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The impact of plasma folate levels of mothers and newborns on intrauterine growth retardation and birth weight

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Abstract

Folate plays an important role in the genomic stability of human cells. In our studies of the impact of environmental pollution on human health, we have found that air pollution can affect pregnancy outcome. As it may be also affected by nutrition, we examined the effect of plasma folate levels of mothers and newborns on intrauterine growth retardation (IUGR) and birth weight (BW) in cohorts from Prague ($N = 319$) and Teplice ($N = 444$). The lower plasma levels (<6.1 nmol/L) were observed in 7.1% of mothers in Prague, and in 9.6% of mothers in Teplice. The higher plasma levels (>36.5 nmol/L) were observed in 28.4% of mothers in Prague, and in 15.7% of mothers in Teplice. The higher plasma levels were observed in 75.4% of newborns in Prague, and 73.2% of newborns in Teplice. When comparing maternal high versus low folate plasma levels and IUGR by logistic regression, the risk of IUGR was significantly decreased for European cohort (according to ethnicity) with gestation age >36 weeks [$N = 536$, OR = 0.44, $P = 0.026$], and even more pronounced in the group of European smokers [$N = 157$, OR = 0.14, $P = 0.015$]. Using multiple regression analysis, plasma folate levels of mothers and newborns significantly affected the birth weight of newborns of smoking mothers ($P < 0.05$). The obtained results seem to indicate a positive effect of folate on pregnancy outcome, especially its potential to decrease the risk of IUGR in European population and lower birth weight in smoking European mothers. It would be warranted to study the effect of folate levels on pregnancy outcomes in the relationship to different environmental pollution and life styles of mothers.

Keywords: Folate; Intrauterine growth retardation; Newborns birth weight; Smoking; ETS

1. Introduction

Folate (FA) is an important micronutrient which plays a significant role in DNA metabolism [1]. It is a long established fact that FA is required for the synthesis of dTMP from dUMP. Under conditions of FA deficiency, dUMP accumulates and as a result,

Abbreviations: BMI, body mass index; BW, birth weight; ETS, environmental tobacco smoke; FA, folate; GA, gestational age (in weeks); IUGR, intrauterine growth retardation; PAHs, polycyclic aromatic hydrocarbons; RDI, recommended dietary intakes

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uracil instead of thymine is incorporated into DNA. This excessive incorporation of uracil into DNA leads to single and double stranded DNA breaks, chromosome breakage, and micronucleus formation [2,3]. The impact of FA on genomic stability has been advocated for a long time especially by Michael Fenech [1,4]. In conditions of deficiency, there is increased chromosome breakage and DNA hypomethylation. FA deficiency (<400 nmol/kg diet) is also related to threefold increase in fetal developmental abnormalities [5]. Folate deficiency is an important risk factor for neural tube defects [6], cancer [7–9] and cardiovascular diseases [10]. These adverse effects are seen at FA level in plasma below 5.5 nmol/L. Nevertheless, it is not known what the optimal concentration of FA in plasma should be in order to suppress the DNA damage. According to Fenech [1,4], the recommended dietary intake (RDI) of FA (=400 μg per day) required to minimize DNA damage are expected to result in plasma >5.0 nmol/L (based on prevention of anemia). However, this RDI is significantly lower than required intake in diet corresponding to the average FA concentration levels (47.7 nmol/L in plasma) in which the DNA damage is minimized [1]. FA plasma level <4.9 nmol/L is associated with an increased risk of early spontaneous abortions [11].

Maternal periconceptional supplementation with FA has been known for more than two decades to be effective in reducing the risk of selected human congenital malformations [12] as neural tube defects, heart defects, and craniofacial malformations [13–17]. A folate deficiency during embryogenesis can significantly alter the gene expression, demonstrating the importance of proper maternal nutrition for transcriptional competence [18,19]. This knowledge became the reason for a broad use of periconceptional supplementation with FA.

The relationship between folate level and birth weight may be related to FA role in genomic stability. Both in vitro and in vivo studies of human cells clearly show that folate deficiency causes expression of chromosome fragile sites, chromosome breaks, excessive uracil in DNA, micronucleus formation, and DNA hypomethylation [1]. For example, we already observed the effect of carcinogenic PAHs (polycyclic aromatic hydrocarbons) on the induction of DNA adducts in vitro [20], in placenta in mothers [21], and IUGR [22]. Recently Perera observed the effect of PAHs to induce DNA adducts and hprt mutations in newborns in relation to birth weight [23]. Therefore, we questioned if such effect can be possibly ameliorated by folate supply.

Insufficient folate means inhibition of nucleic acid synthesis. As nucleic acid and protein synthesis is increased during embryogenesis, the lack of FA may affect IUGR and birth weight. But no such data analyzing the relationship between folate plasma level in mothers and newborns and IUGR and/or birth weight were found in PubMed. Similarly, no studies of a possible relationship of folate and homocysteine with IUGR was listed in the same source. Therefore, the relationship between FA, homocysteine, and IUGR is not discussed further in the present communication.

Higher FA level at 30 weeks gestational age was related to increased birth weight and lower risk of fetal growth retardation [24]. Similarly, Neggers et al. [25] experienced association between FA intake at 30 weeks of gestation and birth weight. Using questionnare, Mitchell et al. [26] observed the association of folate supplementation with the reduced risk of SGA (small for gestation age). Hyperhomocysteinemia in mothers with the history of preeclampsia and fetal growth restriction was corrected by FA [27]. High red cell folate was associated with a decreased risk for abruptio placentae and intrauterine growrh restriction, hyperhomocysteinemia with an increased risk [28]. De Onis et al. [29] analyzed 12 randomized control trials on nutritional interventions to reduce risk of IUGR and proposed that folate supplementation during gestation merit further research.

As the accumulated evidence suggests that FA plays an important role in genomic stability, we have decided to study the level of FA in pregnant mothers and newborn children in regions where we had studied the impact of air pollution on pregnancy outcomes [21,22,30,31].

2. Materials and methods

2.1. Subjects

The background sample was collected in the district of Teplice and the University hospital in Prague 2 (New Town, the City Center). The district of Teplice with about 120,000 inhabitants and 1000 births per year, lies in the brown coal basin of Northern Bohemia, polluted