

# Maternal Supplementation Differentially Affects the Mother and Newborn<sup>1,2</sup>

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## Abstract

Although studying the effect of supplementation on maternal health or the outcome of pregnancy was not a primary goal of the Institute of Nutrition of Central America and Panama Oriente Longitudinal Study, many important findings in these areas were produced. As part of the study, a food supplementation program was implemented. Two villages received *Atole*, a gruel containing protein and energy, and 2 matched villages received a refreshing, low-energy drink containing no protein. Both drinks contained micronutrients. Some women did not choose to consume the supplements and those who did consumed widely varying amounts. More volume of *Fresco* was consumed than *Atole*. The energy in the supplements improved birthweight, with no apparent additional benefit from protein or micronutrients. Researchers identified several groups of women who benefited from supplementation more than others by having babies with higher birthweights, including those with poorer current nutritional status and those who consumed high amounts of the supplement continuously from one pregnancy to the next. Results from the study provided an early indication that supplementation might increase the duration of gestation and, thus, reduce preterm birth. On the other hand, maternal supplementation did not substantially alter the duration of postpartum amenorrhea once concurrent infant supplementation was taken into account. Finally, findings from this study provided evidence of a biological trade-off between maintenance of maternal nutritional status and increasing fetal size that was responsive to both current maternal nutritional status and supplement intake but not to the mother's nutritional status earlier in life. *J. Nutr.* 140: 402–406, 2010.

The most important elements of the design of the Institute of Nutrition of Central America and Panama (INCAP) Oriente Longitudinal Study were related to the improvement of nutritional status and mental development of preschool-aged children (1). Documenting the effects of the supplement on the mother herself or even on birthweight was not initially of interest. At the time the study was designed, protein was considered the limiting nutrient in women's diets (2) and supplementation of women was not expected to have any adverse consequences. Women were treated as a vehicle for improving infant and child health, not as an intervention target in their own right. As a result, the study was well underway before the measurement of maternal anthropometry and birthweight began. Thus, the sample size for the analyses described here is considerably smaller than those based on the 1309 babies born into the Oriente Study (1). Nonetheless, the women who participated in this study have

been the subject of numerous research studies. The contribution of these studies to our knowledge of how to improve the outcome of pregnancy, the effect of supplementation on postpartum amenorrhea, and our understanding of the trade-offs between mothers and infants during the reproductive cycle is reviewed here.

The study included the collection of several kinds of unique data that allowed many important questions to be answered (1). As part of the protocol for surveillance of child illness, women were asked biweekly if their menses had ceased or returned. These data were used to determine the onset of pregnancy, so women could be encouraged to receive the supplements, as well as the duration of both gestation and postpartum amenorrhea. Women's attendance at the supplementation center was recorded along with their consumption of the *Atole* and *Fresco* beverages. In combination with the measurement of home dietary intake, this information enabled researchers to calculate the net impact of supplementation on total intakes.

## Supplementation and the outcome of pregnancy

Women enrolled in the Oriente Study were short (149 cm tall) but of normal weight (49 kg) for their height (BMI ~22 kg/m<sup>2</sup>) at the end of the first trimester of pregnancy. They gained 7 kg during pregnancy (3). Home dietary intake was low, ~1400 kcal/d (1 kcal = 4.184 kJ) (3).

Women were encouraged to come to the supplementation center and consume the supplements. Nevertheless, Johnson (4) reported that 30.4% of the pregnant women did not attend the

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supplementation center at all during the 3rd trimester of pregnancy (32.8% of women in the *Atole* villages and 27.7% of women in the *Fresco* villages). Among those who did attend, there was wide variation in their supplement intake in the last 91 d of pregnancy:  $109 \pm 90$  (SD) kcal/d ( $n = 520$ ) (4). The volume of *Fresco* consumed was ~3 times that of *Atole*, so that even though *Atole* had a higher energy concentration (910 kcal/L compared with 330 kcal/L for *Fresco*), the distributions of energy intake for the 2 beverages were similar. As a result, the amount of micronutrients consumed by women who received *Fresco* was ~3 times that of the women who received *Atole* (because the micronutrients were present in the same concentrations by volume in the 2 beverages). This finding suggests that women were consuming to an energy target, not one for either protein or micronutrients. It is also possible that women found the lighter *Fresco* drink more palatable than the *Atole*. Among those who attended, frequency of attendance was correlated with probable need for supplementation that, in turn, was correlated with the amount of supplement consumed (4).

Women who consumed more than the median amount of supplement over the course of pregnancy (20,000 kcal) consumed 41 kcal/d less from their home diet than those who consumed less than the median amount. However, these women also had a total food intake (mean supplement intake of  $42,000 \pm 19,221$  kcal) that was 323 kcal/d greater than that of those who consumed less than the median amount of supplement (mean supplement intake of  $7200 \pm 6221$  kcal) ( $P < 0.001$ ) (5). Supplement consumption was associated with weight gain during pregnancy. A lower proportion (2.5%;  $n = 80$ ) of women who consumed  $\geq 20,000$  kcal during pregnancy exhibited a lower rate of weight gain ( $< 0.5$  kg/mo) in the last 2 trimesters of pregnancy than those who consumed less than this amount (14.5%;  $n = 55$ ) (3).

Birthweight was available for only 62% of the 651 births that occurred from 1969 to 1973 and was strongly related to maternal energy intake from supplements (6). Higher consumption of the supplement ( $\geq 20,000$  kcal) was also associated with an overall increase in birthweight of 117 g ( $P < 0.05$ ) (3) as well as a corresponding decrease in the proportion of babies who weighed  $< 2500$  g at birth, from ~18 to ~9% ( $P < 0.05$ ) (7). The trimester of pregnancy during which women consumed most of their supplemental energy was not associated with birthweight ( $n = 288$ ) (2). Birthweight differed ( $P < 0.025$ ) between the lower and higher supplement consumption groups and this was similar in the *Atole* and the *Fresco* groups (3). The estimated relationship, 30 g birthweight/10,000 kcal ingested from supplement, was linear and robust to adjustment for possible confounding factors.

Women established patterns of supplement intake, which was exploited by Villar and Rivera (8) to explore whether women who habitually consumed the supplement in larger amounts would be able to increase the size of their infants even more ( $n = 169$  women with 2 consecutive pregnancies). They compared women who habitually consumed higher amounts of supplement ( $> 500$  kcal/wk during 2 pregnancies and the intervening lactation period) with those who consumed less than this amount. Women who habitually consumed the higher amount had infants who were  $246 \pm 157$  (SE) g heavier at birth ( $P < 0.025$ ) than those who habitually consumed the lower amounts; women with other patterns of supplement intake had lower increases in the birthweights of their infants (8). These results suggest that longer periods of supplementation, even with modest daily amounts of supplement, can allow chronically

undernourished women to deliver heavier babies. This proposition has not yet been tested experimentally.

It is noteworthy that the improvement in birthweight associated with supplementation observed in the first half of the study (1969–73) was not present in the second half (1973–77) (9). This may be because some women consumed substantial amounts of the supplement in the first half of the study and, thus, had less potential to benefit from supplementation in the second half of the study. The approach used by Marks (9) to ascertain which women had benefited from ingestion of the supplements, which was based on statistical interaction between individual characteristics and ingestion of the supplements, provided a substantial analytic advantage over that used previously (10). This approach was subsequently used to determine which women had benefited from dietary supplementation during lactation during another study in Guatemala (11) and, within the Oriente Study, to determine which children had benefited from ingesting the supplement themselves (12).

The question of who benefits from supplementation is an important one for targeting. Olson (13) pursued this issue further with an econometric approach to control more adequately than had previously been possible for self-selection related to the individual woman's choices about whether to participate at all and how much supplement to consume. She showed that the effect on birthweight of moving from the lowest to the highest quartile of supplement intake was greatest among women who had lower skinfold thicknesses during the first trimester (190 and 320 g in the case of the midaxillary and subscapular sites, respectively) and who were not breast-feeding at the time of conception (560 g, compared with those who were breast-feeding). These maternal characteristics could serve as indicators of potential to benefit from supplement and, thus, as possible criteria for selecting women for supplementation.

When the supplements were discovered to increase birthweight, this finding was interpreted as an increase in fetal weight, not as an increase in the duration of gestation. Inasmuch as women were asked biweekly about the onset of their menses (1), the quality of the data on gestational age was good in this study. Delgado et al. (14) used data from the 830 singleton deliveries between 1969 and 1977 for which data were available on duration of gestation and supplement intake. Energy consumed in the first or second, but not the third, trimester was associated ( $P < 0.01$ ) with the length of gestation (2.3–7.5 d/10,000 kcal from supplement) in both the *Atole* and *Fresco* villages. Moreover, women in the highest tercile of intake during the first trimester consumed 138 kcal/d more than those in the lowest tercile and had pregnancies that were 1.4 wk longer. The proportions of low birthweight ( $< 2500$  g;  $P < 0.05$ ) and preterm ( $< 37$  wk gestational age;  $P < 0.001$ ) births also differed among women categorized by tercile of supplement intake during the first trimester (14).

In a more sophisticated treatment of these data, Villar et al. (15) separated preterm birth from intrauterine growth retardation (IUGR; birthweight  $< 10$ th percentile of a reference population) in the 623 infants for whom complete data were available. In this sample, IUGR was present in 27.8% of babies and 9.8% were born before term ( $< 37$  wk). In adjusted analyses, only low maternal head circumference and infant sex were independent risk factors for IUGR, but low energy supplementation, no protein supplementation (i.e. consumption of *Fresco*), low maternal arm circumference, and infant sex were independent risk factors for preterm birth. The authors concluded that a history of maternal malnutrition during childhood was associated with IUGR, but current malnutrition was

associated with preterm birth. Recent experimental research in sheep (16) and an observational study in women who experienced substantial seasonal changes in food availability (17) support the concept that maternal nutritional status at the time of conception may have a modest effect on preterm birth (18). The findings from the Oriente Study provided early evidence that preterm birth could be reduced by maternal supplementation during pregnancy.

### Supplementation and the outcome of lactation

Women who gained more weight during pregnancy lost less weight postpartum and continued to breast-feed longer than those who gained less weight during pregnancy (19). This finding led to studies of the association between supplementation and the duration of postpartum amenorrhea, which was an essential method of birth spacing in these communities at the time. The question of whether improving maternal nutritional status via supplementation during pregnancy and lactation would improve fecundity and, thus, fertility (20) is important, because it could lead to increased childbearing, which might be undesirable.

The duration of lactational amenorrhea was defined in the study as the interval between birth and the first incidence of 2 menses occurring within a 3-mo period (21), with the data on the return of menses collected during biweekly home visits. The median durations of lactation and postpartum amenorrhea for women were 18 and 14 mo, respectively (20), and were highly correlated ( $r = 0.63$ ;  $n = 334$ ;  $P < 0.01$ ). Indicators of past and present maternal nutritional status as well as supplement intake were all negatively correlated with the duration of postpartum amenorrhea (20).

Infant supplement intake was also negatively associated with the duration of postpartum amenorrhea. If the mothers desired, infants could receive *Atole* or *Fresco* from birth onward, with a special form of *Atole* used for those  $< 4$  mo of age (1). In addition, infant supplementation was associated with maternal supplement intake (an expected result because the mother usually took the child to the supplementation center) (21). Infant suckling is an essential determinant of milk production and, as a result, often of the duration of both lactation and lactational amenorrhea. In the Oriente Study, women were asked at the end of each trimester of lactation to recall the number of times that their children had been breast-fed on the preceding day (22). These data were used to show that the more frequently her child was breast-fed at 6, 9, and 12 mo of age, the higher the probability that the mother would remain amenorrheic (22).

These complex relationships led to several possible mechanisms by which the supplementation strategy used in the Oriente Study could have affected the duration of lactation (23). Kurz et al. (24,25) modeled these possibilities using data from 343 mothers and their singleton infants born 1973–75. Higher parity ( $P < 0.001$ ) and the child's weight gain during the first 3 mo of life ( $P < 0.01$ ) were independently associated with 1- to 3-mo longer periods of postpartum amenorrhea (25). When the child's intake of foods other than breast milk ( $P < 0.001$ ) was included in the model, maternal nutritional status was no longer a significant predictor of the duration of postpartum amenorrhea. In fact, the difference in amenorrhea was so small ( $\sim 0.5$  mo) that the authors calculated that "even if women experienced a large improvement in their nutritional status, they would not have time to bear even 1 additional child during their reproductive years." Kurz et al. (25) concluded that infant, not maternal, supplementation influences the length of postpartum amenorrhea (25). This result differs from that obtained in Gambia,

where women increased their food consumption much more than in the Oriente Study. The duration of postpartum amenorrhea was not measured in this study, but based on changes in maternal prolactin concentrations, Lunn et al. (26) estimated that supplementation during lactation could have shortened the period of amenorrhea by 21 wk. They did not account for the role of the infant, an important concern, because the Gambian infants were supplemented themselves beginning at 3 mo of age.

### Trade-offs between mother and fetus during pregnancy

The data from the Oriente Study have been unique in advancing our understanding of the nature of the trade-offs in the face of constrained nutrition between mother and fetus or infant during the reproductive cycle as well as among mother, fetus, and nursing when there is overlap of lactation with a subsequent pregnancy.

Direct evidence of a trade-off between maternal nutritional status and birthweight within a single pregnancy was provided by Olson (13), who used data from mothers of 384 singleton infants. She showed that the effect on birthweight of moving from the lowest to the highest quartile of supplement intake was only 80 g among women with higher subscapular skinfold thicknesses, but was 380 g among those with lower subscapular skinfold thicknesses. In contrast, the effects on maternal weight change (from the first trimester of pregnancy until 3 mo postpartum) of changing from lowest to highest supplementation category were 3.1 and  $-0.3$  kg, respectively. Thus, women in the Oriente Study with poorer current nutritional status (lower fat stores) had larger babies instead of increasing their own weight during the reproductive cycle. In contrast, those with better current nutritional status had only modestly larger babies and gained weight themselves during this same period.

When knee breadth was used as a measure of past (i.e. childhood) nutritional status in similar analyses, Olson (13) showed that the women with greater knee breadth had both a larger increase in birthweight (190 g compared with 10 g) and a greater weight gain themselves (1.6 kg compared with 0.9 kg) than those with lower knee breadth when moving from the lowest to highest quartile of supplement intake. This finding suggests that women who were malnourished as children are less able to respond to supplementation either by gaining weight themselves or by producing a larger baby.

Maternal nutritional status varies over the course of a reproductive cycle as women gain fat and weight during pregnancy, lose it during lactation, and then gain it again if they have the opportunity to recuperate nutritionally before becoming pregnant again (27). Women ( $n = 176$ ) with 2 consecutive pregnancies in the Oriente Study were categorized as low weight (initial weight  $\leq 50$  kg) or normal weight (initial weight  $> 50$  kg). Winkvist et al. (28) found that the low-weight women gained weight during the reproductive cycle, but their second infant tended to weigh less at birth than their prior infant. Higher intakes of the supplement were associated with less negative differences in birthweight among these women. In contrast, normal-weight women did not gain weight themselves during the reproductive cycle or have larger infants in the second compared with the prior birth, and these associations were not moderated by supplement intake.

In further modeling of these data, Winkvist et al. (29) illustrated the complexity of these relationships. For "un-supplemented" women (those in the lowest tercile of supplement intake), maternal weight gain and the birthweight of the baby changed from one pregnancy to the next differently as initial maternal weight (e.g. at the time of the first study pregnancy)

increased (Fig. 1). In particular, maternal weight change from one pregnancy to the next was positive (~1 kg) except for women who weighed ~46–50 kg. Birthweight change from one pregnancy to the next was negative until initial maternal weight was ~46 kg. Birthweight change was positive thereafter, but did not increase further after initial maternal weight reached ~48 kg. In contrast, “supplemented” women (those with supplement intakes in the 2 higher terciles) gained weight from one reproductive cycle to the next and their babies were ~175 g larger regardless of their initial weight (Fig. 1). Taken together, these results suggest that several groups of women could be defined by maternal weight: 1) those with lowest maternal weight initially gained weight from one pregnancy to the next, but their babies became smaller; 2) those with somewhat higher maternal weight initially did not gain themselves, but their babies did; and 3) those with the highest maternal weight initially gained themselves and their babies did as well. These results suggest that the maternal response to supplementation in terms of nutrient partitioning is much more complex than previously thought, even among women of ostensibly normal BMI.

Overlap of a new pregnancy with continuing lactation occurred in 50% of the 504 women with term, singleton births who had complete data in the Oriente Study (30). Of these women, 41% continued to breast-feed into the second trimester of pregnancy and 3% into the 3rd trimester. Overlap was associated with increased intake of the supplement during pregnancy but no reduction in birthweight (30). However, women with overlap tend to have short intervals between conceptions and, thus, limited opportunity for nutritional recuperation. Short recuperative intervals were also associated

with increased supplement intake and no reduction in birthweight; however, women with these short recuperative intervals had lower fat stores (30). Thus, in this situation, the trade-off between mother and fetus protected the fetus until the time of birth. There is evidence from subsequent research in Peru, however, that mothers who experience overlap are unable to produce as much milk and their infants do not grow as well as those who did not experience overlap (31).

## Conclusions

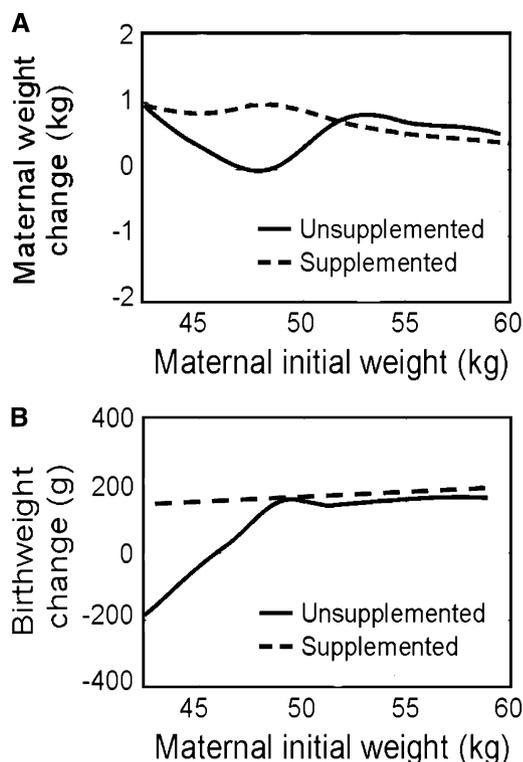
Many women did not choose to consume the supplements in the Oriente Study and those who did consumed widely varying amounts, with the neediest women consuming the most. The effect of supplementation on birthweight, due most likely to energy rather than to protein or micronutrients, was similar to that for other major determinants of birthweight, such as infant sex, primiparity, and smoking (32). Researchers identified several groups of women who benefited more than others by having babies with higher birthweights, including those with poorer current nutritional status and those who consumed high amounts of the supplement continuously from one pregnancy to the next. Results from this trial provided an early indication that supplementation might increase the duration of gestation and, thus, reduce preterm birth. Although the theoretical possibility existed that maternal supplementation during lactation would decrease postpartum amenorrhea, this did not turn out to be the case in the Oriente Study. Finally, exploratory research with data from the Oriente Study provided evidence of a biological trade-off between maintenance of maternal nutritional status and protection of fetal growth that was sensitive to both the mother’s maternal nutritional status and supplement intake but not to her nutritional status in childhood.

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**FIGURE 1** Association between initial maternal weight and change in maternal weight (A) and birthweight (B) from one pregnancy to the next. Mothers ( $n = 176$ ) who gave birth twice between 1971 and 1976 in the Oriente Study were included. The figure was prepared from data partially included in reference (29).

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