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Effects of pre- and post-natal lipid-based nutrient supplements on infant development in a randomized trial in Ghana☆

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ABSTRACT

Background: Maternal and infant undernutrition is negatively associated with infant development.
Aims: We tested the hypothesis that provision of small-quantity lipid-based nutrient supplements (SQ-LNS) to pregnant women and infants positively affects infant development.
Study design: In a partially double-blind randomized controlled trial, we compared the following daily maternal supplements during pregnancy and until 6 months post-partum: iron/folic acid capsule (IFA), capsule containing 18 micronutrients (MMN), or 20 g SQ-LNS. Children in the SQ-LNS group also received SQ-LNS from age 6 to 18 months. The study is registered as NCT00970866.
Subjects: 1320 pregnant women in Ghana enrolled in the trial; 1173 of their children participated in developmental assessment.
Outcome measures: We monitored the acquisition of 10 developmental milestones monthly by parental report, observed the attainment of 6 motor milestones at 6, 12, and 18 months, and conducted detailed assessment of motor, language, socio-emotional, and executive function at 18 months.
Results: By researcher observation, a greater percentage of children in the SQ-LNS group (53%) was able to walk alone at 12 months than in the IFA group (43%; $RR = 1.23$, 95% CI = 1.02–1.49; $p = 0.025$). We found no significant differences between groups in milestone acquisition by parent report or in any scores at 18 months. The difference in mean *z*-scores between groups ranged from 0.03–0.13 for motor ($p = 0.84$), 0.01–0.08 for language ($p = 0.46$), 0.01–0.02 for socio-emotional ($p = 0.75$), and 0.00–0.02 for executive function ($p = 0.95$).
Conclusion: While provision of maternal and child SQ-LNS in Ghana may affect walking at 12 months, it did not affect infant development at 18 months.

1. Introduction

Many children in low and middle-income countries (LMICs) are not reaching their full potential in motor, cognitive, and socio-emotional abilities [1]. Inadequate nutrition is one factor that contributes to this faltering in development, beginning with mothers even before conception and continuing throughout pregnancy and childhood [2]. Many nutrients, such as fatty acids, B-vitamins, iron, iodine, and zinc, are necessary for the neurodevelopmental processes that occur during this period, as cofactors in metabolic reactions and structural components of brain tissue [3,4]. Although many studies have found associations between indicators of maternal and infant undernutrition, including anthropometric measures and micronutrient deficiencies, and developmental scores, few randomized controlled trials of maternal nutritional supplementation in low and middle-income countries (LMICs) have examined developmental outcomes. To our knowledge, only two studies [5,6] have examined the impact of supplementation with a full set of micronutrients and fatty acids throughout both the pre-natal and the post-natal periods on motor, cognitive, and socio-emotional development.

Abbreviations: BMI, body mass index; CDI, communicative development inventory; FCI, family care indicators; Hb, hemoglobin; HFIA, household food insecurity access; iLiNS, International Lipid-Based Nutrient Supplements; IFA, iron and folic acid; KDI, Kilifi developmental inventory; LNS, lipid-based nutrient supplements; MGRS, Multi-center Growth Reference Study; MMN, multiple micronutrients; MUAC, mid-upper arm circumference; PSED, profile of socio-emotional development; SQ-LNS, small quantity lipid-based nutrient supplements; WHO, World Health Organization; ZPP, zinc protoporphyrin.

☆ Trial Registry: The study is registered as clinical trial NCT00970866.

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Small-quantity lipid-based nutrient supplements (SQ-LNS) were designed to provide this full set of nutrients for home fortification of infant complementary foods. Other formulations have also been developed to provide key nutrients for pregnant and lactating women [7]. SQ-LNS are typically made from vegetable oil, peanut paste, milk powder, and sugar, with added vitamins and minerals [7]. While several studies have reported the developmental effects of provision of small- or medium-quantity LNS (20–54 g/day) during infancy [8–11], only one has examined the effects of SQ-LNS beginning during pregnancy on child development [12].

The objective of the current study was to determine whether provision of SQ-LNS to mothers in Ghana during pregnancy and the first 6 months postpartum, and to their children from age 6–18 months, positively affects child development, as compared to provision of iron and folic acid (IFA) during pregnancy only, or a multiple micronutrient (MMN) tablet during pregnancy and the first six months postpartum. We also examined stimulation from the child's environment as a potential mediating and moderating factor. As a mediating factor, well-nourished mothers may be more active in providing stimulating experiences, such as talking to their children and playing with them, and well-nourished children may also elicit more stimulating experiences from their caregivers. As a moderating factor, children who experience different levels of stimulation from the environment may have different developmental responses to nutritional supplementation.

2. Participants and methods

2.1. Study participants and design

The study design was a partially double-blind individually randomized controlled trial. Two intervention groups were double-blind. In the third group, the participants, but not the researchers who assessed and analysed the outcomes, were aware of intervention group. Here, we report the secondary developmental outcomes. We tested the hypothesis that provision of small-quantity lipid-based nutrient supplements (SQ-LNS) to pregnant mothers and infants positively affects motor, language, socio-emotional, executive function, and caregiver-child interaction scores, as compared to maternal supplementation with either IFA or MMN. The trial was conducted as a part of the International Lipid-Based Nutrient Supplements (iLiNS) Project and was performed according to Good Clinical Practice guidelines and the ethical standards of the Helsinki Declaration. Ethical approval for the study procedures was obtained from the Ethics Committees at the University of California, Davis (UC Davis); the Ghana Health Service; and the University of Ghana Noguchi Memorial Institute for Medical Research. All participants provided informed consent. The study was registered with the U.S. National Institutes of Health as a clinical trial (www.ClinicalTrials.gov; NCT00970866).

This study was conducted in the Somanya-Kpong area, a semi-urban settlement in the Yilo Krobo and Lower Manya Krobo districts, about 70 km north of Accra (the capital of Ghana). Women seeking antenatal care at two hospitals, a polyclinic, and a clinic in the area from December 2009 to December 2011 were invited for screening. Eligible women were visited at home and those who met the inclusion criteria and provided informed consent were scheduled for a clinic visit for baseline assessments. Exclusion criteria were: <18 years of age; >20 weeks gestation; antenatal card indicated HIV infection, asthma, epilepsy, tuberculosis, or any malignancy; known milk or peanut allergy; not residing in the study area; intention to move within the next two years; unwillingness to receive home visits from fieldworkers or take the study supplement; and participation in another trial. Further details are published elsewhere [13,14].

Following baseline assessment, women were randomly assigned to one of three groups. The IFA group received one micronutrient capsule per day containing 60 mg iron and 400 μg folic acid from enrolment to delivery and a placebo tablet containing 200 mg calcium from delivery to 6 months post-partum. The MMN group received one micronutrient capsule per day from enrolment to 6 months post-partum that contained 20 mg iron and 400 μg folic acid plus 16 additional micronutrients (Table 1). The SQ-LNS group received daily sachets of SQ-LNS produced by Nutriset SAS (Malaunay, France) from enrolment to 6 months post-partum. The daily dose (20 g) contained the same micronutrients as the MMN capsules, 4 additional minerals (Ca, K, Mg and P), protein, and fat, and it also provided 118 kcal of energy (Table 1). From age 6–18 months, children in the SQ-LNS group also received 20 g per day of SQ-LNS with the same ingredients and with nutrient composition designed for children, as shown in Table 1 [7]. All groups received two doses of intermittent preventive malaria treatment during pregnancy, in accordance with Ghana health policy.

At the baseline assessment, maternal anthropometric data and information concerning parental education and family socio-economic characteristics was collected. Maternal hemoglobin (Hb; HemoCue AG), malaria parasitemia (Vision Biotech), and zinc protoporphyrin (ZPP; hematofluorometer, Aviv Biomedical Co. NJ, USA) were determined using venous blood. Research staff visited women at home bi-weekly until delivery to deliver supplements and monitor supplement consumption. Following delivery, home visits were conducted weekly, but women continued to receive supplements biweekly until 6 months postpartum, and children in the SQ-LNS group received supplements weekly from 6 to 18 months of age. Adherence during pregnancy and the first 6 months postpartum was calculated as the percentage of days that the mother reported consuming the supplement. For the SQ-LNS group, child adherence was calculated as the percentage of days that the child consumed the supplement, based on maternal report. Detailed descriptions of these variables are reported elsewhere [13].

In February 2011, the study team discovered an error in the coded supplement labels for IFA and MMN. Due to this error, between December 2009 and September 2010, 85 women who had been assigned to the IFA group received the MMN supplement during the whole of pregnancy before receiving the intended placebo tablet during the first 6 months postpartum. In addition, 85 women received MMN for part of pregnancy before receiving the intended IFA supplement. Similarly, 78 women who had been assigned to the MMN group received the IFA supplement during all of pregnancy and 92 women received IFA during part of

Table 1
Nutrient and energy contents of the dietary supplements.

	IFA	MMN	Maternal SQ-LNS	Child SQ-LNS
Ration per day	1 tablet	1 tablet	20-g sachet	20-g sachet
Total energy, kcal	0	0	118	118
Protein, g	0	0	2.6	2.6
Fat, g	0	0	10	9.6
Linoleic acid, g	0	0	4.59	4.46
a-Linolenic acid, g	0	0	0.59	0.58
Vitamin A, mg RE	0	800	800	400
Vitamin C, mg	0	100	100	30
Vitamin B-1, mg	0	2.8	2.8	0.3
Vitamin B-2, mg	0	2.8	2.8	0.4
Niacin, mg	0	36	36	4
Folic acid, mg	400	400	400	80
Pantothenic acid, mg	0	7	7	1.8
Vitamin B-6, mg	0	3.8	3.8	0.3
Vitamin B-12, mg	0	5.2	5.2	0.5
Vitamin D, mg	0	10	10	5
Vitamin E, mg	0	20	20	6
Vitamin K, mg	0	45	45	30
Iron, mg	60	20	20	6
Zinc, mg	0	30	30	8
Copper, mg	0	4	4	0.34
Calcium, mg	0	0	280	280
Phosphorus, mg	0	0	190	190
Potassium, mg	0	0	200	200
Magnesium, mg	0	0	65	40
Selenium, mg	0	130	130	20
Iodine, mg	0	250	250	90
Manganese, mg	0	2.6	2.6	1.2