Seasonality Modifies the Effect of a Lipid-Based Nutrient Supplement for Pregnant Rural Women on Birth Length1–3

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Abstract

Background: Maternal nutritional status is a major determinant of low birth weight and fluctuates across seasons. Seasonality may influence the outcome of prenatal nutrition interventions that aim to enhance fetal growth.

Objective: This study investigated seasonal modifications of the efficacy of a randomized controlled prenatal nutrition intervention trial in pregnant women to improve fetal growth in rural Burkina Faso.

Methods: The second Micronutriments et Santé de la Mère et de l’Enfant study compared a lipid-based nutrient supplement (LNS) fortified with multiple micronutrients (MMNs) to an MMN supplement. Truncated Fourier series were used to characterize seasonality in birth outcomes. Models that included the Fourier series and newborn and maternal characteristics were used to assess seasonal effect modifications of prenatal supplementation on birth outcomes.

Results: Birth weight, birth length, small for gestational age as a proxy for intrauterine growth retardation, and preterm birth were significantly related to date of birth and showed important seasonal variations. LNSs, which supply energy in addition to MMNs, resulted in a significant increase in birth length (+13.5 mm, 95% CI: 6.5, 20.5 mm) at the transition from rain to dry season (September to November) compared to MMNs alone.

Conclusions: The climatologic and agricultural seasonal patterns in Burkina Faso affect the efficacy of prenatal LNSs on birth length. In this context, prenatal MMN supplementation programs should be complemented by energy supplementation during the annual rain season to promote fetal growth. This trial was registered at clinicaltrials.gov as NCT00909974. J Nutr 2015;145:634–9.

Keywords: seasonal variations, pregnant women, food supplement, birth weight, birth length, small for gestational age, premature birth, Burkina Faso

Introduction

Birth size is driven by growth processes in the fetus that can be hampered by intrauterine growth retardation (IUGR)1,2 and/or interrupted by preterm birth (PTB), both leading to low birth weight (LBW) (1, 2). Maternal nutritional status before and during pregnancy appears to be the most important determinant of LBW because maternal undernutrition accounts for >50% of LBW cases in many developing countries (3). Seasonal variations in birth size are well known in developing countries (1) and have been attributed to seasonal variations in maternal nutritional status, which are caused by periodical food shortages and agricultural labor (4, 5) that coincide with seasonal epidemics of infectious and parasitic diseases (6). Such variations could partly explain the modest and/or conflicting results achieved by various prenatal nutrition interventions to improve birth size (3, 7, 8).

One study in The Gambia showed that protein-energy supplementation resulted in a more important increase in birth weight during the rain season (June to October) compared to the dry season (November to May) (3).
season (November to May) (9). Yet, a sound investigation of seasonal variations in birth size could allow for more accurate analyses of nutrition interventions and could as such contribute to better-targeted nutrition interventions. The analysis of seasonality in birth size ranges from a simple linear regression (10, 11) to a time series summary of monthly means followed by the fit of a regression model that takes a 12-mo periodicity (annual model) and/or a 6-mo shift (bimodal model) (12, 13) into account. However, those methods can lead to overparameterization or may introduce abrupt changes by the arbitrary choice of seasonal cut-offs. Fulford et al. (14) and Rayco-Solon et al. (15) proposed using truncated Fourier series, which models seasonal variations more naturally.

Burkina Faso is a low-income country where multiple micronutrient deficiencies are common and with a 16.2% LBW incidence in 2006 (16). The country is characterized by 2 distinct seasons, a dry season and a rain season that runs from May/June to September/October. We previously conducted a randomized controlled efficacy trial [Micronutrients et Santé de la Mère et de l’Enfant study 2 (MISAME2)] in which a lipid-based nutrient supplement (LNS) fortified with multiple micronutrients (MMNs) was compared to an MMN supplement in rural Burkina Faso with the aim of improving birth size (8). The study found that prenatal daily LNS use resulted in a significantly higher birth length (4.6 mm, P = 0.001).

This study aimed to investigate seasonal trends in birth weight, birth length, IUGR [approximated by small for gestational age (SGA)], and PTB, and to investigate if the efficacy of the prenatal nutrition supplements on birth outcomes was modified by the seasonal patterns in Burkina Faso.

Methods

Study area and subjects. The data for this study was derived from the MISAME2 study that was conducted in the catchment area of 2 health centers in the Houndé health district of Burkina Faso, West Africa. The climate of the region is Sudano-Sahelian. The rain season runs from May to September/October and the dry season from October to April. The region is malaria endemic. The diet is essentially cereal-based. Maize is the main staple food and is harvested in October/November. In 2004 and 2006, food consumption surveys, conducted by our research team using interactive, repeated 24-h recalls, estimated the mean caloric intake during pregnancy to be 8.6 and 8.1 MJ/d during postharvest and preharvest seasons, respectively (17).

The MISAME2 trial was held from March 2006 to December 2007 (8). Trained community health workers visited the homes of women of childbearing age in the study area monthly. In case of reported amenorrhea, the participating woman was referred to the local health center where a medical doctor confirmed the pregnancy by means of a urine test. After explaining the study aims and modalities in the local languages, written consent was sought and obtained from all participants. A consultant obstetrician assessed gestational age as soon as possible after enrollment. Newborns’ sex, weight, and length were recorded at birth in the health centers. Only measurements taken within 24 h after birth were included for analysis. Length was measured to the nearest 1 mm with a SECA 207 scale. Weight was measured to the nearest 10 g with a SECA 723 scale. Gestational age at birth was computed by ultrasound measurements of fetal size at 10–12 wk of gestation.

Data analysis. A total of 1296 pregnancies were randomly allocated to the 2 groups, i.e., 655 in the intervention group and 641 in the control group. Only singleton pregnancies were included in the analysis because birth anthropometric measures of multiple pregnancies are not primarily nutrition-related. The few data of stillbirths, miscarriages, maternal deaths, and other mothers lost to follow-up (i.e., migration and unknown reasons) were also excluded for analysis. IUGR was approximated by SGA, which is defined by a birth weight for gestational age below the 10th percentile of the reference population by Kramer et al. (18). Preterm birth was defined as being born at <37 wk of gestation. Data on birth weight, birth length, and gestational age in the text are presented as means ± SDs, whereas incidence data of SGA and PTB are presented as mean percentages.

The seasonal trend of birth outcomes was modeled with truncated Fourier terms, as previously done by Fulford et al. (14). Dates of birth were transformed into cyclic data, i.e., a continuous variable with a circular distribution, with the starting point set at 1 January. Each date of birth was represented by an angle θi = 2π (D, mod 365.25)/365.25 expressed in radians, so that the 2π radians covers an average year (365.25 d). D is the number of days between 1 January 1960 and the ith child’s birth. The first p pairs of terms of the Fourier series are included in the regression models as follows:

\[ S(\theta_i, p) = \sum_{i=1}^{p} \beta_i \sin(i\theta_i) + \gamma_i \cos(i\theta_i) \]  

where r is the order of the Fourier term. Seasonal effects acting at the time of delivery are modeled by adding \( S(\theta_i, p) \) to the linear predictor so that \( \beta_i \) and \( \gamma_i \) become parameters in a regular multiple regression model. Pairs of Fourier terms (sine and cosine of the same order) were included in a regression model by increasing order, starting with the 1st order pair up to the 3rd order pair. The first order terms (sinθ and cosθ) model 6-mo cycles, the second order terms (sin2θ and cos2θ) 3-mo cycles, and the third order (sin3θ and cos3θ) 1.5-mo cycles. Fourier terms (sine and cosine) of the same order represent the same period and are orthogonal. Therefore, if one of these components is significantly associated with the outcome of interest, the order is also considered significantly related to this outcome. Regression coefficients are interpreted as in a simple regression equation, except for the coefficients of Fourier terms that have to be interpreted conjointly. The interpretation of these models can be best explained using an example. Assume that after convergence the model for birth weight over time of delivery would be \( y = 2700 + 100\cos\theta - 200\sin\theta + e \). We calculate that on 1 July or at \( \theta = \pi \) radians, the predicted average birth weight would be 2700 + 100 × 1 + −200 × 0 = 2800 g, whereas on 1 April, or \( \theta = \pi/2 \) radians, 2700 + 100 × 0 + −200 × 1 results in a birth weight of 2500 g. A convenient way to calculate the angle where a maximum or minimum of the outcome is situated is with use of the derivative of the model. A derivative or slope equal to zero would indicate local maxima/minima in the outcome of interest over time. If we consider the above equation, the derivative is \( y' = -100\sin\theta - 200\cos\theta \). Set to zero, that gives \( \tan\theta = -2 \). Solving this equation yields 2 angles, 2.03 and 4.25 radians, which represent 29 April and 5 September, respectively.

To determine which orders of Fourier terms fully captured the seasonality of birth outcomes, higher order models were compared to lower order models with use of a likelihood ratio test. Models that include up to 1st, 2nd, or 3rd order Fourier terms are respectively named F1, F2, or F3 models.
Seasonal trends in continuous birth outcomes (birth weight and birth length) were analyzed with use of linear regression models, whereas those of binary outcomes (SGA, a proxy for IUGR, and PTB) were analyzed with use of logistic regression models. The models only included Fourier terms as predictors to model the crude trend of seasonality in birth outcomes.

Seasonal effect modifications of prenatal nutrition supplementation on birth weight, birth length, SGA, and PTB were assessed by comparing a model that included interactions between intervention and Fourier terms (date of birth) and intervention and year of birth to a model without interactions, with use of a likelihood ratio test. The prior crude modeling of birth outcome over date of birth determined the number of pairs of Fourier terms in these models. All regression models were adjusted for season invariant covariates to gain statistical efficiency, i.e., health center, intervention, primigravidity, year of birth, group of malaria prophylaxis (3 vs. 2 doses of sulfadoxine-pyrimethamine), maternal height, and infant sex.

Intervention effects were plotted over time with 95% CI bands, computed by nonparametric bootstrapping (n = 5000) with replacement to visualize the modulating effect of seasonality of prenatal nutrition supplementation on birth outcomes. Furthermore, baseline maternal BMI and midupper arm circumference (MUAC) as well as maternal malarial infection prevalence and blood parasite concentration were plotted over time to characterize the seasonal context of the study setting. All statistical tests were 2-sided and the significance level was set at 5%, except for interactions for which the 10% level was used. Analyses were performed in Stata 12.0 (19) and R 3.0.2 (20).

Ethical considerations. The trial was approved by the ethical committees of the Centre Muraz, Burkina Faso, and the Institute of Tropical Medicine, Belgium, and was registered as NCT00909974 at clinicaltrials.gov.

Results

Maternal characteristics at randomization and birth outcomes are presented in Table 1. Maternal characteristics were similar in both study groups, although maternal height was slightly lower in the LNS group (−0.62 cm, P = 0.06). Birth weight and birth length was 2937 ± 445 g and 478 ± 25 mm, respectively, whereas gestational length was 39.0 ± 2.8 wk. Prematurity incidence was 15.0% and SGA incidence 34.0%.

The comparison of the goodness of fit of different seasonality models with increasing order is presented in Table 2. The data show no evidence that more than the first pair of Fourier terms, i.e., F1 model, and the first 2 pairs, i.e., F2 model, are necessary to explain the seasonality in birth weight and birth length, respectively. Both birth weight (P < 0.01) and birth length (P < 0.0001) were significantly related to date of birth. The seasonal variations in SGA (P < 0.01) and PTB (P < 0.0001) were also found statistically significant and were modeled best by an F3 model.

From these fitted Fourier models it can be concluded that birth outcomes showed marked monthly variations. Birth weight and birth lengths peaked at the end of the dry season, more precisely in April (2994 ± 2 g and 486 ± 0.3 mm, respectively) and May (2979 ± 7 g and 485 ± 1 mm, respectively), whereas their nadirs appeared in the rain season, respectively in September (2879 ± 2 g) and August (470 ± 0.2 mm) (Figure 1). The rain season was characterized by a dramatic rise in PTB cases (August, mean: 31.2%). SGA incidence showed several peaks throughout the year: 39.0%, 34.0%, and 46.5% in February, June, and October, respectively (Figure 2). Interestingly, the nadir of SGA incidence in the rain season coincided with the peak in PTB and was followed by a distinct increase to the SGA maximum in October.

Malaria prevalence increased sharply from August to September, i.e., its annual maximum, and the mean concentration of blood parasites was highest in August (Supplemental Figures 1 and 2). Baseline BMI and MUAC of pregnant women in their first trimester were plotted to describe maternal nutritional status across seasons (Supplemental Figures 3 and 4). Both BMI and MUAC revealed similar patterns, showing a peak in June/July followed by a steady decline toward the annual minimum in November.

Birth weight and birth length data for seasonal effect modification analyses were available for, respectively, 518 and 517 pregnancies in the intervention group and 493 pregnancies in the control group. Seasonality modified the effect of prenatal supplementation on birth length (P < 0.1) (Supplemental Tables 2 and 3). This observation reveals differential efficacy of the intervention group compared to the control group by date of birth. It is also of note that the interaction between prenatal supplementation and year of birth on birth length was statistically significant.

The intervention effect of an LNS on birth length was most pronounced from September to November at the transition from rain to dry season (+13.5 mm, 95% CI: 6.5, 20.5) compared to an MMN supplement only (Figure 3). No significant effect of LNS on birth length was observed in other periods of the year. We did not observe any important effect modification on birth weight or SGA.

Discussion

Fourier seasonality models showed that prenatal supplementation with an LNS, compared to an MMN supplement, has important effect modifications on birth length by date of birth. To our knowledge, this is the first study to demonstrate these seasonal effect modifications for prenatal supplementation with an LNS on birth size.

The seasonality in birth weight and birth length showed distinct patterns with a peak at the end of the dry season and a nadir in the rain season. A study in Malawi demonstrated that both prenatal linear growth and weight gain falter by exposure...
to the rain season. However, the timing of exposure appeared essential in that the direct effect of the seasonal stress was only apparent in third trimester pregnancies (21). Similarly, a study in The Gambia reported a 250-g difference in birth weight between its maximum at the end of the dry season and minimum in the rain season (9). In India, Rao et al. (22) found significant differences of 142-g birth weight and 15-mm birth length between the maximum in early postharvest and minimum at harvest, when intensive agricultural work takes place.

The incidence of SGA, a proxy for IUGR, and PTB demonstrated opposing fluctuations across seasons. The incidence of SGA showed a nadir in the rain season that coincided with a sharp maximum peak in PTB incidence. Of notice, the nadir in SGA and peak in PTB were matched by the nadir in birth weight and 15-mm birth length. Rayco-Solón et al. (15) found the same opposing trend between SGA and PTB in The Gambia. Furthermore, a recent pooled data analysis by Katz et al. (23) showed that the proportion of SGA babies in Asia and Africa is relatively lower before 37 wk of gestation. These findings could suggest that IUGR in the rain season takes greater hold in the last weeks of pregnancy. However, it may also be that SGA incidence was systematically underestimated for preterm babies because of the use of a birth weight reference instead of a fetal growth standard (23, 24). The maximum peak in PTB incidence and subsequent maximum in SGA incidence can be regarded as results of insults in the rain season. Although the presence of intrauterine inflammation/infection, bacterial vaginosis, asymptomatic bacteriuria, and high maternal plasma cortisol concentration in early pregnancy can also lead to PTB (25–27), in our context, the peak in PTB incidence during the rainy season can predominantly be regarded as the result of acute insults such as acute infections and an increased workload. Conversely, SGA is considered to be the consequence of a chronic accumulation of insults. Therefore, when the rain season sets in, preterm birth incidence rises sharply, whereas SGA incidence rises gradually, the longer the exposure to the rain season. In Burkina Faso, the rain season (May to September/October) is characterized by a seasonal increase in agricultural labor and energy expenditure (28) as well as food scarcity because of diminishing food stocks. The arrival of the first rains in early June is the sign for many rural households to start sowing, whereas the period around October is dedicated to harvesting. A survey on physical activity patterns, of a convenience sample of ~250 pregnant women in the research area, showed that women in their third trimester of gestation were not spared from daily seeding, weeding, and harvesting activities in bending or squatting postures (L F Huybregts, unpublished results, 2006). Such long working hours and an increased physical workload have been shown to be associated with a higher risk of preterm delivery (29, 30). Furthermore, the combination of a strenuous workload and limited food availability in the rain season could result in a negative maternal energy balance (4, 9, 22), which probably triggered the descending trend in maternal BMI and MUAC (Supplemental Figures 3 and 4). Finally, additional data from the MISAME2 study and other reports (6) showed characteristic increases in malaria transmission rates in the rain season. It is well documented that acute malarial infections at the end of pregnancy cause an induction of preterm delivery, whereas malaria-associated IUGR was suggested to be associated with placental insufficiency and parasitemia in the wider antenatal period (31–33). As a matter of fact, a malaria-infected placenta acts as a site for active immune response that may stimulate early labor, resulting in premature delivery, or hinder nutrient transport to the fetus, resulting in IUGR (34).

LNSs, which provided energy and MMNs compared to only an MMN supplement, triggered a distinct positive effect on linear growth at the transition from rain to dry season (September–November). This observation brings up a few nonexclusive explanations. First, LNSs could lead to greater length gain the longer the exposure to the rain season in the second and early third trimester of gestation, a time when
linear growth velocity is maximal (35). Second, exposure to the full extent of seasonal stress of the rain (lean) season in the second half of pregnancy requires the provision of additional energy that allows micronutrients to exert a functional effect on linear fetal growth. In this light, it is interesting to compare our results to a Gambian study (9) that showed a maximal effect on birth weight in the lean season and no significant effect on birth length. The pronounced effect on birth weight in The Gambia could be explained by the daily energy dose, which was almost 3 times as high as our LNS (4.25 vs. 1.56 MJ/d), and the fact that our control group received MMNs, which are also known to increase birth weight (7, 36–38). The lack of any effect on birth length is possibly related to the absence of additional MMNs in the Gambian supplement. Providing energy as “empty calories” in the presence of functional micronutrient deficiencies might primarily lead to an accumulation of adipose tissue (39) and, hence, higher birth weight without effects on linear growth. The results of the Gambian and our study therefore lead us to the hypothesis that the sole provision of MMNs, without additional energy, is not sufficient to support linear growth in pregnancies where the second half of pregnancy covers the rain (lean) season, i.e., a time when energy needs are higher because of increased maternal energy expenditure and/or infections.

Our study has some limitations that warrant caution. First, the lack of additional data on individual exposure, e.g., dietary intake and energy expenditure data, over different seasons hampers a straightforward interpretation of the results. Second, the results should be interpreted carefully because of the duration of the intervention. Annual variation was demonstrated by a significant interaction between prenatal supplementation and year of birth. Yet, this variation is rather expected to be the result of harvest yield and market prices because no other interventions were implemented in the research area at the time.

In conclusion, we provide evidence that the previously reported effect of an LNS on birth length in rural Burkina Faso is mainly concentrated in pregnancies where the second half of pregnancy covers the rain season. This result implies that MMN interventions during the annual rain/lean season in Sub-Saharan African countries should be accompanied by additional energy supplementation to be more efficacious in supporting
prenatal linear growth and, ultimately, preventing child stunting during the first 1000 d from conception to 24 mo of age (40).

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