

## Choline, homocysteine, and pregnancy<sup>1-3</sup>

Steven H Zeisel

Choline is a dietary component essential for the structural integrity and signaling functions of cell membranes; it directly affects cholinergic neurotransmission and lipid transport from liver, and it is the major source of methyl groups in the diet (betaine, one of choline's metabolites, participates in the methylation of homocysteine to form methionine) (1). In many mammals, including baboons, prolonged (weeks to months) ingestion of a diet deficient in choline but adequate, though limited, in methionine and folate has consequences that include hepatic, renal, pancreatic, memory, and growth disorders (1). A sign of organ dysfunction that occurs when humans are deprived of choline is the development of fatty liver (2, 3), because a lack of phosphatidylcholine limits the export of excess triacylglycerols from the liver (4). Also, choline deficiency is associated with liver cell death (2). An additional sign of choline deficiency is muscle cell damage, which is measured by greatly elevated creatine phosphokinase activity in serum (5). Another sign of organ dysfunction that develops in humans who are fed a low-choline diet is an exaggerated increase in plasma total homocysteine (tHcy) after a methionine load (6). Hcy can be methylated to form methionine (7) by 2 parallel pathways, both of which lower tHcy concentrations (8). In the first, vitamin B-12 and folic acid are involved in a reaction that is catalyzed by methionine synthase (9). The alternative pathway for the methylation of Hcy to form methionine is catalyzed by betaine homocysteine methyltransferase (10) and uses betaine, a metabolite of choline, as the methyl-group donor. In this issue of the Journal, Molloy et al (11) report that plasma choline and betaine concentrations increase during pregnancy and that this is highly correlated with an increase in plasma tHcy concentrations. This is an unexpected and important observation, because Hcy is thought to be toxic for the fetus. The authors speculate that 2 mechanisms could explain this correlation: 1) pregnancy depletes choline and betaine in the liver (perhaps to maintain plasma choline concentrations for delivery to the fetus), and this results in reduced methylation of Hcy; or 2) pregnancy induces endogenous synthesis of choline via a pathway that also produces Hcy.

The demand for choline is especially high during pregnancy and lactation because of transport of choline from mother to fetus (12, 13). In rats, the concentration of choline in maternal liver falls from a mean of 130  $\mu\text{mol/L}$  in adult nonpregnant rats to 38  $\mu\text{mol/L}$  in late pregnancy (14). Molloy et al (11) report that, as expected, fetal venous plasma choline concentrations are 3-fold higher than are maternal plasma choline concentrations. They observed choline concentrations in the mother's blood at the time of delivery that were within the normal range for nonpregnant

persons and that were not low. Molloy and colleagues speculate that plasma choline concentrations may be preserved at the expense of depleting liver choline concentrations. If so, their data are entirely consistent with hypothesis no. 1, ie, that the rate of Hcy removal by the liver is diminished in pregnancy. If, however, plasma choline concentrations are a direct reflection of hepatic choline concentrations, then one would expect Hcy methylation to proceed at normal rates in the liver.


The only source of choline other than the diet is from the de novo biosynthesis of phosphatidylcholine, which is catalyzed by phosphatidylethanolamine *N*-methyltransferase (PEMT). This enzyme methylates phosphatidylethanolamine using *S*-adenosylmethionine as a methyl donor, forms a new choline moiety, and forms 3 Hcy molecules (15). PEMT expression increases during choline deficiency (16). It is possible that the increased demands for choline during pregnancy lower hepatic choline concentrations and thereby induce PEMT activity. If so, increased Hcy production would be observed, which would be consistent with Molloy's hypothesis no. 2. If, however, plasma choline concentrations are a direct reflection of hepatic choline concentrations, then one would have to postulate that PEMT must be activated by some other factor related to pregnancy, perhaps by estrogen. In fact, it is likely that the *PEMT* gene is an estrogen-responsive gene (17).

Whatever the mechanism, pregnancy is a time when tHcy is thought to negatively influence fetal development, and it is important that future studies determine whether choline supplementation during pregnancy lowers tHcy concentrations. In addition, choline is particularly important during the perinatal period because it appears to change brain development. When rodent dams received choline supplements [during days 12–17 of gestation (E12–17)], their offspring had a significant and lifelong enhancement of spatial memory and attention (18). Dietary sources of choline are enumerated in a website maintained by the US Department of Agriculture (<http://www.nal.usda.gov/fnic/>)

<sup>1</sup> From the Department of Nutrition, School of Public Health and School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC.

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<sup>3</sup> Reprints not available. Address correspondence to SH Zeisel, Department of Nutrition, School of Public Health and School of Medicine, University of North Carolina at Chapel Hill, CB# 7461, Chapel Hill, NC 27599. E-mail: steven\_zeisel@unc.edu.

foodcomp/Data/Choline/Choline.html). A recent paper by Shaw et al (19) reported that dietary intake of choline varied enough in California women to influence pregnancy outcome: in women with low dietary folate intake, those who consumed the lowest choline amounts in the diet had 4 times the risk of having a baby with a neural tube defect that did the women who consumed the highest amounts of choline. Perhaps the observations of Molloy et al in this issue of the Journal (11) begin to explain how choline might modify the risk of birth defects. 

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