Prenatal Nutrient Supplementation and Postnatal Growth in a Developing Nation: An RCT

WHAT’S KNOWN ON THIS SUBJECT: Prenatal lipid-based nutrient supplementation has been demonstrated to increase birth length. However, the impact of this intervention on infant growth and morbidity is unknown.

WHAT THIS STUDY ADDS: Infants from mothers who were given prenatal lipid-based nutrient supplements showed decelerated linear growth. The gain in length at birth related to prenatal lipid-based nutrient supplementation was not sustained during infancy.

abstract

BACKGROUND AND OBJECTIVES: Prenatal lipid-based nutrient supplements (LNS) have been shown to improve birth anthropometry. However, little is known about the effects of such supplements on infant health. We hypothesized that prenatal LNS compared with multiple micronutrient supplement for pregnant and lactating women would improve survival, growth, and morbidity during infancy.

METHODS: Infants’ weight, length, head, chest, and mid-upper arm circumferences were measured during monthly home visits from birth to 12 months of age in the Micronutriments et Santé de la Mère et de l’Enfant—2 trial. Differences in stunting and wasting episodes between study arms were assessed by Cox regression for recurrent event models. Morbidity signs during the 2 weeks before the visits and death cases were also assessed by multilevel analysis accounting for repeated individual measurements.

RESULTS: Infant length-for-age growth (−0.033 z score/month; 95% confidence interval: −0.601 to −0.006; P = .018) for the LNS group was inferior to that of the control group. We did not find evidence of significant difference in mortality or morbidity between groups.

CONCLUSIONS: The previously reported positive effect of prenatal LNS on birth length was not sustained during the postnatal phase. Prenatal LNS does not appear to make a long-lasting difference in child linear growth. Pediatrics 2014;133:e1001–e1008
Size at birth and growth in early infancy are important indicators of early childhood survival and health. Newborns with small birth size, reflecting poor intrauterine nutrition and/or prematurity, have an increased risk of infant mortality and morbidity, impaired child cognitive development, and adverse health outcomes in adulthood. Poor infant growth is associated with higher mortality and neurocognitive delays. Stunted growth during the first 2 years is also associated with shorter adult height, reduced economic productivity, and decreased reproductive performance. In 2011, an estimated 165 million children aged <5 years worldwide had stunted growth, with the majority residing in Asia and sub-Saharan Africa.

Prenatal multiple micronutrient (MMN) and balanced energy and protein supplementation result in a significant reduction in small-for-gestational age births (9% and 31%, respectively). However, the results of such interventions on postnatal growth yielded more dispersed results. In 2 prenatal multiple MMN trials in Burkina Faso and Vietnam, the rate of stunting was reduced during infancy and at 2 years, although no difference was seen at 2.5 years in the first trial. The attained weight at 2 years was improved in the supplemented group in other trials. In another trial in Nepal, there was no difference in height between school-age children prenatally supplemented with MMN compared with folic acid.

Few studies evaluated the combined effect of prenatal food supplements and MMN on postnatal outcomes. In Bangladesh, food rations combined with micronutrients tablets given in early gestation resulted in a reduced proportion of stunting from early infancy up to 54 months for boys and a higher infant mortality. We previously reported that providing pregnant women with lipid-based nutrient supplementation (LNS) increased birth length by 4.6 mm (P = .001) and weight by 31 g (P = .197).

In the current study, we assessed the effect of prenatal LNS compared with MMNs on postnatal growth and nutritional status during the first year of life.

### METHODS

The original trial was conducted in Houndé (Tuy province), a rural health district in midwest Burkina Faso. From March 2006 to September 2007, 1296 pregnant women of the catchment areas of 2 health centers were randomly assigned to receive either an LNS or an MMN cocktail. The composition of the MMN cocktail was equal to that of the International Multiple Micronutrient Preparation cocktail. The LNS was a ready-to-serve mix (72 g/dose) composed of peanut butter, soy flour, vegetable oil, sugar, and the MMN cocktail; it provided the recommended daily allowance for pregnant women and 1.56 MJ (372 kcal) and 14.7 g of protein (Table 1). The methods and the supplements have previously been described in detail.

Briefly, Burkina Faso is a low-income country characterized by a dry season from October to March. The population is predominantly young (mean age = 21.8 years) and illiterate (67%–80%), and three-quarters of the population live in rural areas. The diet is essentially cereal-based with an average caloric intake during pregnancy of 8.1 to 8.6 MJ. At birth, almost all children are breastfed (99%), but 7% receive other liquids at 2 months and 10% receive solid food at 4 months. Houndé is located along the highway that connects the 2 major cities, the capital Ouagadougou and Bobo-Dioulasso; it has a population of ~40 000 of which 50.9% are female and 44.0% <15 years of age. The province of Tuy is a cereal production zone and houses a major cotton fiber production plant in the center of Houndé. In 2005, 63% of pregnant women were anemic (hemoglobin <11 g/dL), and 17.8% of newborns were low birth weight.

### Subjects and Measurements

Participants were also randomly assigned to receive either a double or a triple dose of combined sulfadoxine-pyrimethamine in the second and third trimesters as part of a different study on malaria prevention. A community-based locally trained network of home visitors visited all women of childbearing age monthly at their homes to screen for amenorrhea. In case of a suspected pregnancy, women were referred to the health center for a formal pregnancy test. Once pregnancy was confirmed, the field coordinator explained individually, in a private room, the purpose of the study and procedures to each participant and gathered maternal and family information. After enrollment, the home visitors followed up participants daily to directly observe intake of MMN and LNS.

### Table 1 Nutritional Composition of a Unitary Dosage (72 g) of LNS and an MMN

<table>
<thead>
<tr>
<th>Nutrient</th>
<th>LNS</th>
<th>MMN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy, MJ</td>
<td>1.56</td>
<td>—</td>
</tr>
<tr>
<td>Energy from protein, %</td>
<td>15.8</td>
<td>—</td>
</tr>
<tr>
<td>Energy from fat, %</td>
<td>67.0</td>
<td>—</td>
</tr>
<tr>
<td>Carbohydrates, g</td>
<td>15.9</td>
<td>—</td>
</tr>
<tr>
<td>Protein, g</td>
<td>14.7</td>
<td>—</td>
</tr>
<tr>
<td>Fat, g</td>
<td>27.6</td>
<td>—</td>
</tr>
<tr>
<td>SAFA, g</td>
<td>8.1</td>
<td>—</td>
</tr>
<tr>
<td>MUFA, g</td>
<td>12.1</td>
<td>—</td>
</tr>
<tr>
<td>PUFA, g</td>
<td>7.3</td>
<td>—</td>
</tr>
<tr>
<td>Omega-3 FAs, g</td>
<td>0.4</td>
<td>—</td>
</tr>
<tr>
<td>Omega-6 FAs, g</td>
<td>7.0</td>
<td>—</td>
</tr>
<tr>
<td>Total dietary fiber, g</td>
<td>9.1</td>
<td>—</td>
</tr>
<tr>
<td>Vitamin A, RE</td>
<td>881</td>
<td>800</td>
</tr>
<tr>
<td>Vitamin D, IU</td>
<td>200</td>
<td>200</td>
</tr>
<tr>
<td>Vitamin E, mg</td>
<td>10</td>
<td>—</td>
</tr>
<tr>
<td>Thiamin, mg</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Riboflavin, mg</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Niacin, mg</td>
<td>21</td>
<td>18</td>
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<tr>
<td>Vitamin B9, mg</td>
<td>2.0</td>
<td>1.9</td>
</tr>
<tr>
<td>Folic acid, µg</td>
<td>461</td>
<td>400</td>
</tr>
<tr>
<td>Vitamin B12, µg</td>
<td>2.6</td>
<td>2.6</td>
</tr>
<tr>
<td>Vitamin C, mg</td>
<td>71</td>
<td>70</td>
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<tr>
<td>Zn, mg</td>
<td>17</td>
<td>15</td>
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<td>Fe, mg</td>
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<td>Cu, mg</td>
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<td>Se, µg</td>
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<tr>
<td>I, µg</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>Ca, mg</td>
<td>90</td>
<td>—</td>
</tr>
</tbody>
</table>

FAs, fatty acids; MUFA, monounsaturated FAs; PUFA, polyunsaturated FAs; RE, retinol equivalent; SAFA, saturated fatty acids.
supplements until delivery. Additionally, the home visitors recorded gestational morbidity such as nausea, fatigue, or abdominal pain on a daily basis and monitored miscarriages and stillbirths.

After delivery, mothers were invited to monthly visits at the nearest health center to assess infant growth and health. Every child was vaccinated according to the national schedule and received vitamin A at 6 months (100 000 IU) and at 12 months (200 000 IU). Infants who were sick and/or had lost weight since the previous visit were referred to curative services for appropriate clinical management. The study was approved by the ethics committees of the Center Muraz, Bobo-Dioulasso, Burkina Faso, and the Institute of Tropical Medicine, Antwerp, Belgium. The trial was registered at clinicaltrials.gov (identifier NCT00909974).

**Data Analysis**

Infants with $\geq 1$ set of anthropometric measurements after delivery were included in the analysis. In cases lost to follow-up, data up to the last visit were used in the analysis. Lost to follow-up was defined as infants who missed 3 consecutive visits during the first year. Continuous variables included weight, length, MUAC, head circumference, chest circumference, and the anthropometric indices weight-for-age z score, length-for-age z score, and weight-for-length z score. These indices were calculated by using the Stata command zscore06 (Stat Corp, College Station, TX),23 based on the 2006 World Health Organization child growth standards.24 The MUAC-for-age z score was computed using the software WHO Anthro.25 For the analysis of these outcomes, mixed effects models were used. The fixed effects in these equations included the intervention allocation (LNS versus MMN), primiparity, child gender, child age, type of malaria prevention, and health center to account for the study design. We tested if the addition of a quadratic term for age improved the fit as was previously suggested.9 The random effects comprised the individual subject (measurements were repeated in the same individuals) and a random slope to account for the variations in individual growth trajectories. We tested if the intervention effect changed over time by introducing interaction terms between “intervention” and “child age” variables of the model. Stunting, underweight, and wasting were defined as length-for-age, weight-for-age, and weight-for-length $\leq 2$ z score. The effect of the prenatal intervention on the repetitive state of stunting, wasting, and underweight during follow-up period was analyzed by using a Cox proportional hazards regression with shared frailty for recurrent events model. In this model, the different time periods to each event for the same subject are analyzed separately and adjusted for the fact that time periods within each subject are dependent.26 Difference in infant mortality rate between trial arms was assessed by Cox proportional hazards regression model. The survival analysis was carried out on data generated from the monthly follow-up. Proportional hazard assumptions were inspected graphically. Infants who did not develop the outcome, either because they died or were lost to follow-up, were censored at the time of their last visit.

Incidence of diarrhea, cough, or fever (number of episodes in the 15 days preceding the monthly visit) were compared between the study arms by using generalized linear and latent mixed models. This procedure in Stata 12.0 allows the fitting of multilevel mixed-effects Poisson regression models.27 The fixed effects are the same as previously described, and the cluster effect by child was added as
a random effect to the models. We opted to use Poisson regression modeling to be able to present an adjusted risk ratio rather than an odds ratio, as recommended for prospective studies. A robust estimation of the variance was adopted to relax the assumption of a Poisson distribution. P < .05 was considered statistically significant for all analyses, except for the appreciation of interaction terms, for which we used P < .10. All statistical analyses were carried out by using Stata 12.0.

RESULTS

From March 2006 to December 2007, 1296 mothers were enrolled in the study. From this sample, 1023 women had singleton infants whose postnatal event data were retained for analysis (Fig 1). Women were predominantly young: mean (SD) age = 24.1 (6.3) years, 18.7% were nulliparous, and 89.4% did not attend school. The mean (SD) gestational age was 16.6 (6.7) weeks at recruitment and 39.0 (2.5) weeks at delivery. The nutritional status of the participants was suboptimal: 12.0% had a BMI <18.5, and 44.9% were anemic (hemoglobin <110 g/L).

Nineteen infants (1.6%; n = 10 in MMN and n = 9 in LNS group) died during the neonatal and 36 (3.1%; n = 17 in MMN and n = 19 in LNS group) during the follow-up period, with no significant difference in the mortality rate between study arms. Cases lost to follow-up represented 27.2% (n = 164 in LNS and n = 150 in MMN group) of the cases and were mainly due to the children’s...

FIGURE 1
Trial profile. Growth monitoring was scheduled monthly from birth to age 12 months. Fifty-five children died during the follow-up period, of which 19 deaths occurred during the neonatal period. The total duration of follow-up during the first year was 11,968 infant-months.
of the initial analysis (data not shown). Finally, we did not observe any differences in morbidity symptoms (cough, fever, and diarrhea) between study groups (Table 5).

DISCUSSION

The results of this study suggest that prenatal LNS did not improve linear growth velocity for LNS infants compared with MMN infants. Hence the previously reported benefit on birth length15 leveled off during infancy. Some hypotheses can be put forward to explain the lack of benefit of LNS on infant growth over MMN. First, the physiology of LNS infants, adapted to better nutritional conditions in utero, could have made them more sensitive to the suboptimal nutritional and environmental factors during the postnatal period. Animal studies and natural human experiments suggest that adverse nutritional environment during fetal growth can permanently alter anatomy, physiology, and metabolism of the body.31,32 In a nutritionally scarce environment, the fetal body prioritizes typical brain development at the expense of other organ development. These adaptations during fetal life become detrimental in cases of normal or plentiful nutrition.32,33 Our study could have provided the opposite scenario of the much-documented hypothesis of development of disease origin.34 Mothers who were given prenatal LNS developed significantly larger placentas, which might be associated with a better placental flow of essential micronutrients toward the fetal compartment.15 Therefore, it is likely that LNS infants might have suffered more from a mismatch between a relatively better intrauterine and a poorer postnatal nutrition with a smaller linear growth velocity as a result compared with MMN infants.

Second, in the current study, the control group received MMN. We previously reported that prenatal MMN, compared with iron and folic acid supplementation, reduced the proportion of stunted infants at 12 months.9 In another trial in Nepal, children prenatally supplemented with MMN were found to weigh more than their counterpart who received iron and folic acid at 30 months.12 Given the active comparator, it is not unlikely that the initial difference in length at birth was diluted during the postnatal phase. There are few studies to which we can compare our results. Two studies assessing the effect of prenatal food supplementation on infant growth in...
Indonesia and in Bangladesh yielded different results. In the first study, a high-energy (465 kcal/day) compared with low-energy (52 kcal/day) dietary supplement given during the third trimester of gestation among chronically energy-deficient women resulted in better linear growth of children during the first 5 years.35 However, this study had been criticized because the groups of supplementation were compared only among compliers. A second study providing food supplementation combined with MMN14 at 9 weeks’ gestation showed a reduced proportion of stunting from infancy to age 5 years, compared with a supplementation initiated in midpregnancy. The reason our results contrast with previous studies is unclear, but a possible explanation could be the different study context. The nutritional status of women at the start...
of pregnancy might have played a role. Only 12% to 13% of pregnant women in our study were underweight (BMI < 18.5), and their daily caloric intake reached a median of 2096 (interquartile interval 997) kcal/day, whereas the habitual diet provided a mean 1464 (SD = 416) kcal per day in Bangladeshi women and 1550 kcal/day in Indonesian women. The suboptimal nutritional status of mothers might have resulted in a preferential effect for the maternal compartment, the benefits for infants afterward involving other mechanisms such as better breast milk output and hence less morbidity as proposed by the authors in the Indonesian trial. In the 2 studies, the effects on growth were indeed only observed in the postnatal period and not at birth. Our study has a number of limitations that need to be addressed. First, no additional data on breastfeeding and complementary feeding practices was collected during follow-up. A differential effect of such factors might have affected our results. Second, it is possible that our results are influenced by the proportion of infants who were lost to follow-up. However, the missing data pattern was similar between both study groups, and the characteristics from defaulters were similar to infants with complete data.

**CONCLUSIONS**

Prenatal LNS increased birth length, but this benefit could not be translated into better nutritional status or improved growth during infancy. The result of this study, although limited by the lack of data on breastfeeding and complementary feeding, might suggest that prenatal food and micronutrient are not sufficient to make a long-term difference in child linear growth. Future studies should focus on the effects of nutritional supplementation during the pre- and postnatal periods on child growth.

**ACKNOWLEDGMENTS**

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**REFERENCES**

7. Haider BA, Yakoob MY, Bhutta ZA. Effect of multiple micronutrient supplementation...


18. Demographic and Health Survey (HDSS) Burkina Faso. Preliminary Report. Ouagadougou, Burkina Faso: Institut National de la Statistique et de la Démographie (INSID); 2010


An error occurred in the article by Lanou et al, titled “Prenatal Nutrient Supplementation and Postnatal Growth in a Developing Nation: An RCT.” Published in the April 2014 issue of Pediatrics (2014;133(4):e1001–e1008; doi:10.1542/peds.2013-2850). On page e1003 under the heading “Data Analysis” on line 21 this reads: “The fixed effects in these equations included the intervention allocation (LNS versus MMN), primiparity, child gender, child age, type of malaria prevention, and health center to account for the study design.” This should have read: “The fixed effects in these equations included the intervention allocation (LNS versus MMN), maternal height, primiparity, child gender, child age, type of malaria prevention, and health center to account for the study design.”

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Prenatal Nutrient Supplementation and Postnatal Growth in a Developing Nation: An RCT
Hermann Lanou, Lieven Huybregts, Dominique Roberfroid, Laetitia Nikièma, Séni Kouanda, John Van Camp and Patrick Kolsteren

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/content/133/4/e1001.full.html
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