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Infant growth after maternal dietary supplementation before and during pregnancy

Per Ashorn^{1,2}, MD, PhD

¹Tampere University, Faculty of Medicine and Health Technology, Center for Child Health Research, Tampere, Finland, ²Tampere University Hospital, Department of Paediatrics, Tampere, Finland

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Dr. Per Ashorn, Tampere University, Faculty of Medicine and Health Technology, Arvo Building, room D519, FIN-33014 Tampere University, Finland. Telephone: +358 40 7280 354, e-mail: per.ashorn@tuni.fi. Reprints will not be available from the author.

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EDITORIAL TEXT

Of the approximately 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 as small-for gestational age (SGA)². Besides having a markedly increased risk of mortality, these small new-borns are vulnerable to growth failure, malnutrition, morbidity, and developmental delay in childhood, and adverse health consequences in adult life³⁴.

Prevention of fetal growth restriction (FGR) and low birthweight (LBW) is therefore considered a public health priority, especially in Sub-Saharan Africa and South Asia where the incidence is highest.

Since maternal undernutrition is a major risk factor for FGR and LBW, antenatal dietary supplementation is a logical intervention to prevent these adverse pregnancy outcomes.

Several recent evidence syntheses have indeed shown that 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 two questions were addressed in the “Women First” trial, in which non-pregnant women from Democratic Republic of Congo, Guatemala, India, and Pakistan were randomised 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 / day, containing protein, fat, carbohydrates, multiple micronutrients, and 118 kcal energy); women who became malnourished or failed to gain 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 contexts⁷. 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 higher length-for-age (LAZ) and 0.14 units higher weight-for age (WAZ) at birth than babies in control arm⁸. In today's issue of the *Journal of Pediatrics*, Krebs and her collaborators report six-month post-natal follow-up results for 2421 infants in the Women First trial⁹. For these infants, there was a 3-4 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 prior to conception or at the end of the first trimester. Compared to the control Arm, the overall adjusted relative risk (95% CI) for the prevalence of stunting (LAZ <-2) during the follow-up period was 0.76 (0.66 to 0.87) for infants in Arm 1 and 0.77 (0.67 to 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 grams of LNS during pregnancy, there was a slightly bigger difference in new-born 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 delivery¹⁰. In contrast, in two 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 five 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 don't 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 new-born 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, since weight-for-length follows dynamically the child's post-natal nutritional status, whereas accrued bone length will not be reduced even in adverse subsequent growth conditions. Intergroup differences in new-born length can, however, disappear if the taller group has a higher 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 new-born size between the participants who started receiving supplements at least three months before pregnancy and those for whom the onset was around 11 weeks of gestation. In the six-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 soon provide more information on the relative importance of the pre-conceptional support for maternal diets¹³.

There is one further issue that is worth highlighting in the Women First follow-up findings, namely the reported safety data. Compared to the control group, infants whose mothers received dietary supplementation with SQ-LNS both before and during pregnancy had a relative risk (95% confidence interval) of 1.56 (0.87 to 2.81) for neonatal mortality, 1.80 (1.09 to 2.97) for hospitalization, and 1.11 (0.99 to 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 to 2.97), 1.30 (0.77 to 2.21), and 1.05 (0.95 to 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 acid⁷ and conclude that the safety findings are probably due to chance. Whilst I, too, consider this the most likely explanation, there is also a possibility that increased mean birth size could increase the prevalence of cephalo-pelvic disproportion, leading to more frequent obstructed labour and possibly increased neonatal mortality, especially among stunted women¹⁴. Alternatively, an early nutritional intervention could influence the immunity or other biological pathways in the offspring. Normally this effect would be expected to be positive¹⁵ 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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