Metabolic programming of offspring by vitamin B₁₂/folate imbalance during pregnancy

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With two reports in the current issue of *Diabetologia*, C. S. Yajnik and his international cast of collaborators have created conceptual bridges between some of the most important global public health challenges of our time: obesity (or is it adiposity?), fetal or early life origins of adult disease, and prevalent and persisting micronutrient malnutrition [1, 2]. One study from the cohort within the Pune Maternal Nutrition Study allows analysis of the relationship between maternal nutritional status and mid- and late pregnancy and childhood outcomes at 6 years of age [1]. A striking finding was that two-thirds of the mothers had low circulating levels of vitamin B₁₂; their offspring were short and thin, but had more body fat. This was associated with a high prevalence of insulin resistance, presumably presaging later entry into the epidemic of type 2 diabetes among adults in India. From this novel focus comes the observation that the combination or interaction of vitamin B₁₂ deficiency and high erythrocyte folate in mothers is associated with the highest prevalence of insulin resistance according to homeostatic model assessment of insulin resistance.

This provides confirmation of a previous study reporting childhood insulin resistance in association with higher

adiposity and thinness (presumably with low lean mass) [3]. The observation of low vitamin B₁₂ status in mothers [1] was not surprising, given the high prevalence of vegetarian dietary habits, but the relationship to later insulin resistance and adiposity in the offspring provides a powerful challenge for further work to explain this relationship and its persistence in the offspring.

While the evidence presented by Yajnik et al. [1] does not distinguish between the positive relationship between adiposity and insulin resistance, as opposed to an inverse relationship between low lean or muscle mass and insulin resistance, these data call out for a mechanistic explanation of the relationship between micronutrient changes in the mother in late pregnancy and persisting metabolic/functional abnormalities in the offspring. Some suggestions are offered by the authors, although with no supporting data as yet. The concept of fetal or early infancy programming of later metabolic and disease outcomes is well described [4, 5], even though the mechanism by which programming in fetal life or infancy might be sustained remains unexplained. We know that the two micronutrients in this report are related metabolically, and that both folate and vitamin B₁₂ are involved in DNA synthesis and methylation—actions at the core of what has been called epigenetics.

Folate in particular is related to the efficiency of DNA methylation, which in turn has lasting effects on selected metabolic processes through the ability of strategic DNA methylation to promote or silence gene expression. One of the two known functions of vitamin B₁₂ as a cofactor in the methionine synthase reaction (Fig. 1), which converts homocysteine into methionine, depends on methylfolate to provide the methyl group, and methionine is converted into S-adenosyl methionine, which is subsequently utilised in dozens of methylation reactions, including methylation of

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Fig. 1 Vitamin B₁₂/folate interactions

DNA. It is possible that the imbalance of adequate cytosolic folate methyl donor and insufficient vitamin B₁₂ cofactor might drive the reaction towards methionine synthesis, leading to the further depletion of mitochondrial vitamin B₁₂ stores. This could result in an even greater dysfunction of the other B₁₂-dependent reaction, methylmalonyl coenzyme A mutase, which may well be a key reaction in the synthesis and control of fatty acid and adipose tissue. The possibility of epigenetic manipulation of those processes in metabolic programming might be paired with metabolic blockade induced by vitamin B₁₂ deficiency at both methylation and mutase reactions.

In addition to the great need for studies that examine this relationship between vitamin B₁₂ and folate, there are other intriguing observations emerging from the follow-up of folic acid fortification of flour in the USA and Canada [6], which suggest that too much folate in the presence of vitamin B₁₂ insufficiency may be a formula for adverse effects. Such effects were not considered at the time of the decision to fortify flour with folic acid to prevent neural tube defect births. In the face of this current study and other

observations, the clamour for global flour fortification with folic acid to prevent neural tube defects will need to be tempered by increasing consideration of the need to reverse vitamin B₁₂ deficiency in those populations at special risk, such as vegetarians in India. The Pune group and their collaborators have provided us with a strong stimulus towards further understanding of the possibly fundamental relationship between micronutrient insufficiency in mothers and metabolic outcomes in offspring, which seriously overlap with the growing global concern about obesity and adiposity. These studies also add to the growing realisation that vitamin B₁₂ insufficiency deserves to be considered, along with some of the other micronutrient deficiencies, as a problem of paramount public health importance.

References

1. Yajnik CS, Deshpande SS, Jackson AA et al (2008) Vitamin B₁₂ and folate concentrations during pregnancy and insulin resistance in the offspring: The Pune Maternal Nutrition Study. *Diabetologia* DOI [10.1007/s00125-007-0793-y](https://doi.org/10.1007/s00125-007-0793-y)
2. Yajnik CS, Joglekar CV, Lubree HG et al (2008) Adiposity, inflammation and hyperglycaemia in rural and urban Indian men: Coronary Risk of Insulin Sensitivity in Indian Subjects (CRISIS) Study. *Diabetologia* DOI [10.1007/s00125-007-0847-1](https://doi.org/10.1007/s00125-007-0847-1)
3. Bavdekar A, Yajnik CS, Fall CHD et al (1999) Insulin resistance in 8 year old Indian children, small at birth, big at 8 years, or both? *Diabetes* 48:2422–2429
4. Hales CN, Barker DJP (1992) Type 2 (non-insulin dependent) diabetes mellitus: the thrifty phenotype hypothesis. *Diabetologia* 35:595–601
5. Gopalan C (1994) Low birthweight: significance and implications. In: Sachdev HPS, Chaudhary P (eds) *Nutrition in children: developing country concerns*. Imprint, New Delhi
6. Morris MS, Jacques PF, Rosenberg IH, Selhub J (2007) Folate and vitamin B-12 status in relation to anemia, macrocytosis, and cognitive impairment in older Americans in the age of folic acid fortification. *Am J Clin Nutr* 85:193–200