

学位論文内容の要旨

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学 位 論 文 題 名

Maternal smoking and polymorphism in the folate-metabolizing enzyme gene 5,10-*MTHFR* affects infant's birth weight

(出生時体重に影響を及ぼす母の喫煙と葉酸代謝酵素遺伝子多型との関連)

Background: The complexities surrounding the aetiopathophysiological processes associated with infant's sub-optimal birthweight owing to the short and long term health consequences has drawn enormous epidemiologic research interest. Adequate maternal folate status is an index of optimal fetal growth. Conversely, tobacco smoke depletes folate and impairs fetal growth and 5,10-*MTHFR* 677TT homozygosity is also associated with low folate status, we hypothesized that maternal smoking in the presence of 5,10-*MTHFR* C677T and A1298C polymorphisms may adversely reduce offspring's birthweight.

Methods : Participants were 4121 native Japanese mother-child pairs drawn from the ongoing birth cohort of The Hokkaido Study on Environment and Children's Health. Data was extracted from the February 2003 to March 2006 recruitment. Biochemical assays of first trimester maternal serum folate and genotyping of 5,10-*MTHFR* C677T and A1298C polymorphisms were obtained using chemiluminescent immunoassay and Taqman allelic discrimination assay respectively.

Results : Maternal mean serum folate was 17.4 ± 7.0 nmol/L. Prevalence of low folate status was 28.4%. Use of folic acid supplement was positively associated with folate status and users were more likely to have used other forms of nutritional supplements previously, AOR [95%CI] = 10.9 [8.5, 14.0], $p < 0.001$; had previous sub-fertility treatment, AOR [95%CI] = 1.7 [1.0, 2.9], $p = 0.034$; higher years of education, AOR [95%CI] = 1.7 [1.1, 2.5], $p = 0.013$ and higher maternal age, AOR [95%CI] = 1.8 [1.1,

3.3], $p = 0.031$. Active and passive smokers had reduced folate levels by B [95%CI] = -1.6 [-2.2, -1.0] nmol/L, $p < 0.001$ and -0.7 [-1.2, -0.3] nmol/L, $p = 0.001$ respectively. Moderate smokers with normal folate status had reductions in their infants' mean birthweight by 79g B (SE) [95%CI] = -79.1 (30.3) [-138.5, -19.7]g, $p < 0.05$, while those with low folate status had infants whose mean birthweight was 106g lower compared to nonsmokers. B (SE) [95%CI] = -106.7 (40.5) [-186.2, -27.2]g, $p < 0.01$. Passive smokers with low folate status had 46.5g reduction in mean birthweight B (SE) [95%CI] = -46.5 (20.0) [-85.7, -7.3]g, $p < 0.05$. 5,10-*MTHFR* 1298AA was associated with low folate status. Smokers with 5,10-*MTHFR* 1298AA genotypes had reduced mean infants' birthweights by 107grams (95%CI, -180 to -34, $p = 0.004$) and the reduction was more in male infants by 117grams (95%CI, -218 to -15, $p = 0.025$).

Conclusion: Maternal 5,10-*MTHFR* 1298AA genotype may be associated with folate impairment and may interact with tobacco smoke to decrease offspring's birthweight. Male fetuses seemed to be more responsive to 5,10-*MTHFR* activities.