Differential effects of seasonality on preterm birth and intrauterine growth restriction in rural Africans\textsuperscript{1–4}

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ABSTRACT

Background: Low birth weight (LBW) can result from prematurity or intrauterine growth restriction (IUGR) and result in small-for-gestational-age (SGA) infants. Prematurity and IUGR may have different etiologies and consequences.

Objective: Our objective was to analyze seasonal patterns of prematurity and SGA in a rural African community and to compare them against variations in nutritional and ecologic variables that may provide insight into likely causative factors.

Design: Fourier series were used to compare the seasonality of prematurity (<37 wk) and SGA (<10th percentile of the reference standard) among 1916 live infants born over 26 y in 3 Gambian villages. The resultant patterns were compared against monthly variations in birth frequency, maternal energy status, maternal work, and malaria infections.

Results: The incidence of LBW was 13.3\%, of prematurity was 12.3\%, and of SGA was 25.1\%. Prematurity and SGA showed divergent patterns of seasonality. Incidence of SGA was highest at the end of the annual hungry season, from August to December (peaking in November at 30.6\%), with a nadir of 12.9\% in June. Rates of SGA varied inversely with maternal weight changes. This pattern was not seen for rates of prematurity, which showed 2 peaks—in July (17.2\%) and October (13.9\%). The lowest proportion of preterm births occurred in February (5.1\%). The peaks in prematurity closely paralleled increases in agricultural labor (July) and malaria infections (October).

Conclusion: We conclude that a reduction in LBW in such communities may require multiple interventions because of the variety of precipitating factors. Am J Clin Nutr 2005;81:134–9.

KEY WORDS Low birth weight, prematurity, intrauterine growth restriction, season, developing countries, pregnancy, gestational age, birth weight

INTRODUCTION

Birth weight is the product of the length of gestation and the rate of fetal growth. Low birth weight (LBW), defined as a birth weight <2500 g, could be the product of prematurity (<37 wk), intrauterine growth restriction (IUGR), or both. Because of the difficulty of diagnosing pathologic restrained or growth retardation in the fetus, weight-for-gestational age at birth is often used as a proxy measure for IUGR. Small-for-gestational age (SGA) is defined as a birth weight below the 10th percentile for gestational age on the basis of a sex-specific reference standard (1, 2). It is important to distinguish between the 2 types of LBW because of differences in the consequences to the infant in terms of mortality and morbidity (3–5). Furthermore, the etiologies for both types of LBW are also heterogeneous (6–8).

Seasonality of LBW is a well-known phenomenon in developing countries (9–11). This has been attributed to the seasonal deterioration of nutritional status due to food shortages and an increase in agricultural labor that is often coincident with seasonal epidemics of infectious and parasitic diseases (12–14). There have, however, been no studies separating LBW seasonality according to prematurity or IUGR.

The West Kiang District in the Gambia has a seasonal agricultural system that revolves around an annual rainy season from July to November. Studies that have looked at the seasonality of weight gain among pregnant mothers in rural areas of the Gambia show that weight gain during the rainy season is \(\approx 400–500\) g/mo less than weight gain during the dry season (15–17). Birth weight has also been shown to be almost 90 g lower in the rainy season than in the dry season (17–19), with a greater difference from peak to trough.

The villages of Keneba, Manduar, and Kantong Kunda in the West Kiang District have been part of longitudinal demographic and health surveys since 1949. Data on maternal pregnancies, birth anthropometric measures, and gestational ages have been collected since 1978. The availability of these data enabled us to separately analyze the seasonality of prematurity and IUGR and to compare them against the external environmental factors that may play a precipitating role.

SUBJECTS AND METHODS

This was a retrospective cohort study of all live births in 3 subsistence-farming villages of the West Kiang District in the

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Gambia from 1976 to the present. The West Kiang District is an area of savannah and farmland, roughly 750 km², bounded on 3 sides by the River Gambia and its tributaries. The villages are rural and are ≈100 km from Banjul, the capital. There is a seasonal agricultural system that revolves around an annual rainy season, which occurs from July to November.

Regular ante- and postnatal care has been provided by resident midwives to all women of childbearing age since the mid-1970s. Birth weights were first recorded from the 3 villages in 1976. Birth weights were recorded to the nearest 10 g with a Salter spring balance and tared sling (Salter Industrial Measurements Ltd, West Bromwich, United Kingdom), which was calibrated regularly. LBW was defined as weight <2500 g. Measurement of gestational age was introduced in 1978, which was assessed by using the physical and neurologic scoring system validated by Dubowicz et al (20) by medical doctors within 5 d of delivery. Prematurity was defined as a gestational age <37 completed wk. SGA was defined as a birth weight less than the 10th percentile of gestational age based on the reference standard by Williams et al (1, 2).

Since regular antenatal clinics were started, pregnant women from the 3 villages were seen every 4 wk until the 28th wk and then fortnightly until term. Thick and thin blood smears for malaria were routine during these visits. The percentage of positive malaria smears among pregnant or lactating mothers during routine follow-up per calendar month were taken from records of these consults. There were a total of 43 385 visits and 3276 cases of malaria among 940 mothers from 1978 to 2003.

Regular anthropometric measurements from an earlier study of women of reproductive age from the same 3 villages from 1978 to 1988 were used to define the monthly change in body weight (15). Over this 11-y period, 13 833 weights from 529 women were collected—an average of 26 weights per woman. Within-subject regression was used to adjust for stage of pregnancy or lactation and year of measurement. The mean (±SD) annual weight was 52.8 ± 7.8 kg.

Maternal workload measured as the mean duration (h/d) in which pregnant women were active per calendar month was taken from a previous study of 73 pregnant women in Keneba from 1978 to 1979 with the use of a combination of activity diaries and 24-h activity recall (21). The amount of activity among pregnant women was markedly seasonal. The women were active 50% of a 15-h day from January to April, but this activity increased dramatically at the start of the farming season in June and July to 83%. Total energy expenditure was at a minimum at 9.6 MJ/d from January to March and at a maximum at 11.3 MJ/d from July to October.

Although the women’s weight data, physical activity, and malaria infection rates were not contemporaneous with the 1916 deliveries we describe, we considered these data acceptable because of the consistent seasonality that we observed over many years and because the 1916 births were themselves spread over 26 y.

There were 2 previous supplementation trials, which included ≥1 of the 3 villages (18, 19). The first-order effects of supplementation (fitted with the use of a single indicator variable) on preterm births and on SGA were not significant. The seasonality of either the preterm births or SGA was not significantly modified by supplementation when season was modeled by a simple binary variable indicating the hungry season (July to November). Thus, we ignored supplementation in the rest of the analysis.

The recording of births and deaths in these villages predated the formation of the Joint Gambian Government/Medical Research Council Gambia Ethics Committee. Approval for the continuation of the demographic surveillance was granted when the committee was formed in 1981.

Statistics

Fourier series are the natural mathematical models for seasonality. They are smooth linear functions whose terms are approximately orthogonal to one another and are inherently cyclic: the smoothness carries over from December to January. They also offer flexibility in the dimensionality of the fitted seasonal effect: truncating the higher-order terms of the series removes higher-frequency noise. If we use the first $p$ pairs of terms of the series, the seasonal component of the linear predictor would be as follows:

$$\sum_{r=1}^{p} \beta_r \sin(r \theta_i) + \gamma_r \cos(r \theta_i)$$

where angle $\theta_i$ is the point in the annual cycle that the $i$th child’s birthday occurred. Denoting the number of days between 1 January 1976 and the $i$th child’s birthday as $D_i$, we calculated this angle in radians:

$$\theta_i = 2\pi(D_i \mod 365.25)/365.25$$

In these data we found that only the first 3 pairs of terms (F3 model) were significant in these data.

We then investigated the seasonality of 2 binary outcome variables—SGA and prematurity—separately (univariate analysis) using logistic regression. Then, to compare the seasonality of the 2 outcomes simultaneously (bivariate analysis), we applied “seemingly unrelated biprobit regression” analysis (22). This method allowed us to fit separate models for SGA and prematurity simultaneously and to compare their goodness-of-fit when the same or different parameters were used in the seasonal component. We used the likelihood ratio test to compare models that fitted a separate set of underlying seasonality parameters for SGA and prematurity with models in which the underlying seasonality parameters were constrained to be identical for both outcomes. All analyses were performed with STATA 8 (Stata Corp, College Station, TX).

RESULTS

There were 2977 live births in Keneba, Manduar, and Kantong Kunda from 1976 to 2003. Of these live births, 2472 (83.0%) had recorded birth weights. Of the 2550 births since 1978, 1918 (75.2%) had recorded gestational ages. Those without gestational ages were not significantly different from those with recorded gestational ages in terms of mean birth weight (difference in means = 17 g; 95% CI: −25, 59 g; $P = 0.433$), sex (Pearson’s $\chi^2 = 2.96$ on 1 df, $P = 0.085$), and month of birth (Pearson’s $\chi^2 = 15.4$ on 11 df, $P = 0.166$). Missing gestational ages were usually due to logistical problems (eg, doctor indisposed, no transport to village, and late information) and were more likely in the earlier years when the records were less complete. There were 2 infants with gestational ages but whose birth weights were not recorded. In all, there were 1916 infants with both birth weight and gestational age. The exact date of birth was known for all.
The incidence of LBW in this population was 13.3%, of prematurity was 12.3%, and of SGA was 25.1%. The relation between LBW, prematurity, and SGA is shown in Figure 1. Note that the 10th percentile of the reference standards falls almost exactly across the intersect of 2500 g and 37 wk gestation but does generate a small group of 15 term infants (12 at 37 completed weeks of gestation and 1 each at 38, 39, and 41 wk) with birth weights between 2100 and 2500 g. They were a paradoxical cluster of LBW infants who were born at term and were appropriate-for-gestational age.

The month-by-month percentage of SGA infants is shown in Figure 2. The percentage of SGA infants was highest from August to December (peaking in November at 30.6%), with a gradual decrease in the percentage of SGA infants until the nadir in June at 12.9%. The percentage of preterm infants showed 2 peaks: one in July (17.2%) and one in October (13.9%). The lowest percentage of preterm births occurred in February (5.1%), which was followed by a gradual increase in the percentage of preterm infants until the peak in July.

Logistic regression applied separately to each variable, fitting the first 3 pairs of Fourier terms, showed that both outcomes were significantly dependent on the season of birth (SGA: likelihood ratio \( \chi^2 = 24.73 \) on 6 df, \( P = 0.0004 \); preterm: likelihood ratio \( \chi^2 = 20.07 \) on 6 df, \( P = 0.0027 \)). Use of a monthly 12-level stratification of the year did not result in a significant improvement over the F3 model of seasonality for either outcome (SGA: likelihood ratio \( \chi^2 = 10.54 \) on 11 df, \( P = 0.48 \); preterm: likelihood ratio \( \chi^2 = 9.35 \) on 11 df, \( P = 0.59 \)).

To test whether these prima facie patterns of seasonality of SGA and preterm deliveries (the unconstrained fitted curves in Figure 2) were significantly different, both outcomes were fitted simultaneously to the F3 model of seasonality by using seemingly unrelated biprobit regression. The regressions gave a significantly poorer fit to the data when the coefficients of Fourier variables are constrained to be identical than when a separate set of seasonality parameters was used for each outcome (likelihood ratio \( \chi^2 = 23.06 \) on 6 df, \( P = 0.0008 \)), which confirmed that the patterns of seasonality are different for SGA and preterm births.

The temporal similarity between rates of SGA and the annual variation in birth frequency and alterations in maternal energy balance are shown in Figure 3 and Figure 4. The number of births per month among all the births from the 3 study villages from 1978 to 2003 is shown in Figure 3. There was a marked fluctuation in birth frequency. The lowest birth rates were from April to July, coinciding with the lowest rates of SGA. Seasonal changes in maternal weight taken from a previous study by Cole (15) for women of reproductive age from the same population are shown in Figure 4. The gap between food intake and the energy costs of physical activity that occurs at the onset of the rainy season, because of dwindling food stores coincident with increased agricultural labor, causes an annual cycle of weight loss and gain in these rural villages. During the hungry season, an average woman in this population loses \( \approx 2.6 \) kg, \( \approx 5\% \) of her body weight, or 25% of body fat. This weight loss is equivalent to an energy deficit of 10–15%/d, which closely parallels the rate of SGA in the community with the lowest rates during the months with the heaviest body weights.

Fluctuations in the rates of preterm births, with variations in material workload and malaria infections, are shown in Figure 5 and Figure 6, respectively. The percentage of preterm infants
born per month relative to the proportion of a 15-h d in which pregnant women from Keneba are active, as measured from a previous study by Roberts et al (21), is shown in Figure 5. Agricultural work increases in the area, which may start with clearing and manuring of fields, as early as April or May and intensifies to a peak in June and July when the first rains necessitate long hours of hoeing, planting, and weeding. This abrupt increase in workload from April to July is matched by an increase in the rate of preterm births during the same period. The percentage of pregnant or lactating mothers with positive findings on malaria smears, which were conducted during routine 2- to 4-weekly follow-ups per calendar month in the 3 study villages from 1978, is shown in Figure 6. The highest rates of parasitemia were seen late in the rainy season, from September to November. This was tracked by an increase in the rate of preterm births during these months.

FIGURE 5. Daily hours of activity in which pregnant rural Gambian women are active per calendar month (vertical bars). The annual mean was 10.4 h/d. The data were adapted from the study by Roberts et al, 1982 (21). The line graph represents the percentage of preterm infants born per month ($n = 1916$).

DISCUSSION

The monthly percentages of prematurity and SGA showed 2 distinctly divergent patterns, which emphasized the different etiologies. Elsewhere we argued that the underlying seasonal factors affecting SGA and prematurity could be explained by a common synchronicity if we make the reasonable assumption that fetal growth retardation leading to SGA accumulates over the duration of gestation but that the factors precipitating early parturition act essentially instantaneously (AJ Fulford, unpublished observations, 2004). This does not, however, confirm that the causes definitely are synchronous nor does it imply that they are the same.

Inferences about the likely casual factors for SGA and prematurity can be drawn by evaluating the effects of other ecologic data on seasonality in this population. The following discussion considers the possible effects of selective conception, maternal energy balance, maternal workload, and malarial infections on SGA.

In the population studied, there was a clear seasonal variation in birth frequency (Figure 3). The nadir from April to July comes 9 mo after the annual hungry season in which weight loss occurs from July to September. This would fit with the Frisch hypothesis that the pituitary-gonadal reproductive axis is regulated by maternal energy flux (23, 24), but alternative explanations involving seasonal variation in coital frequency cannot be ruled out. If the former (ie, physiologic) explanation were true then it would imply that the infants born in the nadir of birth frequency represent a selected subgroup defined by greater maternal or embryonic fitness. In separate studies we are investigating possible “thrifty genes” that might confer a greater likelihood of conception or fetal survival during these times of especially harsh nutritional conditions. In the current context it is necessary to ask whether these factors might also be associated with differences in fetal growth or length of gestation. There is a tolerably close fit between the seasonality in birth frequency and SGA births, which is consistent with there being a higher proportion of “fitter” fetuses implanted when conception rates are at their lowest. However, alterations in substrate supply to the fetus might offer a more straightforward explanation.
There is a gap between food intake and the energy costs of physical activity that occurs at the onset of the rainy season because of dwindling food stores coincident with increased agricultural labor. This imbalance causes an annual cycle of weight loss and gain among women of reproductive age in these rural villages. The resulting variation in maternal weight reflects this energy balance. This fluctuation corresponded closely to rates of SGA, as shown in Figure 4. Rates of SGA get progressively lower as the harvest season progresses from February to June and are highest in the hungry season from August to December. This association supports findings from a systematic review of 13 randomized controlled trials involving 4665 women to treat or prevent IUGR (25). Balanced energy and protein supplementation (when the protein content of the supplement was <25% of the total energy content) was associated with moderate increases in maternal weight gain (difference in means: 17 g/wk; 95% CI: 5, 29 g/wk) and mean birth weight (difference in means: 25 g; 95% CI: 4, 55 g) and a considerable decrease in risk of SGA births (odds ratio: 0.64; 95% CI: 0.53, 0.78). A path analysis done by Susser (26) showed that the causal pathway between dietary intake and birth weight bypass maternal weight change outside famine conditions, which may partly explain the modest weight gain alongside a substantial decrease in SGA seen in the review. In our setting of intense and acute annual nutritional deprivation, this relation between maternal weight and SGA is more noticeable. Indeed, in the Gambian supplementation study (18), the high-energy food supplement had a relatively large effect on fetal growth and SGA.

The rate of prematurity did not follow this same trend. There is little evidence in the published literature of an association between maternal nutritional status and risk of premature delivery. Studies of gestational weight gain (27), food supplementation (25), and nutritional advice (28) failed to show conclusive evidence of relations between nutritional status in pregnancy and the resultant length of gestation.

The prematurity rate was highest in July. This corresponds with the increase in agricultural work in the area from April to July (Figure 5). In the pregnant women from these 3 rural villages, there was only a small decrease in total energy expenditure of =0.6 MJ/d from the 28th wk of gestation until 4 wk postpartum (29). Heavy work, especially agricultural work among women in developing countries, is a risk factor for prematurity (30–34). The fact that much of the work involves standing and bending may exacerbate this risk.

A recent study of sheep gestation showed that undernutrition in the periconceptual period can cause premature birth (35). Ewes who were undernourished from 60 d before to 30 d after conception, such that they lost 15% of their weight, gave birth after an average of 139 d of gestation as compared with 146 d in well-nourished ewes. In our study, the lowest maternal weights in October would closely correspond to the highest rates of prematurity 9 mo later in July (P Rayco-Solon, unpublished observations, 2004). Thus, an alternative explanation for the July peak could be that there is a critical period in which a nutritional insult around the time of conception might affect gestational length.

There was a second peak in prematurity in October. This was also the peak time for malaria infection among pregnant women in the Gambia (Figure 6). The proportion of all antenatal attendees, of primigravid mothers with parasitemia, or of placentas with malaria pigments are highest from October to November (36, 37). Malaria in pregnancy has been shown to be a risk factor for prematurity (38–42). However, controlled trials of the effect on prematurity of chemoprophylaxis (43, 44) or of the use of bed nets (39, 45) during pregnancy have been few and have had conflicting results. No firm conclusion regarding an association can be drawn from the current study.

In the rural, subsistence-farming women in the Gambia, the agricultural system, which revolves around an annual rainy season, creates an “experiment of nature” with regular hungry and harvest seasons that result in yearly mobilization and redeposition of body fat stores (15). Coupled with meticulous record keeping throughout the years, the seasonal agricultural system provides a unique setting in which to study factors affecting reproductive outcomes. In summary, our data show that seasonal patterns of maternal weight change closely parallel the rate of SGA births in rural Gambia. This pattern is not seen in rates of prematurity that, for the July peak, more closely parallel increases in agricultural labor and possibly in periconceptual energy status and, for the October peak, might be related to malaria infection rates. Because many factors are likely involved in the seasonality of LBW and preterm births, there is a need for further study to understand this phenomenon and plan targeted strategies for implementation in various settings.

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PR-S was responsible for the conception of the study, data interpretation, and manuscript preparation. AJF was responsible for the data analysis and interpretation and manuscript preparation. AMP assisted in the conception of the study, interpretation of results, and critical revision of the report. All authors contributed to the writing of the final manuscript. None of the authors had a conflict of interest.

REFERENCES


