Abstract


**Moderate folic acid supplementation and MTHFD1-synthetase deficiency in mice, a model for the R653Q variant, result in embryonic defects and abnormal placental development.**


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**BACKGROUND:** Moderately high folic acid intake in pregnant women has led to concerns about deleterious effects on the mother and fetus. Common polymorphisms in folate genes, such as methylenetetrahydrofolate dehydrogenase-methenyltetrahydrofolate cyclohydrolase-formyltetrahydrofolate synthetase (MTHFD1) R653Q, may modulate the effects of elevated folic acid intake.

**OBJECTIVES:** We investigated the effects of moderate folic acid supplementation on reproductive outcomes and assessed the potential interaction of the supplemented diet with MTHFD1-synthetase (Mthfd1S) deficiency in mice, which is a model for the R653Q variant.

**DESIGN:** Female Mthfd1S+/+ and Mthfd1S+/- mice were fed a folic acid-supplemented diet (FASD) (5-fold higher than recommended) or control diets before mating and during pregnancy. Embryos and placentas were assessed for developmental defects at embryonic day 10.5 (E10.5). Maternal folate and choline metabolites and gene expression in folate-related pathways were examined.

**RESULTS:** The combination of FASD and maternal MTHFD1-synthetase deficiency led to a greater incidence of defects in E10.5 embryos (diet × maternal genotype, \( P = 0.0016 \); diet × embryonic genotype, \( P = 0.054 \)). The methylenetetrahydrofolate reductase (MTHFR) protein and methylation potential [ratio of S-adenosylmethionine (major methyl donor):S-adenosylhomocysteine] were reduced in maternal liver. Although 5-methyltetrahydrofolate (methylTHF) was higher in maternal circulation, the methylation potential was lower in embryos. The presence of developmental delays and defects in Mthfd1S+/- embryos was associated with placental defects (\( P = 0.003 \)). The labyrinth layer failed to form properly in the majority of abnormal placentas, which compromised the integration of the maternal and fetal circulation and presumably the transfer of methylTHF and other nutrients.

**CONCLUSIONS:** Moderately higher folate intake and MTHFD1-synthetase deficiency in pregnant mice result in a lower methylation potential in maternal liver and embryos and a greater incidence of defects in embryos. Although maternal circulating methylTHF was higher, it may not have reached the embryos because of abnormal placental development; abnormal placentas were observed predominantly in abnormally developed embryos. These findings have implications for women with high folate intakes, particularly if they are polymorphic for MTHFD1 R653Q.

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