The Journal of Nutrition
Commentary

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Adequate Intake of Biotin in Pregnancy: Why Bother?[1,2]

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Frank, symptomatic biotin deficiency is a rare occurrence. The only well-documented cases have occurred in association with total or near total intravenous feeding without biotin supplementation, during chronic consumption of un-denatured egg white, and with inborn errors of metabolism that lead to biotin wasting (1, 2). A single case that does not fit any of these established associations is that of an infant fed a rice-based formula that was presumably very low in biotin (1). However, there are observations suggesting that the absence of overt biotin deficiency does not imply optimal biotin nutritional status.

Pregnancy is a clinical condition of particular concern. Studies in several animal species, including mice, hamsters, chickens, and turkeys, showed that biotin deficiency is teratogenic (3). For example, fetuses of marginally biotin-deficient mouse dams have a high incidence of skeletal malformations including >50% incidences of cleft palate, micrognathia, microglossia, and fore- and hind-limb shortening (4). Yet, these mouse dams show only metabolic abnormalities. The dams gain weight normally and show no physical signs of biotin deficiency (3, 4); neither reproductive efficiency nor fetal weight gain is affected.

Several observations suggest that this mouse model of biotin deficiency is relevant to human gestation. In these biotin-deficient mouse dams, a 2- to 3-fold increase in urinary excretion of 3-hydroxyisovaleric acid (3HIA)[3], which reflects reduced activity of the biotin-dependent enzyme methylcrotonyl–CoA carboxylase, occurs early in the pregnancy; the timing and magnitude of the increase is similar to the 3HIA increase that occurs spontaneously during the first trimester of human pregnancy (3). The increase in 3HIA tends to persist throughout pregnancy and will normalize (or at least return to near normal) with 2 wk of supplementation with 300 μg/d of biotin (5), which is 10 times the current Adequate Intake (AI) for biotin. The women who develop this marginal degree of biotin deficiency gain weight normally during pregnancy and show no overt signs of biotin deficiency (3).

The apparent disconnect between a modest reduction in murine maternal biotin status and the major effects on fetal skeletal development might result from the mouse fetus being a notably poor parasite for biotin (3). Indeed, marginal biotin deficiency in the mouse dam results in severe biotin deficiency in the fetus. For example, in dams fed a 5% egg-white diet, hepatic propionyl-CoA carboxylase activity decreases to 70% of that in control dams; however, in the fetuses of these same biotin-deficient dams, hepatic propionyl-CoA carboxylase activity decreases to 14% of the activity of fetuses of the control dams (4, 6). Consistent with this observation, placental transport of biotin is likely inadequate both in human pregnancy and in mice (1, 3).

In this context, the article by Perry et al. (7) reported in this issue of *The Journal of Nutrition* is a landmark study. This is the first human pregnancy study that controlled dietary biotin intake and is also the first to quantitate the biotin content of the diet. This is the first ever study that controlled and quantitated biotin intake in lactating women and in the comparison nonpregnant women. Solid evidence of increased 3HIA excretion is provided, confirming previous reports that marginal biotin deficiency occurs spontaneously in a substantial proportion of women during normal human pregnancy. Moreover, reasonable evidence is provided to support the inference that a biotin intake at least 2–3 times the AI is likely needed to meet the requirement of pregnancy.

Whether caused by genetic defects or by biotin deficiency (1, 2), reduced activity of methylcrotonyl-CoA carboxylase leads to accumulation of its substrate 3-methylcrotonyl CoA. Because acyl-CoA compounds are compartmentalized within the mitochondria, accumulation of 3-methylcrotonyl CoA and 3-hydroxyisovaleryl CoA would lead to a disruption of the esterified CoA to free CoA ratios and, ultimately, to potentially lethal mitochondrial toxicity (8, 9). To prevent this, 3HIA-CoA is detoxified by carnitine transesterification to 3HIA-carnitine (3HIAc). The reaction is catalyzed by carnitine acetyltransferase, which is one of a family of enzymes with varying chain length specificity and organelle and organ distribution; these act in concert with transfer of the acylcarnitine out of the mitochondria by carnitine-acylcarnitine translocase to defend the CoA ratios (9). Accumulating 3HIAc is transferred across the inner mitochondrial membrane by the translocase, leading to increased plasma and urinary 3HIAc and 3HIA (10, 11) and potentially to secondary carnitine deficiency (12). 3HIA likely arises preferentially from hydrolysis of 3HIAc in the cytosol.

Urinary 3HIAc is a sensitive indicator of marginal biotin deficiency in healthy adults in whom biotin deficiency is induced experimentally (10). Interestingly, urinary excretion of 3HIAc was actually lower among pregnant women than in nonpregnant control women, indicating that urinary 3HIAc is not a reliable indicator of marginal biotin deficiency in pregnancy. We have observed this same unreliability of urinary 3HIAc in pregnancy (unpublished data). Our research group confirmed the metabolic pathogenesis presented above in hepatocyte culture by inducing separate and combined biotin and carnitine deficiency (13).

[1] Supported by NIH grants R37 DK 36823 (DMM), R37 DK36823-26S1 (DMM), RO1 DK79890, and DK79890-01S1 (DMM) and the University of Arkansas for Medical Sciences Clinical Translation Science Award UL1 TR000039.

[2] Author disclosures: DM Mock, no conflicts of interest.

[3] Abbreviations used: AI, Adequate Intake; 3HIA, 3-hydroxyisovaleric acid; 3HIAc, 3-hydroxyisovaleric acid–carnitine.

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Manuscript received September 8, 2014. Initial review completed September 29, 2014. Revision accepted September 29, 2014.
First published online October 15, 2014; doi:10.3945/jn.114.203356.

Thus, the assertion by Perry et al. that failure of urinary 3HIAc to increase in parallel with urinary 3HIA is evidence of functional hepatic carnitine deficiency is reasonable and consistent with established biochemical mechanisms. This observation raises the possibility that this functional carnitine deficiency impairs an important cellular detoxification mechanism that defends mitochondrial energetics.

The article by Perry et al. also offers intriguing observations concerning biotin metabolism. Accelerated biotransformation of biotin to bisnorbiotin, an inactive metabolite created by β oxidation of the valeric acid side chain, has been observed in early pregnancy, but bisnorbiotin excretion had returned to normal by late in pregnancy (14), consistent with the observations of Perry et al. who observed normal metabolite excretion as well as normal plasma concentrations of biotin and biotin metabolites. Thus, the pathogenesis of biotin deficiency in pregnancy remains to be elucidated. Of note, Perry et al. did observe substantially increased excretion of bisnorbiotin during lactation, which was accompanied by decreased, rather than increased, 3HIA excretion.

Finally, the work of Perry et al. (7) is commendable from an additional standpoint. In a time in which competition for extramural and intramural funding to support biomedical research in an academic environment is particularly difficult, these investigators demonstrated admirable foresight in conducting the original randomized choline intervention study in a way that permitted further research. Moreover, these investigators exhibit admirable creativity in considering an additional micronutrient, admirable resourcefulness in adapting the sample availability to study biotin nutrition, and appropriate candor in describing the adaptation.

In summary, the article by Perry et al. makes fundamental observations about biotin status in pregnancy and lactation, offers reasonable inferences concerning inadequacy of the current AI for biotin in pregnancy, and raises intriguing questions about the resulting metabolic disturbances and interactions of those disturbances with carnitine status that might impair a mitochondrial defense mechanism. Hamid Said, an eminent investigator in biotin nutrition and physiology, asked more than a decade ago (15): "Biotin bioavailability and adequate intake: why bother?" The study by Perry et al. provides new evidence that the bother is worthwhile.

Acknowledgments

The sole author had responsibility for all parts of the manuscript.

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