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The Effect of Synthetic Folic Acid Surplus on Neurological Symptoms in Offspring

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Abstract: The effect of folic acid on the vital activity of macro- and microorganisms has long been known. It is necessary for methylation processes, nucleotide synthesis, methionine formation and reduction of the toxic effect of homocysteine. Adding synthetic folic acid to the diet of pregnant women, as well as at the stage of pre-pregnancy preparation, significantly reduces the risks of developing neural tube defects in the fetus, heart defects, in addition, folic acid can help improve fertility. However, there is also data on the adverse effects of folic acid surplus on the health of the elderly (concealment of B12 deficiency conditions) and children whose mothers took high doses as prescribed by medical specialists. Among them are the risks of developing infectious and inflammatory and allergic diseases of the upper respiratory tract, eczema, as well as impaired psychomotor development and insulin resistance. In 1980, the direct stimulating effect of folic acid on synaptic transmission in the central nervous system was proven. This is due to the molecular structure, it contains L-glutamate.

Keywords: folic acid, surplus, seizure threshold, synaptic density, myoclonus, gestation.

Folic acid is an essential biologically active substance in a living organism, it ensures the process of DNA replication and nucleotide synthesis. Since it is vitally important, it is used in metabolic processes not only by multicellular organisms, but also by microorganisms. One of the main pathways of its metabolism is methionine and homocysteine metabolism: a methylating agent is formed - S-adenosine methionine (SAM), which is involved in the methylation of proteins, mediators, nucleotides, phospholipids and hormones [1]. Figure 1 shows the polymorphism of folic acid transformations in macroorganisms [2]. N5,N10-methyltetrahydrofolate (MTHF) and N10-formyltetrahydrofolate are directly involved in the biosynthesis of nucleotides de novo, in particular, a deficiency of these forms of folic acid can lead to severe defects of the neural tube as a result of the incorporation of uracil into DNA instead of thymine. The positive effects of folic acid on intrauterine fetal development have long been known: reduced risks of neural tube defects (NTDs), as well as heart defects [2]. Embryonic cells, syncytiotrophoblast or symplastotrophoblast, are extremely sensitive to folic acid deficiency, since this is a rapidly proliferating pool of cells; folate deficiency leads to cell stress, since methylation processes are disrupted, including DNA, which can lead to the development of various types of differentiation and proliferation abnormalities of both embryonic axial rudiments and more differentiated tissues. Children whose mothers received folates during pre-pregnancy preparation and during pregnancy (first trimester) show a higher level of cognitive functions in the preschool and early school period. The concentration of folic acid in maternal erythrocytes also correlates with the weight and height of newborns. In the group of mothers with low plasma and red blood cell folate levels, the incidence of intrauterine growth retardation is higher than in the group with normal folate levels [4]. Insufficient folate intake during pregnancy in the first, second and third trimesters also correlates with an increased risk of autism spectrum disorders in children, since they have lower levels of methylating agents and folate metabolites in their blood [5, 6]. Hyperhomocysteinemia is associated with folate metabolism, and high blood homocysteine levels are a proven risk factor for cardiovascular disease [7]. Homocysteine increases with mutations in the MTHFR, DHFR genes (the most common 677C-

>T), as well as with insufficient folate intake, for example, in countries where there are no mandatory fortification programs. The risk of arterial hypertension (AH) during pregnancy was not associated with mandatory folate support of mothers, but the risk of developing preeclampsia (PE) was higher in the group of pregnant women without folate support [8]. Polymorphism of the MTHFR gene, associated with high levels of homocysteine,also turned out to be a cause of menstrual dysfunction. This was shown in the prospective long-term BioCycle Study (2005–2007), which involved 259 women with a normal menstrual cycle. An increase in homocysteine concentration in the control group (CG) increased the risk of an anovulatory cycle (sporadic anovulation) by 33%. These indicators were associated with the lack of adequate folate support. Thus, folates are not only an essential micronutrient, but also a drug for the prevention of a fairly wide range of diseases. Folic acid and related compounds are based on dihydropteroic acid conjugated with L-glutamate, the latter being the main excitatory neurotransmitter in the brain, and data on the excitatory nature of folic acid itself for the central nervous system (CNS) in vitro have been previously obtained. Synthetic folic acid in an unmetabolized inactive form can also enter the systemic circulation and be captured by cells. As a result of activation of the unsaturable pathway, it accumulates in the blood. Excess synthetic folic acid during the formation of the NT and subsequently during the differentiation of nervous tissue in the CNS (in particular, in the third trimester with the massive appearance of glutamatergic receptors) can affect the processes of neurogenesis and the formation of neural networks [4]. However, there is evidence that taking physiological folic acid after the closure of the NT (after the first trimester) has a positive prospective effect on the cognitive functions of the offspring. At 7 years of age, children of mothers who received folic acid had significantly higher scores than the placebo group when assessing verbal thinking based on the BSITD-III and WPPSI-III test systems [3]. There are two mechanisms of folate absorption - saturable and unsaturable. The first is widespread in the upper part of the small intestine and is sensitive to reduced forms of folate and especially to MTHF. When the critical level for this mechanism is exceeded (200 μg of folates), the activity of the transporter apparently decreases due to a decrease in the expression of folate receptor genes [9, 10]. The second mechanism, the non-saturable one, is realized in the ileum; it is non-specific and is capable of transporting both reduced and unreduced folates in unlimited quantities. This mechanism may be the main reason for a significant increase in the level of folic acid in the body and the development of associated folate-dependent pathological conditions [11]. Therefore, since the late 1990s, discussions have arisen in the scientific and medical practical environment about the advisability of prescribing high doses of synthetic folic acid, as well as adjusting the dose in accordance with preventive measures and a specific nosology. Some patient cohorts are prescribed higher folate dosages up to 5 mg/day, although in the EU and the US,and in Russia (Rospotrebnadzor) have already formed an idea of the upper permissible level of consumption - 800-1000 mcg. In particular, pregnant women with an increased body mass index can be prescribed 1-2 tablets of 1 mg of folic acid per day in connection with the hyperdiagnosis of the prevention of B9 deficiency, hypertension and PE. The high risk of neural tube defects and other folate-dependent developmental anomalies is a recommendation to take up to 4000 mcg of folates per day at least 3 months before conception and up to the 12th week of pregnancy. In this case, 800 mcg should come from multivitamin complexes, and the rest - in the form of synthetic folic acid [12]. Additional intake of folic acid is also recommended with a rational diet and sufficient micronutrient content [13]. However, it is known that excess folic acid in the postnatal period can increase the risk of manifestation and recurrence of malignant neoplasms. In a cohort study with a sample of 619 patients, it was shown that increased folic acid intake increases the risk of recurrence of non-invasive bladder cancer and multifocal tumors at diagnosis. On this basis, the researchers suggested that excess synthetic folic acid intake is unsafe for such patients [14]. In a randomized controlled trial (RCT) of 643 men who were randomly assigned to placebo or folic acid supplements, the estimated probability of being diagnosed with prostate cancer over a 10-year period was 9.7% in the folic acid group and 3.3% in the placebo group. These results emphasize the possible potential complex role of folic acid in prostate cancer [15]. During the development of NT and differentiation of the fetal nervous tissue, it is the enhancement of such transmission that can provoke a qualitative and quantitative acceleration of the development of neural connections, which in physiological concentrations has a positive effect,

eliminating severe neurodegenerative developmental defects, as well as possible autism spectrum disorders. However, with an excess of synthetic folic acid, excessive neural and synaptic activity can be observed [5]. Folic acid is also involved in methylation processes - the formation of S-adenosylmethionine, which is also involved in the methylation of cytosine in the DNA structure. In excess of methylating agents, control over epigenetic phenomena can be disrupted, which will lead to excessive DNA methylation and possible neurological symptoms. In addition, folic acid is directly involved in the biosynthesis of nucleotides de novo, they can be synthesized in excess (with sufficient plastic and energy supply), which can also be the cause of a decrease in the seizure threshold. Further study of the problem of excess intake of synthetic folic acid in the diet of various groups of patients is necessary, and a discussion of the effect of excess folates on the fetus.as well as dose adjustments in accordance with all perinatal risks and certain folate deficiency nosologies of the mother during pregnancy.

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