Maternal methylenetetrahydrofolate reductase deficiency and low dietary folate lead to adverse reproductive outcomes and congenital heart defects in mice [1,2,3]

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Abstract

Background: Genetic or nutritional disturbances in folate metabolism may affect embryonic development because of the critical role of folate in nucleotide synthesis and methylation reactions. The possible role of a mild deficiency in methylenetetrahydrofolate reductase (MTHFR) and low dietary folate in pregnancy outcomes and heart morphogenesis requires further investigation.

Objective: We investigated the effect of mild MTHFR deficiency, low dietary folate, or both on resorption rates, on length and weight, and on the incidence of heart malformations in murine embryos.

Design: Female *Mthfr* +/+ and +/− mice were fed a control diet (CD) or a folic acid–deficient diet (FADD) before mating with male *Mthfr* +/− mice. On gestational day 14.5, implantation and resorption sites were recorded and viable embryos were examined for gross malformations, growth delay, and congenital heart defects.

Results: Plasma homocysteine in *Mthfr* +/− dams and in FADD-treated dams was significantly higher than that in *Mthfr* +/+ dams and CD-treated dams, respectively. A significantly higher rate of resorption and greater developmental delay were observed in hyperhomocysteinemic mice than in CD-treated +/+ dams. Heart defects were identified in 4 of 11, 5 of 10, and 4 of 10 litters from CD-treated +/−, FADD-treated +/+, and FADD-treated +/− dams, respectively, but not in any of those from CD-treated +/+ dams (0/11 litters).

Conclusion: Our findings suggest that mild MTHFR deficiency, low dietary folate, or both in the dams increase the incidence of fetal loss, intrauterine growth retardation, and heart defects. These data support the benefit of folic acid supplementation in pregnant women, particularly in those with MTHFR deficiency.