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Infant Growth After Maternal Dietary Supplementation Before and During Pregnancy

Of the estimated 140 million infants born each year in the world, approximately 20 million babies are born with a low birth weight (<2500 g),[1] and a partially overlapping 23 million are small for gestational age.[2] Besides having a markedly increased risk of mortality, these small newborns are vulnerable to growth failure, malnutrition, morbidity, and developmental delay in childhood and adverse health consequences in adult life.[3,4] Prevention of fetal growth restriction and low birth weight is therefore considered a public health priority, especially in Sub-Saharan Africa and South Asia, where the incidence is greatest.

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Because maternal undernutrition is a major risk factor for fetal growth restriction and low birth weight, antenatal dietary supplementation is a logical intervention to prevent these adverse pregnancy outcomes. Birth size can be increased by supplementing maternal diets with micronutrients or more comprehensive products with micro- and macronutrients and energy.[5,6] What has been less clear is whether it is important to start the dietary supplementation before or during pregnancy and whether the possible fetal growth gains in size are preserved after birth. These 2 questions were addressed in the Women First trial, in which nonpregnant women from Democratic Republic of Congo, Guatemala, India, and Pakistan were randomized to receive no supplementation (Arm 3) or dietary supplementation starting either before pregnancy (Arm 1) or at around 11 weeks of gestation (Arm 2) and continuing until delivery. All participants in Arms 1 and 2 received small-quantity, lipid-based nutrient supplements (SQ-LNS, 20 g/d, containing protein, fat, carbohydrates, multiple micronutrients, and 118 kcal energy). Women who became malnourished or failed to gain

LNS Lipid-based nutrient supplements
SQ Small-quantity

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weight adequately received an additional daily dose of medium-quantity LNS, providing macronutrients and 300 kcal but no micronutrients.

Results from an earlier meta-analysis indicated that provision of LNS to pregnant women has the potential of increasing mean birth-size, but the effect is modest and not seen in all contexts.[7] The primary results of the Women First trial, published last year, aligned well with the meta-analysis findings. There was no difference between the study arms in the duration of pregnancy, but babies in the intervention arms had on average approximately 0.2 z-score units greater length-for-age and 0.14 units greater weight-for age at birth than babies in control arm.[8] In this volume of *The Journal*, Krebs et al report 6-month postnatal follow-up results for 2421 infants in the Women First trial.[9] For these infants, there was a 3- to 4-mm difference in length and 60-g difference in weight at birth between both intervention arms and the control. In a 6-month follow-up, the differences remained essentially the same, indicating a persistence of growth benefits that resulted from maternal nutritional supplementation initiated before conception or at the end of the first trimester. Compared with the control arm, the overall adjusted relative risk (95% CI) for the prevalence of stunting (length-for-age <–2) during the follow-up period was 0.76 (0.66-0.87) for infants in Arm 1 and 0.77 (0.67-0.88) for infants in Arm 2.

There are surprisingly few earlier reports on infant growth from studies testing the impact of an antenatal maternal dietary intervention without a child supplementation component. In one earlier trial in Burkina Faso, in which women were daily provided with 72 g of LNS during pregnancy, there was a slightly bigger difference in newborn length at birth between the intervention and control group than observed in Women First trial, but the difference was lost within 6-12 months after delivery.[10] In contrast, in 2 Asian studies, one in Indonesia and the other one Bangladesh, antenatal dietary supplementation resulted in linear growth benefits that were reflected in a lower stunting prevalence until 5 years of age.[11,12] The Women First team attributes the contrasting findings to possible differences in study settings, baseline maternal nutritional status, and timing of the dietary intervention. These are feasible alternatives, but they do not fully explain the mechanism why fetal gains in size would persist in infancy in some contexts but not in others.

In most of the studies done so far, antenatally achieved gains in newborn size have persisted postnatally if they were achieved through faster linear growth in utero (as in the Women First trial), whereas gains obtained through ponderal growth (increase in weight for height) or elongation of pregnancy were mostly lost after birth. This is understandable, because weight-for-length follows dynamically the child's postnatal nutritional status, whereas accrued bone length will not be reduced even in adverse subsequent growth conditions. Intergroup differences in newborn length can, however, disappear if the taller group has a greater mean gestational age at birth, because immediate postnatal length gain velocity is inversely associated with the duration of pregnancy.

Besides the duration of effect, an important question related to maternal dietary supplementation is the optimal timing of the intervention and the relative importance of pre- and post-conception nutritional support. In the Women First Trial, there were no differences in the mean newborn size between the participants who started receiving supplements at least 3 months before pregnancy and those for whom the onset was around 11 weeks of gestation. In the 6-month follow-up, the point-estimates for attained size were slightly larger in the group that started getting the supplement already before pregnancy, but women in this group also received more often an additional therapeutic supplement, there was no group that would have received the intervention only later in pregnancy, and none of the observed differences were statistically significant. Hence, findings from the Women First trial must be considered inconclusive in terms of optimal time of onset for the dietary intervention. There is, however, a large, multicomponent trial going on in India, the results from which will hopefully provide more information on the relative importance of the pre-conceptional support for maternal diets.[13]

There is one further issue that is worth highlighting in the Women First follow-up findings, namely the reported safety data. Compared with the control group, infants whose mothers received dietary supplementation with SQ-LNS both before and during pregnancy had a relative risk (95% CI) of 1.56 (0.87-2.81) for neonatal mortality, 1.80 (1.09-2.97) for hospitalization, and 1.11 (0.99-1.24) for any reported health problem. For infants whose mothers received SQ-LNS only during pregnancy, the respective relative risks were 1.79 (1.08-2.97), 1.30 (0.77-2.21), and 1.05 (0.95-1.15). For the overall mortality between birth and 6 months of age, there were no intergroup differences. The authors refer to an earlier review that found no difference in neonatal mortality among infants whose mothers had received either SQ-LNS or iron-and folic acid[7] and conclude that the safety findings are probably due to chance. Although I, too, consider this the most likely explanation, there is also a possibility that increased mean birth size could increase the prevalence of cephalopelvic disproportion, leading to more frequent obstructed labor and possibly increased neonatal mortality, especially among stunted women.[14] Alternatively, an early nutritional intervention could influence the immunity or other biological pathways in the offspring. Normally this effect would be expected to be positive[15] but there is no reason why it could not paradoxically increase the vulnerability of the baby. Given the hospitalization and mortality data from the Women First trial, it seems important to monitor safety data also in any future trials providing LNS to women before or during pregnancy. ■

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Improving Advance Care Planning for Seriously Ill Children: Engaging a Diverse Research Population Early and Often

In this volume of *The Journal* DeCourcey et al describe the development of a new pediatric serious illness communication program to support providers in advance care planning conversations with their patients and families.[1] Despite advanced care planning long being considered the standard of care for patients with life-limiting or life-threatening conditions,[2] there is increasing awareness that pediatric providers still have room to improve.[3] To address this meaningful gap, the authors used a step-wise, rigorous approach to adapt an adult communication guide for children. Study participants found the work to have the potential to "augment current practice and reduce variation" in advance care planning for children with serious illness. This patient group, identified in the study by Feudtner et al, complex chronic conditions,[4] may be familiar to many readers as overlapping with if not synonymous with children with medical complexity.

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In addition to describing the development of the toolkit itself, the authors identified barriers to current advance care planning. These challenges will ring familiar to those providing time-intensive, conversation-focused medical care such as care coordination or mental and behavioral health, to include: barriers to incorporate care into current workflows, limited provider time, a need for usable documentation of the conversation in the electronic health record, and a gap in training impacting provider comfort with the care task itself. In particular, the authors highlighted that although interviewed providers expressed fears that initiating advanced care planning many cause anxiety or stress in their

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