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Commentary

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Antenatal Micronutrients and the Mitochondrial Genome: A Glimpse of Future Nutritional Investigation

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Antenatal micronutrient deficiency is a common threat to maternal health and pregnancy outcomes in low- and middle-income countries (1). Although effects of nutrient-dense dietary interventions during pregnancy remain to be clarified (2), large trials in undernourished regions, such as South Asia, indicate that antenatal multiple micronutrient (MM) supplementation, beyond iron–folic acid alone, can attenuate, if not eliminate, nutrient deficiencies (3), and reduce risks of low birth weight, fetal loss, and infant mortality (4, 5). These effects have been broadly affirmed across low-income regions of the world (6). Whereas compelling evidence of pregnancy benefit accrues, molecular, cellular, and physiological pathways that explain overall, as well as differential, effects of antenatal MM interventions remain largely presumptive. This is a gap in knowledge and insight that promises to be filled by a nutritional omics revolution in the coming decades (7).

Materno-feto-placental cellular health, a sine qua non for successful gestation, is affected by nutriture in a myriad of ways (1). Although all cellular organelles have critical roles in nutrient metabolism, we focus this commentary on the mitochondrion (mt). This organelle is unique in having its own DNA which codes for respiratory chain complex proteins essential to transform nutrients into ATP that fuels cellular growth, replication, differentiation, redox balance, and programmed death (8). Typically, 1–15 circular mitochondrial DNA (mtDNA) molecules (16.6 kb in size) reside in each organelle providing 100–10,000 copies within each human cell. The mtDNA copy number (CN) varies by cell type and has been observed to be elevated in the presence of nutritional stresses, reflected in blood samples (9) and placentas (10) of pregnancies ending in fetal growth restriction or low birth weight.

In this issue, Priliani et al. (11) report, in pregnant women participating in SUMMIT (Supplementation with Multiple Micronutrients Intervention Trial) in Lombok, Indonesia (4), that mtDNA-CN from maternal blood samples collected at baseline and postsupplementation during pregnancy increased less (and thus, stabilized) in response to MM relative to IFA supplementation. This was interpreted to indicate that gestational MM exposure attenuated the need for mtDNA replication (or mitogenesis) because it prevented impaired mt function that may have resulted from micronutrient deficiencies. Supporting this inference, the authors cite roles of vitamins C and E and zinc as antioxidants; zinc, copper, and selenium in antioxidant enzymes; and B-vitamins as cofactors in mt energy metabolism, among other functions. The effect of MM supplementation on mtDNA-CN was more pronounced in women with a higher baseline CN, suggesting greater benefit in higher-risk women, and appeared rapidly, evident within 33 d of exposure to the supplements.

The study by Priliani et al. (11) provides initial supportive evidence for the hypothesis that antenatal MM supplementation may improve mt efficiency and function during pregnancy, offering a plausible bioenergetics pathway by which birth weight could increase via improved micronutrient nutriture. Some caution, however, is advised in drawing inferences from variation in mtDNA-CN alone, which can be aided by additional measurements. Specifically, the qPCR assay used for detection fails to distinguish DNA from mts that are functional compared with dysfunctional owing to mtDNA deletions that may occur, for example, after nutritional stress (12). The assay also does not distinguish DNA retained within functional mts from DNA that may leak into cytoplasm from damaged mts, the latter being important because of its proinflammatory and autoimmune properties (13). Measurement of both features of mtDNA (i.e., deletions and content) would provide insight into mitochondrial functionality. Future studies would also benefit from concurrently assessing the extent of mitophagy (autophagy of mts), which is inhibited during nutrient excess, leading to accumulation of defective mts, and activated during micronutrient deprivation to eliminate dysfunctional mts (14). A further rational extension of the present work is to also consider assessing nutritional effects on the nuclear genome, which strongly regulates mt biogenesis, to include biomarkers of genomic instability such as micronuclei, shortened telomere length, and DNA methylation that are measurable in blood or buccal cells and may be predictive of developmental and degenerative diseases (15).

Close attention to features of study design may also assist future research into mtDNA and extended biomarker responses

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Abbreviations used: CN, copy number; MM, micronutrient; mt, mitochondrion; mtDNA, mitochondrial DNA; SUMMIT, Supplementation with Multiple Micronutrients Intervention Trial.

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to antenatal nutrient supplementation. In the current study, baseline and follow-up mtDNA-CNs were assessed between ~4 and 36 weeks of gestation, with IQRs of MM and IFA supplement receipt of 51 and 88 d, respectively, over which metabolic demands of pregnancy are known to greatly increase. With far less known about variation in mtDNA-CN and other maternal cellular health biomarkers over the course of pregnancy, gains in precision can be expected by achieving uniformly timed early and late gestational measurement and comparable duration of randomly assigned supplement receipt. Postpartum assessment would also provide information about whether differences extend beyond pregnancy. Larger sample sizes per group would improve power to examine the influence of potentially important maternal nutritional factors such as anemia status or body mass (e.g., assessed by anthropometric indicators) on mtDNA-CN, both of which have been shown to interact with MM supplementation in affecting birth outcomes (4, 16). A final concern, more for epidemiological studies than randomized trials, relates to a need to count numbers and ratios of white blood cell subsets and platelets in which mtDNA content can vary substantially and thus confound associations (17).

The SUMMIT, on the rural island of Lombok, offers a glimpse of the future in this emerging century of public health nutriomics: one that integrates applied transomics research to probe molecular pathways that can explain diverse effects of nutrition interventions. Alone, neither area of research is sufficient, illustrated by a lack of mechanisms invoked to explain the many possible health effects of antenatal MM supplementation (6), and the uncertain meaning of a relative reduction in mtDNA-CN on its own. With further expansion of the nutritional omics repertoire (18), we are likely to have a far better chance to reveal, understand, and prevent micronutrient deficiencies in the decades ahead.

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References

1. Gernand AD, Schulze KJ, Stewart CP, West KP, Jr, Christian P. Micronutrient deficiencies in pregnancy worldwide: health effects and prevention. Nat Rev Endocrinol 2016;12(5):274–89.
2. Potdar RD, Sahariah SA, Gandhi M, Kehoe SH, Brown N, Sane H, Dayama M, Jha S, Lawande A, Coakley PJ, et al. Improving women's diet quality preconceptionally and during gestation: effects on birth weight and prevalence of low birth weight—a randomized controlled efficacy trial in India (Mumbai Maternal Nutrition Project). Am J Clin Nutr 2014;100:1257–68.
3. Schulze KJ, Mehra S, Shaikh S, Ali H, Shamim AA, Wu LS-F, Mitra M, Arguello MA, Kmush B, Sungpuag P, et al. Antenatal multiple micronutrient supplementation compared to iron-folic acid affects micronutrient status but does not eliminate deficiencies in a randomized controlled trial among pregnant women of rural Bangladesh. J Nutr 2019;149:1260–70 .
4. Supplementation with Multiple Micronutrients Intervention Trial (SUMMIT) Study Group, Shankar AH, Jahari AB, Sebayang SK, Aditiawarman, Apriatni M, Harefa B, Muadz H, Soesbandoro SD, Tjiong R, et al. Effect of maternal multiple micronutrient supplementation on fetal loss and infant death in Indonesia: a double-blind cluster-randomised trial. Lancet 2008;371(9608): 215–27.
5. West KP, Jr, Shamim AA, Mehra S, Labrique AB, Ali H, Shaikh S, Klemm RDW, Wu LSF, Mitra M, Haque R, et al. Effect of maternal multiple micronutrient vs. iron-folic acid supplementation on infant mortality and adverse birth outcomes in rural Bangladesh: the JiVitA-3 randomized trial. JAMA 2014;312:2649–58.
6. Keats EC, Haider BA, Tam E, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy. Cochrane Database Syst Rev 2019;3:CD004905.
7. Fenech M, El-Sohemy A, Cahill L, Ferguson LR, French T-AC, Tai ES, Milner J, Koh W-P, Xie L, Zucker M, et al. Nutrigenetics and nutrigenomics: viewpoints on the current status and applications in nutrition research and practice. J Nutrigenet Nutrigenomics 2011;4:69–89.
8. Dhillon VS, Fenech M. Mutations that affect mitochondrial functions and their association with neurodegenerative diseases. Mutat Res Rev Mutat Res 2014;759:1–13.
9. Priliani L, Febinia CA, Kamal B, Shankar AH, Malik SG. Increased mitochondrial DNA copy number in maternal peripheral blood is associated with low birth weight in Lombok, Indonesia. Placenta 2018;70:1–3.
10. Lattuada D, Colleoni F, Martinelli A, Garretto A, Magni R, Radaelli T, Cetin I. Higher mitochondrial DNA content in human IUGR placenta. Placenta 2008;29(12):1029–33.
11. Priliani L, Prado EL, Restauadi R, Waturangi DE, Shankar AH, Malik SG. Maternal multiple micronutrient supplementation stabilized mitochondrial DNA copy number in pregnant women in Lombok, Indonesia. J Nutr 2019;149:1309–16.
12. Chou Y-F, Huang R-FS. Mitochondrial DNA deletions of blood lymphocytes as genetic markers of low folate-related mitochondrial genotoxicity in peripheral tissues. Eur J Nutr 2009;48(7):429–36.
13. West AP, Khoury-Hanold W, Staron M, Tal MC, Pineda CM, Lang SM, Bestwick M, Duguay BA, Raimundo N, MacDuff DA, et al. Mitochondrial DNA stress primes the antiviral innate immune response. Nature 2015;520(7548):553–7.
14. van Niekerk G, du Toit A, Loos B, Engelbrecht AM. Nutrient excess and autophagic deficiency: explaining metabolic diseases in obesity. Metabolism 2018;82:14–21.
15. Fenech MF. Dietary reference values of individual micronutrients and nutriomes for genome damage prevention: current status and a road map to the future. Am J Clin Nutr 2010;91(5):1438S–54S.
16. Smith ER, Shankar AH, Wu LS, Aboud S, Adu-Afarwuah S, Ali H, Agustina R, Arifeen S, Ashorn P, Bhutta ZA, et al. Modifiers of the effect of maternal multiple micronutrient supplementation on stillbirth, birth outcomes, and infant mortality: a meta-analysis of individual patient data from 17 randomised trials in low-income and middle-income countries. Lancet Glob Health 2017;5(11):e1090–e100.
17. Moore AZ, Ding J, Tuke MA, Wood AR, Bandinelli S, Frayling TM, Ferrucci L. Influence of cell distribution and diabetes status on the association between mitochondrial DNA copy number and aging phenotypes in the InCHIANTI study. Aging Cell 2018;17(1): e12683.
18. Cole RN, Ruczinski I, Schulze K, Christian P, Herbrich S, Wu L, DeVine LR, O'Meally RN, Shrestha S, Boronina TN, et al. The plasma proteome detects expected and novel proteins correlated with micronutrient status in undernourished Nepalese children. J Nutr 2013;143:1540–8.

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