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B-vitamin intake in human pregnancy and imprinted gene methylation in the offspring

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It has been proposed that altered epigenetic status at imprinted loci may play a role in the early programming of disease susceptibility[(1)]. The ultimate methyl donor for methylation reactions is the folate-methylation cycle and feeding pregnant dams diets deficient in methyl donors results in altered regulation of specific genes in the offspring which are under imprinting control[(2)]. The aim of this study was to determine whether a similar phenomenon may occur in human pregnancy.

The study was approved by Grampian Research Ethics Committee and all participants gave informed written consent. We collected data on dietary and supplement intake and cord blood DNA from pregnancies sequentially recruited at Aberdeen Maternity Hospital. Energy-adjusted intake of the B-vitamins (thiamine, niacin, biotin, riboflavin, folate, B_6 and B_{12}) from the diet was assessed at 19 weeks gestation using a self-administered food frequency questionnaire[(3)]. The use of folic acid supplements (type/brand, amount per day, timing and duration of consumption in relation to stage of pregnancy) were also recorded. Multiple methylation sites were measured in three imprinted genes (IGF2, *n* 374; SNRPN, *n* 363; PEG3, *n* 377) and LINE1 (*n* 372) which was thought to contribute to the differential expression of paternally and maternally imprinted genes. Methylation was determined by pyrosequencing using a PyroMark MD system (Qiagen, Crawley, UK) after bisulphite conversion of DNA using Epitect Bisulfite kits (Qiagen, Crawley, UK). Statistical analysis was carried out using STATA 11MP (Stata Corp, College Station, TX, USA).

All the B vitamins from diet were included in the regression model. There was no evidence that dietary intake of B vitamins was related to LINE1 or SNRPN methylation. Dietary intake of riboflavin, vitamin B_6 and folate were associated with the average methylation status of both IGF2 (riboflavin, $P = 0.012$; vitamin B_6, $P = 0.047$; folate, $P = 0.024$; model $r^2 = 3.9\%$) and PEG3 (riboflavin, $P = 0.016$; vitamin B_6, $P = 0.014$; folate, $P = 0.001$; model $r^2 = 2.6\%$). Although responsive to the same nutrients, there were differences between PEG3 and IGF2 in the sign of the response. Separate analysis of supplement use provided no evidence for an effect on the methylation of folic acid intake in line with current advice.

The way in which parental diet influences the methylation of individual genes and the health consequences for the offspring merit further study. Further work on this phenomenon in larger numbers of pregnancies is proposed.

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