiles in the study's full dataset.
[3] Baseline plasma zinc concentrations were associated with CRP concentrations (rho = −0.17, $P = 0.007$); baseline plasma zinc concentrations were adjusted according to the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia method for CRP only [21].
[4] Plasma zinc deficiency is defined as a plasma zinc concentration <56 μg/dL in the first trimester (<14 wk), and <50 μg/dL in the second trimester (≥14 wk) [24].

TABLE 3
Plasma zinc concentrations and the prevalence of zinc deficiency among pregnant women, at 36 weeks of gestation, by intervention group[1]

	IFA ($n = 121$)	MMS ($n = 125$)	Minimally adjusted *P* value
Plasma zinc, μg/dL[2]			
36 weeks of gestation	52.2 ± 8.1	52.9 ± 9.5	0.25
Zinc deficiency, *n* (%)[3]			
36 weeks of gestation	52 (43.0%)	48 (38.4%)	0.24

Abbreviations: IFA, iron and folic acid; MMS, multiple micronutrient supplement.
[1] The IFA group received 60 mg iron and 400 μg folic acid per day. The MMS group received 1 to 2 recommended dietary allowances of 18 vitamins and minerals (including 30 mg zinc, 20 mg iron, and 400 μg folic acid per day).
[2] Values are means ± SD or *n* (%). Results are based on analysis of covariance and Poisson regression models for continuous and categorical outcome variables, respectively. The minimally adjusted models control for C-reactive protein–adjusted baseline plasma zinc concentration. None of the additional potential covariates evaluated (baseline BMI, gestational age at enrollment, maternal age, maternal education, assets index, household food insecurity index, primiparity, season at enrollment, hemoglobin concentration at baseline, hemolysis of blood sample, time of day of blood collection, sample processing time, and study duration) were associated with the outcomes at $P < 0.10$, so results of the fully adjusted models do not differ from those of the minimally adjusted *P* values.
[3] Plasma zinc deficiency is defined as a plasma zinc concentration <50 μg/dL in the third trimester [24].

SQ-LNS) have reported significant increases in plasma zinc concentrations [10,28], whereas several other trials (providing 15–30 mg Zn/d, as zinc + IFA or MMS supplements) have reported no effect of the intervention on zinc status [29–31]. The observed lack of a consistent plasma zinc response to zinc supplementation during pregnancy, and consistently high prevalences of zinc deficiency remaining across all studies in spite of supplementation, may be due to the following: *1*) an inadequate amount of zinc in the MMS supplement, *2*) inadequate absorption of zinc from the MMS supplement, and/or *3*) nonnutritional causes of zinc deficiency.

In this study, the MMS contained 30 mg Zn/d, which is almost 3 times the United States Food and Nutrition Board/Institute of Medicine and International Zinc Nutrition Consultative Group (IZiNCG) RDA for zinc intake during pregnancy (11 mg/d and 13 mg/d, respectively) [24,32] and twice the amount of zinc in the UNIMMAP formulation of MMS [13]. Thus, it seems unlikely that the lack of response to zinc supplementation and high prevalence of zinc deficiency, even with supplementation, are due to an inadequate amount of zinc in the supplement. However, it is possible that pregnant women in the present study experienced poor zinc absorption from the supplement, in spite of expected enhanced zinc absorption in the third trimester of pregnancy to meet physiological needs [33]. It is also possible that pregnant women may transfer more of the absorbed zinc to other tissues rather than increasing plasma zinc concentrations. Although we do not have individual-level dietary data for participants, the study area's predominantly maize-based diet is high in phytate, 1 of the main inhibitors of zinc absorption [34,35]. Second, the MMS supplement also included iron, which has been shown to impair zinc absorption [34,36,37]. However, the ratio of iron: zinc was <1:1 (20 mg iron, 30 mg zinc) in this supplement, which should limit the negative impact of iron on zinc absorption [38]. Third, when supplemental zinc is consumed in the diet as a daily bolus dose, the fractional absorption of zinc has been shown to decrease [39]. However, the amount of zinc provided by the MMS supplement (30 mg/d), in addition to dietary intake, should have been enough to meet physiological requirements for absorbed zinc in pregnancy (estimated range: 2.27–5.02 mg/d) [24,40,41], even if the fractional absorption of zinc from the supplement was ≤15% [24]. Finally, it is possible that there are nonnutritional causes of zinc deficiency in this population, leading to plasma zinc concentrations not being responsive to zinc supplementation in this population. At baseline, the estimated prevalence of zinc deficiency decreased by 20 percentage points when controlling for inflammation (from 36% to 16%). Diarrheal diseases and intestinal infections increase zinc losses, and other infections increase zinc requirements (e.g., malaria) [42,43]. At baseline, ~10% of pregnant women in the iLiNS-DYAD Ghana (parent) trial tested positive for malarial antigenemia [44], and 7% of women reported severe diarrhea, and >33% of women reported fever and respiratory symptoms during each of the 2nd and 3rd trimesters of their pregnancies [44]. Therefore,

TABLE 4
Associations between zinc deficiency, at baseline and 36 wk, and birth outcomes (adjusting for treatment arm at 36 wk); multivariable model controlling for all covariates[1]

Birth outcome	Low plasma zinc concentration	Normal plasma zinc concentration	*P* value[2] for continuous zinc	*P* value for binary zinc
Zinc status at baseline (adjusted for inflammation)[3], *n*	41	208		
Birth weight (g)	3111 (408)	3043 (364)	0.24	0.14
Weight-for-age *Z*-score (WAZ)[4]	−0.42 (0.87)	−0.55 (0.82)	0.22	0.19
Weight-for-gestational age *Z*-score (WGAZ)	−0.44 (0.93)	−0.57 (0.88)	0.14	0.35
Low birth weight (<2500 g)	2.4%	6.0%	0.72	0.66
Small for gestational age (<10th percentile)	17.1%	20.6%	0.92	0.99
Length-for-gestational age *Z*-score (LAZ)	−0.62 (0.76)	−0.51 (0.94)	0.61	0.87
LAZ < −2 SD	4.9%	4.5%	0.60	0.49
Length-for-gestational age *Z*-score (LGAZ)	−0.62 (0.75)	−0.46 (0.98)	0.45	0.46
LGAZ < −2 SD	2.5%	4.5%	0.54	0.63
BMI-for-age *Z*-score (BMIZ)	−0.26 (1.0)	−0.55 (0.99)	0.26	0.07
Low BMIZ < −2 SD	4.9%	6.5%	0.84	0.96
Head circumference-for-age *Z*-score (HCAZ)	−0.18 (1.02)	−0.34 (1.03)	0.93	0.30
Low HCAZ < −2 SD	4.9%	4.5%	0.66	0.78
Head circumference-for-gestational age *Z*-score (HCGAZ)	0.02 (094)	−0.16 (1.05)	0.64	0.41
Low HCGAZ < −2 SD	0%	3.5%		
Duration of gestation, wk	39.7 (1.3)	39.7 (1.4)	0.49	0.50
Zinc status at endline (not inflammation adjusted), *n*	100	147		
Birth weight (g)	3078 (348)	3044 (387)	0.29	0.34
Weight-for-age *Z*-score (WAZ)	−0.49 (0.76)	−0.54 (0.88)	0.33	0.48
Weight-for-gestational age *Z*-score (WGAZ)	−0.52 (0.90)	−0.55 (0.89)	0.72	0.59
Low birth weight (<2500 g)	4.1%	5.8%	0.29	0.56
Small-for-gestational age (<10th percentile)	22.5%	18.7%	0.44	0.35
Length-for-gestational age *Z*-score (LAZ)	−0.56 (0.96)	−0.50 (0.89)	0.93	0.62
LAZ < −2 SD	4.1%	5.0%	0.17	0.12
Length-for-gestational age *Z*-score (LGAZ)	−0.52 (1.0)	−0.46 (0.9)	0.63	0.66
LGAZ < −2 SD	6.1%	2.9%	0.08	0.11
BMI-for-age *Z*-score (BMIZ)	−0.41 (0.98)	−0.55 (0.99)	0.15	0.17
Low BMIZ < −2 SD	6.1%	5.8%	0.39	0.79
Head circumference-for-age *Z*-score (HCAZ)	−0.29 (0.95)	−0.3 (1.1)	0.84	0.84
Low HCAZ < −2 SD	6.1%	2.9%	0.18	0.31
Head circumference-for-gestational age *Z*-score (HCGAZ)	−0.11 (0.99)	−0.12 (1.1)	0.60	0.80
Low HCGAZ < −2 SD	3.1%	2.9%	0.99	0.72
Duration of gestation, wk	39.8 (1.3)	39.7 (1.4)	0.32	0.70

[1] Plasma zinc deficiency (low plasma zinc concentration) is defined as a plasma zinc concentration <56 μg/dL in the first trimester (<14 wk), and <50 μg/dL in the second or third trimesters (≥14 wk) [24]. Normal plasma zinc concentration is defined as a plasma zinc concentration ≥56 μg/dL in the first trimester (<14 wk), and ≥50 μg/dL in the second or third trimesters (≥14 wk).

[2] Values are means ± SD or *n* (%). Results are based on modified Poisson regression. All models include the following variables: baseline BMI, gestational age at enrollment, maternal age, maternal education, assets index, household food insecurity index, primiparity, season at enrollment, hemoglobin concentration at baseline, intervention arm, hemolysis of blood sample, time of day of blood collection, sample processing time, and study duration.

[3] Baseline, but not endline, plasma zinc concentrations were associated with C-reactive protein (CRP) concentrations (rho = −0.17, $P = 0.007$); baseline plasma zinc concentrations were adjusted according to the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia method for CRP only [21].

[4] WAZ, LAZ, BMIZ, and HCAZ are calculated based on the WHO growth standards [17,18]. WGAZ, LGAZ, HCGAZ, and small for gestational age are calculated based on the International Fetal and Newborn Growth Consortium for the 21st Century growth standards [19].

the provision of zinc supplements may not be enough to control zinc deficiency; other strategies to address infection and inflammation may also be necessary.

Associations between zinc status and birth outcomes

Two systematic reviews published in 2012 and 2015 demonstrated that preventive zinc supplementation during pregnancy resulted in a 14% reduction in preterm birth (RR: 0.86; 95% CI: 0.75, 0.99; and RR: 0.86; 95% CI: 0.76, 0.99, respectively) [12,13] but had no detectable benefits on fetal growth. A more recent meta-analysis that included data from 4 new trials reported a similar 13% reduction in preterm birth; however, this effect estimate did not reach statistical significance (RR: 0.87; 95% CI: 0.74, 1.03) [14], and again, there was no impact of the intervention on fetal growth. In addition, a recent meta-analysis by Smith et al. [1] reported that MMS reduced risk of preterm birth by 8% (RR: 0.92; 95% CI: 0.88, 0.95) in comparison with IFA [8]. However, in the iLiNS-DYAD Ghana (parent) trial, there was no impact of the intervention (MMS compared with IFA) on gestational age at birth or preterm birth [12]. However, there was a marginally significant reduction in the incidence of low birth weight among infants whose mothers received MMS compared with IFA [12].

It is in this context that we examined associations between plasma zinc concentrations (at ~16 weeks and ~36 weeks of gestation) and birth outcomes. In the present study, however, there were no significant associations between plasma zinc concentrations or zinc deficiency at ~16 and 36 weeks of gestation and birth outcomes (e.g., birth weight, small-for-gestational age, stunting, etc.). Although we were unable to examine associations with preterm birth, there were no significant associations between zinc status during pregnancy and duration of gestation. It has been well established that adequate maternal zinc status is critical for normal embryonic and fetal development throughout pregnancy. In animal models, zinc deficiency at any stage has been shown to disrupt key developmental processes and increase risk of growth restriction, congenital abnormalities, and impaired organ development, ultimately leading to adverse birth outcomes [45,46]. However, the literature on relationships between maternal plasma zinc concentrations and birth outcomes in human populations is mixed. In previous systematic reviews, approximately half of the studies reported significant associations between zinc status and birth outcomes, whereas the other half reported no significant associations [47,48]. For example, 1 study in Ethiopia reported that plasma zinc concentrations in the first trimester were positively correlated with birth weight [49]. However, another study in Ethiopia reported that 2nd and 3rd trimester plasma zinc concentrations were not significantly associated with low birth weight [50]. The Women First trial, conducted in the Democratic Republic of Congo, Pakistan, India, and Guatemala, observed that maternal plasma zinc concentrations at ~12 weeks of gestation were not associated with birth outcomes. However, maternal plasma zinc concentrations at ~34 weeks of gestation were associated with birth weight and length but not preterm birth [10].

Strengths and weaknesses

This analysis had several strengths, including a fully randomized controlled design with an active control group, standardized biological sample collection and laboratory analyses based on procedures recommended by the IZiNCG [51], and the analysis of samples for AGP and CRP to adjust for inflammation. However, this analysis also had several limitations. Adherence to supplementation was assessed by self-report, and not direct observation, although participants were visited biweekly in their homes, and the study team established a strong collaboration with the local antenatal health service providers. Second, plasma zinc concentrations are a relatively insensitive indicator of zinc nutritional status because they are under homeostatic control. In addition, the cutoffs for plasma zinc concentrations during pregnancy used to indicate zinc deficiency account for hemodilution in pregnancy; they are based on limited data and do not account for time of day/fasting status [24]. Therefore, although the high prevalence of low plasma zinc concentrations in this population appears to highlight a potential to benefit from zinc interventions, additional research is needed on cutoffs for plasma zinc concentrations indicative of zinc deficiency during pregnancy. Third, we do not have data on dietary zinc and phytate intake or biomarkers of environmental enteric dysfunction, which might help further elucidate underlying factors for the lack of responsiveness. Fourth, the sample size for these analyses was constrained by logistical and budgetary factors and was calculated to be able to detect an intervention effect of $\geq$0.36 SD; a larger sample size might have allowed us to detect a smaller intervention effect, although it may not have been clinically meaningful. Finally, because biological samples were collected at 36 weeks of gestation, this sample does not include women who had a miscarriage or who gave birth before 36 wk, which may introduce survivor bias and limit our ability to examine preterm birth as an outcome. However, the number of miscarriages and preterm births was similar between groups.

Conclusions

In the present analysis, the estimated prevalence of zinc deficiency was high, but plasma zinc concentrations did not respond to an MMS providing 30 mg Zn/d, which is twice the amount contained in UNIMMAP supplements; thus, supplements containing $\leq$30 mg zinc may not be adequate to improve plasma zinc concentrations in deficient populations. However, simply increasing the dose of zinc provided in MMS may also not be sufficient. Other complementary interventions to address underlying nonnutritional causes of zinc deficiency, including infection and inflammation control strategies, may be necessary to improve zinc status during pregnancy in vulnerable populations.

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Author contributions

The authors' responsibilities were as follows – SA-A, AL, KGD: designed the research; SA-A, AL, HO: conducted the research; CDA: performed the statistical analysis; KRW, CMM: wrote the manuscript; SA-A, AL, HO, CDA, KGD: reviewed the draft manuscript; KRW: primarily responsible for final content; and all authors: read and approved the final manuscript.

Conflict of interest

All authors report no conflicts of interest.

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Data availability

Data described in the manuscript, code book, and analytic code will be made publicly and freely available without restriction at https://osf.io/ek2gn.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tjnut.2026.101725.

References

[1] E.R. Smith, A.H. Shankar, L.S. Wu, S. Aboud, S. Adu-Afarwuah, H. Ali, et al., Modifiers of the effect of maternal multiple micronutrient supplementation on stillbirth, birth outcomes, and infant mortality: a meta-analysis of individual patient data from 17 randomised trials in low-income and middle-income countries, Lancet Global Health 5 (11) (2017) e1090–e1100, https://doi.org/10.1016/s2214-109x(17)30371-6.

[2] E.C. Keats, C. Oh, T. Chau, D.S. Khalifa, A. Imdad, Z.A. Bhutta, Effects of vitamin and mineral supplementation during pregnancy on maternal, birth, child health and development outcomes in low- and middle-income countries: a systematic review, Campbell Syst. Rev. 17 (2) (2021) e1127, https://doi.org/10.1002/cl2.1127.

[3] A.D. Gernand, K.J. Schulze, C.P. Stewart, K.P. West Jr., P. Christian, Micronutrient deficiencies in pregnancy worldwide: health effects and prevention, Nat. Rev. Endocrinol. 12 (5) (2016) 274–289, https://doi.org/10.1038/nrendo.2016.37.

[4] G.A. Stevens, T. Beal, M.N.N. Mbuya, H. Luo, L.M. Neufeld, O.Y. Addo, et al., Micronutrient deficiencies among preschool-aged children and women of reproductive age worldwide: a pooled analysis of individual-level data from population-representative surveys, Lancet Glob. Health 10 (11) (2022) e1590–e1599, https://doi.org/10.1016/s2214-109x(22)00367-9.

[5] S.Y. Hess, K.R. Wessells, D. Haile, L.M. Rogers, X. Tan, J.G. Barros, et al., Comparison of published estimates of the National prevalence of iron, vitamin A, and zinc deficiency and sources of inconsistencies, Adv. Nutr. 14 (6) (2023) 1466–1478, https://doi.org/10.1016/j.advnut.2023.08.011.

[6] World Health Organization, WHO Recommendations on Antenatal Care for a Positive Pregnancy Experience, World Health Organization, Geneva, 2016.

[7] E.C. Keats, B.A. Haider, E. Tam, Z.A. Bhutta, Multiple-micronutrient supplementation for women during pregnancy, Cochrane Database Syst. Rev. 2019 (3) (2019) CD004905, https://doi.org/10.1002/14651858.cd004905.pub6.

[8] World Health Organization, WHO Antenatal Care Recommendations for a Positive Pregnancy Experience. Nutritional Interventions Update: Multiple Micronutrient Supplements During Pregnancy, World Health Organization, Geneva, 2020.

[9] F. Gomes, R. Agustina, R.E. Black, P. Christian, K.G. Dewey, K. Kraemer, et al., Multiple micronutrient supplements versus iron-folic acid supplements and maternal anemia outcomes: an iron dose analysis, Ann. N. Y. Acad. Sci. 1512 (1) (2022) 114–125, https://doi.org/10.1111/nyas.14756.

[10] J.F. Kemp, K.M. Hambidge, J.L. Westcott, S.A. Ali, S. Saleem, A. Garces, et al., Zinc supplementation initiated prior to or during pregnancy modestly impacted maternal status and high prevalence of hypozincemia in pregnancy and lactation: the women first preconception maternal nutrition trial, J. Nutr. 154 (6) (2024) 1917–1926, https://doi.org/10.1016/j.tjnut.2024.04.018.

[11] S. Adu-Afarwuah, A. Lartey, H. Okronipa, P. Ashorn, M. Zeilani, L. M. Baldiviez, et al., Impact of small-quantity lipid-based nutrient supplement on hemoglobin, iron status and biomarkers of inflammation in pregnant Ghanaian women, Matern, Child Nutr. 13 (2) (2017) e12262, https://doi.org/10.1111/mcn.12262.

[12] S. Adu-Afarwuah, A. Lartey, H. Okronipa, P. Ashorn, M. Zeilani, J. M. Peerson, et al., Lipid-based nutrient supplement increases the birth size of infants of primiparous women in Ghana, Am. J. Clin. Nutr. 101 (4) (2015) 835–886, https://doi.org/10.3945/ajcn.114.091546.

[13] The Multiple Micronutrient Supplement Technical Advisory Group (MMS-TAG), The Micronutrient Forum (MNF), Expert consensus on an open-access United Nations International Multiple Micronutrient Antenatal Preparation - multiple micronutrient supplement product Specification, Ann. N. Y. Acad. Sci. 1470 (1) (2020) 3–13, https://doi.org/10.1111/nyas.14322.

[14] P. Kaestel, K.F. Michaelsen, P. Aaby, H. Friis, Effects of prenatal multimicronutrient supplements on birth weight and perinatal mortality: a randomised, controlled trial in Guinea-Bissau, Eur. J. Clin. Nutr. 59 (9) (2005) 1081–1089, https://doi.org/10.1038/sj.ejcn.1602215.

[15] S.J. Zhou, R.A. Gibson, C.A. Crowther, M. Makrides, Should we lower the dose of iron when treating anaemia in pregnancy? A randomized dose-response trial, Eur. J. Clin. Nutr. 63 (2) (2009) 183–190, https://doi.org/10.1038/sj.ejcn.1602926.

[16] J. Coates, A. Swindale, P. Bilinksky, Household Food Insecurity Access Scale (HFIAS) for Measurement of Household Food Access: Indicator Guide (v. 3). FHI 360/FANTA, Washington, D.C. [Internet]. Available from: https://www.fantaproject.org/monitoring-and-evaluation/household-food-insecurity-access-scale-hfias (accessed 7 November 2013).

[17] WHO Multicentre Growth Reference Study Group, WHO Child Growth Standards: Head Circumference-for-Age, Arm Circumference-for-Age, Triceps Skinfold-for-Age and Subscapular Skinfold-for-Age: Methods and Development, World Health Organization, Geneva, 2007.

[18] WHO Multicentre Growth Reference Study Group, WHO Child Growth Standards: Length/Height-for-Age, Weight-for-Age, Weight-for-Length. Weight-for-Height and Body Mass Index-for-Age: Methods and Development, World Health Organization, Geneva, 2006.

[19] J. Villar, L. Cheikh Ismail, C.G. Victora, E.O. Ohuma, E. Bertino, D. G. Altman, et al., International standards for newborn weight, length, and head circumference by gestational age and sex: the newborn cross-sectional study of the INTERGROWTH-21st project, Lancet 384 (9946) (2014) 857–868, https://doi.org/10.1016/s0140-6736(14)60932-6.

[20] D.W. Killilea, B.N. Ames, Magnesium deficiency accelerates cellular senescence in cultured human fibroblasts, Proc. Natl. Acad. Sci. U.S.A. 105 (15) (2008) 5768–5773, https://doi.org/10.1073/pnas.0712401105.

[21] C.M. McDonald, P.S. Suchdev, N.F. Krebs, S.Y. Hess, K.R. Wessells, S. Ismaily, et al., Adjusting plasma or serum zinc concentrations for inflammation: biomarkers reflecting inflammation and nutritional determinants of anemia (BRINDA) project, Am. J. Clin. Nutr. 111 (4) (2020) 927–937, https://doi.org/10.1093/ajcn/nqz304.

[22] K.R. Wessells, C.D. Arnold, C. McDonald, S. Adu-Afaruwah, K. G. Dewey, Efficacy of multiple micronutrient supplements (MMS) during pregnancy on zinc status among pregnant women in Ghana, Open Sci. Framework (2025) [Internet]. Available from: https://osf.io/ek2gn/. (Accessed 15 December 2025).

[23] B.C. Johnston, G.H. Guyatt, Best (but oft-forgotten) practices: intention-to-treat, treatment adherence, and missing participant outcome data in the nutrition literature, Am. J. Clin Nutr. 104 (5) (2016) 1197–1201, https://doi.org/10.3945/ajcn.115.123315.
[24] International Zinc Nutrition Consultative Group (IZiNCG), K.H. Brown, J.A. Rivera, Z. Bhutta, R.S. Gibson, J.C. King, et al., International Zinc Nutrition Consultative Group (IZiNCG) Technical Document #1. Assessment of the risk of zinc deficiency in populations and options for its control, Food Nutr. Bull. 25 (1 Suppl 2) (2004) S99–S203.
[25] G. Zou, A modified poisson regression approach to prospective studies with binary data, Am. J. Epidemiol. 159 (7) (2004) 702–706, https://doi.org/10.1093/aje/kwh090.
[26] V.H. Moran, A.L. Skinner, M.W. Medina, S. Patel, F. Dykes, O. W. Souverein, et al., The relationship between zinc intake and serum/plasma zinc concentration in pregnant and lactating women: a systematic review with dose-response meta-analyses, J. Trace Elem. Med. Biol. 26 (2-3) (2012) 74–79, https://doi.org/10.1016/j.jtemb.2012.04.003.
[27] C. Oh, E.C. Keats, Z.A. Bhutta, Vitamin and mineral supplementation during pregnancy on maternal, birth, child health and development outcomes in low- and middle-income countries: a systematic review and meta-analysis, Nutrients 12 (2) (2020) 14, https://doi.org/10.3390/nu12020491.
[28] K.J. Schulze, S. Mehra, S. Shaikh, H. Ali, A.A. Shamim, L.S. Wu, et al., Antenatal multiple micronutrient supplementation compared to iron-folic acid affects micronutrient status but does not eliminate deficiencies in a randomized controlled trial among pregnant women of rural Bangladesh, J. Nutr. 149 (7) (2019) 1260–1270, https://doi.org/10.1093/jn/nxz046.
[29] P. Christian, T. Jiang, S.K. Khatry, S.C. Leclerq, S.R. Shrestha, K. P. West Jr., Antenatal supplementation with micronutrients and biochemical indicators of status and subclinical infection in rural Nepal, Am. J. Clin. Nutr. 83 (4) (2006) 788–794, https://doi.org/10.1093/ajcn/83.4.788.
[30] S. Ziaei, A. Rahman, R. Raqib, B. Lonnerdal, E.C. Ekstrom, A prenatal multiple micronutrient supplement produces higher maternal vitamin B-12 concentrations and similar folate, ferritin, and zinc concentrations as the standard 60-mg iron plus 400-mug folic acid supplement in rural Bangladeshi women, J. Nutr. 146 (12) (2016) 2520–2529, https://doi.org/10.3945/jn.116.235994.
[31] B. Utomo Sunawang, A. Hidayat, Kusharisupeni, Subarkah, Preventing low birthweight through maternal multiple micronutrient supplementation: a cluster-randomized, controlled trial in Indramayu, West Java, Food Nutr, Bull 30 (4 Suppl 4) (2009) S488–S495, https://doi.org/10.1177/15648265090304s403.
[32] Institute of Medicine,Food and Nutrition Board, Dietary Reference Intakes for Vitamin C, E Vitamin, Selenium and Carotenoids, National Academy Press, Washington, D.C., 2000.
[33] C.M. Donangelo, C.L. Zapata, L.R. Woodhouse, D.M. Shames, R. Mukherjea, J.C. King, Zinc absorption and kinetics during pregnancy and lactation in Brazilian women, Am. J. Clin. Nutr. 82 (1) (2005) 118–124, https://doi.org/10.1093/ajcn/82.1.118.
[34] B.O. Lonnerdal, Dietary factors influencing zinc absorption, J. Nutr. 130 (5) (2000) 1378S–1383S.
[35] R.S. Gibson, V. Raboy, J.C. King, Implications of phytate in plant-based foods for iron and zinc bioavailability, setting dietary requirements, and formulating programs and policies, Nutr. Rev. 76 (11) (2018) 793–804, https://doi.org/10.1093/nutrit/nuy028.
[36] N.W. Solomons, M. Ruz, Zinc and iron interaction: concepts and perspectives in the developing world, Nutr. Res. 17 (1) (1997) 177–185, https://doi.org/10.1016/s0271-5317(96)00243-6.
[37] K. Simmer, C.A. Iles, C. James, R.P. Thompson, Are iron-folate supplements harmful? Am. J. Clin. Nutr. 45 (1) (1987) 122–125, https://doi.org/10.1093/ajcn/45.1.122.
[38] N.W. Solomons, R.A. Jacob, Studies on the bioavailability of zinc in humans: effects of heme and nonheme iron on the absorption of zinc, Am. J. Clin. Nutr. 34 (4) (1981) 475–482, https://doi.org/10.1093/ajcn/34.4.475.
[39] J. Kim, H.Y. Paik, H. Joung, L.R. Woodhouse, S. Li, J.C. King, Zinc supplementation reduces fractional zinc absorption in young and elderly Korean women, J. Am. Coll. Nutr. 23 (4) (2004) 309–315, https://doi.org/10.1080/07315724.2004.10719373.
[40] Institute of Medicine, Food and Nutrition Board, Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Iodine, Iron, Manganese. Molybdenum, Nickel, Silicon, Vanadium, and Zinc, National Academy Press, Washington, D.C., 2001.
[41] World Health Organization (WHO), Zinc. Trace Elements for Human Nutrition and Health, WHO, Geneva, 1996, pp. 265–288.
[42] R.S. Gibson, J.M. Huddle, Suboptimal zinc status in pregnant Malawian women: its association with low intakes of poorly available zinc, frequent reproductive cycling, and malaria, Am. J. Clin. Nutr. 67 (4) (1998) 702–709, https://doi.org/10.1093/ajcn/67.4.702.
[43] K.M. Hambidge, Zinc and diarrhea, Acta. Paediatr. Suppl. 381 (1992) 82–86, https://doi.org/10.1111/j.1651-2227.1992.tb12377.x.
[44] S. Adu-Afarwuah, C.D. Arnold, A. Lartey, H. Okronipa, K. Maleta, P. Ashorn, et al., Prevalence of morbidity symptoms among pregnant and postpartum women receiving different nutrient supplements in Ghana and Malawi: a secondary outcome analysis of two randomised controlled trials, Matern, Child Nutr. 19 (3) (2023) e13501, https://doi.org/10.1111/mcn.13501.
[45] G. Terrin, R. Berni Canani, M. Di Chiara, A. Pietravalle, V. Aleandri, F. Conte, et al., Zinc in early life: a key element in the fetus and preterm neonate, Nutrients 7 (12) (2015) 10427–10446, https://doi.org/10.3390/nu7125542.
[46] J.Y. Uriu-Adams, C.L. Keen, Zinc and reproduction: effects of zinc deficiency on prenatal and early postnatal development, Birth Defects Res. B. Dev. Reprod. Toxicol. 89 (4) (2010) 313–325, https://doi.org/10.1002/bdrb.20264.
[47] T. Tamura, R. Goldenburg, What is the relationship between zinc status and pregnancy outcome? Based on zinc nutriture and pregnancy outcome (1996) in nutrition research 16 (1), MotherCare Matters 6 (1996) 16–18.
[48] R.L. Wilson, J.A. Grieger, T. Bianco-Miotto, C.T. Roberts, Association between maternal zinc status, dietary zinc intake and pregnancy complications: a systematic review, Nutrients 8 (10) (2016) 641, https://doi.org/10.3390/nu8100641.
[49] B. Alemu, D. Gashu, Association of maternal anthropometry, hemoglobin and serum zinc concentration during pregnancy with birth weight, Early Hum. Dev. 142 (2020) 104949, https://doi.org/10.1016/j.earlhumdev.2019.104949.
[50] S. Gebremedhin, F. Enquselassie, M. Umeta, Independent and joint effects of prenatal zinc and vitamin A deficiencies on birthweight in rural Sidama, Southern Ethiopia: prospective cohort study, PLoS One 7 (12) (2012) e50213, https://doi.org/10.1371/journal.pone.0050213.
[51] International Zinc Nutrition Consultative Group, Assessing population zinc status with serum zinc concentration. IZiNCG technical brief no. 2, 2012 [Internet]. Available from: http://www.izincg.org. (Accessed 26 March 2014).