

POSITION OF FOLIC ACID IN FORTIFICATION OF NUTRITION IN NEONATAL PERIOD

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ABSTRACT

Folic acid is an essential vitamin which has been known in recent 50 years. It plays an important role in period of neurogenesis. The substitution of folic acid is one of the important parts in the complex treatment of anaemia in premature newborns. It is also a component of artificial milk formulae or breast milk following mother's intake. Fortification of foods with folic acid for population in the world is still discussed. To determine optimal dose of folic acid in premature newborns is difficult. Daily recommended doses of folic acid in infants under the six months were identified. The needs of folic acid in newborns vary. It depends upon the gestational age, body reserves at birth or maternal status of folates during gravidity. On the other hand there is a risk of accumulation of unmetabolised folic acid in circulation of newborns after mandatory folic acid fortification in some countries, which were reported in some studies. The safe upper limits of folic acid intake in premature newborns are not known.

In this review article authors inform about the clear positive effect of folic acid in prenatal and neonatal period, but excessive doses of folic acid could present risk of accumulation and possible adverse effects. To follow up these notions further studies are required.

Keywords: newborn; folic acid; fortification; milk fortifier

INTRODUCTION

Folic acid is an essential vitamin which has been known in recent 50 years. It is synthetic form of folates which are substantial parts of many biochemical processes in the human body (Jackson, 2006). In the period of rapid growth of organism or in cell growth, body's demands for folate increase. Fortification of foods with folic acid for population in the world is still discussed. Its impact in neonatal period varies even in premature newborns. Substitution of folic acid is one of the important parts in the comprehensive treatment of anaemia in premature newborns (Hoffbrand and Weir, 2001). It is also a component of artificial milk formulae or breast milk following mother's intake. To determine optimal doses for each age group is difficult. Other influence should also be considered. On the other hand excessive intake of folic acid is not a concern as folate is water-soluble and easily excreted by kidneys when in excess but on the other side growing organism of preterm newborn and disruption of metabolic balance could be potential risks for optimal development (Hybenova, 2012).

In the beginning of 20th century, the link between folic acid deficiency and anaemia was assumed. Among the first who explored these findings was the English Lucy Wills in 1931. She left for India and investigated macrocytic anaemia in pregnancy, prevalent in female textile workers. Wills and Evans reported cases of patients with tropical megaloblastic anaemia who were treated with crude liver extract (Hoffbrand and Weir, 2001). The name of folic

acid comes from the Latin word folium because it was isolated from spinach leaves in 1941. Folic acid is a synthetic form of folate used in nutritional supplements or food fortification. Folate exists as many structural forms, natural occurring and synthetic, which are known as vitamin B₉. The active form is used at the cellular level for DNA synthesis and the regulation of homocysteine among other functions (Schiff, 2011).

Rich sources of folate are liver, yeast extracts and green leafy vegetables such as spinach, kale, beans, cabbage and broccoli and also pork, poultry, shellfish and liver (Jackson, 2006). In some countries as United States the folic acid intake can come from multiple sources including supplements enriched cereal grain products or other types of fortified food (Crider et al., 2011).

Folates are an integral part of important biochemical processes in the human body. Folate-mediated one-carbon metabolism is essential for metabolic processes in organism. The most important functions are nucleotide biosynthesis, methionine biosynthesis, and cellular methylation reactions (Beaudin and Stover, 2007). In organism folates can be absorbed as one-carbon forms of tetrahydrofolate or polyglutamyl tetrahydrofolate. Folate polyglutamates are broken down in the gut by folate conjugase in the mucosal brush borders to the monoglutamate forms. In this process is reduced the bio-availability of natural folates (Jackson, 2006). The monoglutamates are subsequently absorbed and converted to 5-methyltetrahydrofolate. Synthetic folic acid is not conjugated and is therefore more bio-available. Before it

can become active, folic acid has to be reduced in cells to dihydro forms and tetrahydro forms, which are chemically unstable. The reduction is catalysed by dihydrofolate reductase and tetrahydrofolate is then converted to 5-methyltetrahydrofolate, the form found in the circulation. These reduced and polyglutamylated forms are essential for the DNA (deoxyribonucleic acid) biosynthesis. Also vitamin B₁₂ is required in as co-factor in the methylation cycle. The methylation cycle and DNA cycle regenerate tetrahydrofolate (Gregory, 1997). For healthy embryonic growth the optimal folate status in cells is needed to secure optimal DNA methylation status. It is also known that the aging process by itself is accompanied by alterations in DNA methylation. Age and reduced folate intake can alter folate metabolism (Kim et al., 2009).

Also some polymorphism in gene for metabolism of folate can interact on RBC folate. Interaction between the DHFR polymorphism and folic acid intake was also seen with respect to RBC folate. It suggests a functional DHFR polymorphism, because it limits assimilation of folic acid into cellular folate stores at high and low folic acid intakes (Kalmbach et al., 2008). Some single-nucleotide polymorphism in MTHFR genes are considered to be risk factors for NTD (Evinova et al., 2012). The genetic polymorphisms of the MTHFR can be also associated with some neuropsychiatric disorders, such as major depressive disorders (Capra et al., 2013).

Folates and vitamin B₁₂ play an important role in methylation cycle. In the liver it is performed via recycling homocysteine (Pristoupilova et al., 1999).

DISCUSSION

The benefits of intake of folic acid in periconceptional period were reported. The folic acid supplementation in periconceptional period decreases the recurrent risk of neural tube defects significantly by 85-100 % (Gross and Collins, 2007). Daily dose of 400 µg of folic acid during pregnancy is recommended for reduction of neural tube defects and oro-facial clefts (Canfield et al., 2005; Wilcox et al., 2007; Johnston, 2009). Due to several studies in the prevention of NTD the periconceptual use of folic acid (0,4 mg) per day was recommended by World Health Organisation.

Bánhidý et al. (2011) reported the reduction of structural birth defects in offsprings of pregnant women with diabetes mellitus type 1 after folic acid supplementation. They described it in specific congenital anomalies such as renal dysgenesis, obstructive anomalies of urinary tract, cardiovascular anomalies and caudal dysplasia sequence. Relevant decrease in incidence of neural tube defect by more than 49 % in northern Jordan after folic acid fortification of flour was reported by Amarin and Obeidat (2010).

In South Africa through the program of folic acid fortification of staple foods was for the first time observed in African population a benefit in prevention of neural tube defects. It was significant decline of neural tube defects by 30.5 % and spina bifida by 41.6 % compared to 10.9 % for anencephaly (Sayed et al., 2008). Distribution of neural tube defects shows considerable geographical and ethnic variation (Gupta and Gupta, 2004). Some limiting factors are seasonal and geographic differences, but also

cultural and ethnical variabilities (Zhu and Ling, 2008; Hoyo et al., 2011). Hoyo et al. (2011) assumed that Caucasian race and ethnicity, advanced maternal age and higher education represent greater wherewithal to supplemental folic acid access.

The specific group includes newborns and mostly very low birth weight newborns. Supplementation depends upon the gestational age, which is related to the placental transfer. Body reserves at birth, vitamin content of breast milk with maternal status interact with total amounts of folate in newborn's blood (Jain, 1994). The influence of breastfeeding on folate and cobalamine status was reported. Folate was positively correlated with duration of exclusive breastfeeding. On the other side low cobalamin status is a characteristic finding in breastfed children (Hay et al., 2012). Beneficial effect of supplementation with folate throughout lactation were documented on folate-supplemented women had lower total homocysteine and higher folate levels (Ramlau-Hansen et al., 2006).

In some developing countries folic acid and iron supplementation of pregnant woman could be beneficial to prevent children's malnutrition. Early childhood stunting predicts poor human capital including decreased offspring birth weight and shorter adult height (Sachdev, 2012). The prenatal supplementation with folic acid decrease risk of low birth weight in newborns (Takimoto et al., 2011; Peña-Rosas et al., 2012). In some countries young woman with low socioeconomic status has limited accesses to prenatal care and adequate nutrition during pregnancy. Maternal and newborn health status could be improved by reinforcing the use of folate-enriched diet (Couto et al., 2007).

The requirement of periconceptual supplementation with folate was documented repeatedly. Risk factors associated with birth defects of central nervous system include deficiency of folate supplementation, cigarette smoking and exposure to x-rays (Raza et al., 2012). In some countries maternal micronutrient supplementation does not have impact on early neonatal morbidity (Christian et al., 2008). On the other side pertinent ongoing intervention as delaying early child birth, adequate antenatal care and maternal iron-folate supplementation are beneficial but have sub-optimal coverage (Sachdev, 2012). Also the folate supplementation during pregnancy can lead to preventing allergic diseases in childhood. To follow up these notions further studies are required (Peroni et al., 2012). Intake of folic acid supplementation around the time of conception can protect against neurodevelopmental disorders as autism spectrum disorders. The use of prenatal folic acid supplements was associated with a lower risk of autistic disorder in Norwegian mother (Surén et al., 2013). The supplementation of folic acid as a part of comprehensive treatment with erythropoietin, intravenous iron and vitamin B₁₂ reduce the need for transfusion in extremely low birth weight newborns (Haiden et al., 2006; Eghbalian a Monsef, 2005).

In last ten years folic acid is conjugated with specific anticancer drugs, which are used for treatment of ovarian, breast and lung cancer (Pribylova et al., 2010).

The needs of folic acid in newborns vary. Current recommendations of folic acid intake after birth are different compared with older. Rapid growth of organism

or cell growth, body's demands for folate are increasing after birth. It is influenced by several factors on the mother's side, as well as on the newborn's side or other associated complications. Daily recommended doses for infants under six months are 60 µg of folic acid in Slovak Republic (Kajaba et al., 1997). Also other researchers reported the lower reference nutrient intake for children under the first year of life with 60 µg of folic acid (Gregory, 1997).

Food fortification is a massive exercise and requires multidisciplinary co-operation and on the other side many obstacles as financial barriers and centrally processed food cannot adopt to this approach (Gupta and Gupta, 2004). The mandatory folic acid fortification of food (flour, cereals) was initiated in some countries of the world for example USA, Canada and Chile (Crider et al., 2011).

Folic acid fortification in some countries of the world refers to the risk of accumulation of unmetabolised folic acid in serum. In one week-long study of folate-replete adults consuming folic acid-fortified bread, the dose at which unmetabolised folic acid appeared in the blood lay between 200-400 µg daily (Sweeney et al., 2007). The lower limits of detection offered by the electrochemical detection allow the analysis of folate form distribution in small specimens as human red blood cells and lymphocytes. Measurement in biological samples is provided by means of fully automated combination of affinity chromatography and HPLC with electronical detection (Bagley and Selhub, 2000). Currently the microbiological assays based on growth of microorganisms are used rarely. Highly effective liquid chromatography showed better sensitivity and was suitable for determination of folate in food samples (Strandler, 2012).

Obligation to monitor unmetabolised amounts of folic acid in national programmes of fortification is required. A specific group are newborns who intake folates in perinatal period and after birth in breast milk, milk formulae or human milk fortifiers subsequently. Sweeney et al. reported cases of seven newborns with high level of unmetabolised folic acid in serum. In that time fortification was not mandatory in Ireland and also none of the mothers took folic acid supplementation (Sweeney, 2005). In preterm newborns the positive effect of human milk fortification was significantly confirmed. It improves the growth of preterm very low birth weight babies and predominantly of small for gestation babies (Mukhopadhyay et al., 2007). On the other side potential risks of necrotizing enterocolitis in association have been reported. Some authors reported after addition of human milk fortifiers a significant increase in osmolality of breast milk (Agarwal et al., 2004). Preterm formula milks and breast milk fortifiers provide sufficient folic acid to prevent folate deficiency in preterm infants. The supplementation may also benefit in preterm newborns to reduce the risk of brain injury as a result of decreased plasma homocysteine concentration (Jyothi et al., 2007). High intakes of folic acid have also been associated with theoretical risks of adverse effects. It could delay the diagnosis of vitamin B₁₂ deficiency in treating the anaemia at high doses of folic acid and lead to irreversible neurological damage if treatment with vitamin B₁₂ is not

provided. The safe upper limit for the intake of folate is considered to be 1 mg for adults (Smith et al., 2008). The potential of folic acid is to mask pernicious anaemia and possibly accelerate the growth of existing cancer after mandatory fortification (Sweeney, 2009). The safe upper limits in newborns are not known.

CONCLUSION

Folates participate in multiple different biochemical pathways and their metabolism intersects on an important step in one-carbon metabolism. Folate is required in period of neurogenesis in brain and spinal cord. Folate deficiency may cause disruption of myelination and inflammatory processes. Folic acid seems to be protective against development of other disease such as atherosclerosis and vascular disease. Fortification with folic acid appears to be beneficial but after mandatory fortification the low levels of circulatory unmetabolised folic acid have been reported. On the other side it could be potentially hazardous and depends on the type of food, time interval and amounts of folic acid and individuality of organism in neonatal age. Unmetabolised folic acid in circulation of newborns could have potentially adverse effects. Toxicity of folic acid is not a concern as folate is water-soluble and easily excreted by kidneys when in excess but on the other side growing organism of preterm newborn and disruption of metabolic balance could be potential risks. More studies are necessary to ascertain this issue.

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