Review

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Ewa Cieřlik*, Iwona Cieřlik

Occurrence and significance of folic acid

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Abstract: Folic acid is a naturally occurring pteridine, which was originally isolated from plants.

Folic acid (pteroyl-glutamic acid) is composed of pteridine (6-methylptero), p-aminobenzoic acid (PABA) and glutamic acid. Folic acid (folacin) is a compound of major importance for the proper functioning of the human body. Its adequate supply is essential for the proper course of many biochemical processes in the body, including the process of neural tube closure in the fetus, DNA and amino acid synthesis, growth of red blood cells, and the function of the nervous system. Folic acid is a compound of a high sensitivity to physical and chemical factors, and its bioavailability is limited by interactions with multiple food components. Therefore, folate deficiency is one of the most common deficiencies. This paper presents the structure and characteristics of folic acid as a pteridine, it also discusses dietary sources of folate and the effects of its deficiency.

Keywords: folic acid; folate; structure; intake; deficiency.

Introduction

Folic acid (CAS Number 59-30-3; pteroyl-glutamic acid, folate, folacin) is composed of pteridine (6-methylptero), p-aminobenzoic acid (PABA) and glutamic acid. Folic acid and its derivatives belong to the group of folates and differ in the degree of oxidation of the pteridine ring and the number of glutamic acid residues (1-11) [1]. These compounds are characterized by similar biological activity, with folic acid being the most stable and the best assimilable compound of this group [2]. It rarely occurs naturally in food, but it is often used as a medicine, a supplement, and also as an ingredient added to food

products for their enrichment. Due to its high biological activity, folic acid has both direct and indirect effects on the metabolism of the body's cells. Its deficiency or lack in the human diet causes disturbances in many vital metabolic processes and may lead to impaired growth and development of the body.

Folic acid was discovered at the turn of the 1930s and 1940s. Lucy Wills observed that anemia in women in India can be treated with yeast extract. Experiments conducted with the participation of apes showed the therapeutic effect of this, and the agent fighting anemia was called the "Wills factor" [3]. In 1941, this vitamin was first isolated from spinach leaves, which was shown in its name, Latin *folium*-leaf. Five years later, a group of American chemists received a crystalline form and then synthesized folic acid [4]. Folic acid is a compound of great importance for the proper functioning of the human body. The biologically active form of folates in the body is tetrahydrofolic acid. Its polyglutamine derivatives are involved as coenzymes in many biochemical processes taking place in the body. Their main role is to provide single-carbon rests to many compounds that participate in cell division (production of nucleic acids), protein synthesis, amino acid transformation (mutual conversion of serine and glycine), histidine catabolism to glutamic acid and transformation of homocysteine to methionine [5]. It is indispensable in the processes of the formation of a protective coating from myelin on nerve fibers. In addition, it reduces the risk of congenital malformations associated with improper spinal cord closure. The presence of folate in tissues in which very intense cell division occurs, i.e. in the marrow, the epithelium of the gastrointestinal tract and in fetal tissues is of particular importance [4]. For this reason, even small folic acid deficiencies can have a significant impact on the functioning of the body.

*Corresponding author: Ewa Cieřlik, University of Agriculture in Krakow, Krakow, Poland, E-mail: rrciesli@cyf-kr.edu.pl

Iwona Cieřlik: University of Agriculture in Cracow, Department of Culinary Technology And Consumption, Krakow, Poland

Figure 1: Different natural pterin moieties.

Figure 2: Natural pterins.

Pteridines: Structure and folic acid characteristics

Pteridines are a group of heterocyclic compounds composed of fused pyrimidine and pyrazine rings and the numbering system is shown below (Figure 1) [6].

There are three main classes of naturally occurring pteridines, namely lumazines, isoalloxazine and pterins. Lumazines and isoalloxazines possess oxo-substituents at the 2- and 4- positions, with the difference being a phenyl ring annealed in the 6- and 7- positions on the isoalloxazine. The most common class of naturally occurring pteridines are the pterins which have an amino group at the 2-position and an oxo group at the 4- position. Naturally occurring pteridines have been isolated from (a) insects, examples include xanthopterin and isoxanthopterin; (b) plants, an example being folic acid; and (c) mammals, an example being neopterin (Figure 2) [6]. In addition, the presence of pterines in anoles [7] and in fish [8] was found.

Most of the pteridines isolated belong to the pterin family and some are incorporated in a number of redox cofactors [9]. There are three main redox states of pterins: the fully oxidized, the semi-reduced or dihydro and the fully reduced or tetrahydro state.

The term “folate” is defined as a group of compounds with similar biological activity and a complex molecular structure. Folic acid or folate has a molecular formula of $C_{19}H_{19}N_7O_6$ and a molecular weight of 441.39746 g/mol. It is

very slightly soluble in water and in alkaline hydroxides and carbonates but insoluble in alcohol [10]. Folic acid is a yellow or yellowish-orange crystalline powder, it is a B vitamin which contains pteridine linked to para-aminobenzoic acid by a methylene bridge and is linked to glutamic acid by a peptide linkage. The basic structure is pteroyl-glutamic acid composed of a 6-methylpteridine system, p-aminobenzoic acid (PABA) and L (+) glutamic acid (Figure 3). Folic acid and its derivatives differ in the degree of oxidation of the pteridine ring and the number of glutamic acid residues, from 1 to 11 [1, 10].

These compounds are characterized by similar biological activity, with folic acid being the most stable and the most easily absorbed compound of this group [2]. These compounds differ in the degree of oxidation of the pteridine ring, the type of one-carbon fragments (methyl, methylene, methenyl, formyl and formimino), as well as the number of attached glutamic acid residues, from 2 to 12 [1]. Forms found in the natural environment include, among others, 5-Methyl-tetrahydrofolate (MTHF), 5-formyl-THF, 10-formyl-THF, 5,10-methylene-THF, 5,10-methenyl-THF, 5-formimino-THF, 5,6,7,8-tetrahydrofolate (THF) and dihydrofolate (DHF) [10]. The active form of folic acid is its hydrogenated form - tetrahydrofolic acid (THF).

The human body is able to synthesize the pteridine ring, however it is not possible to combine it with other compounds [11]. Therefore, it is not possible to endogenously synthesize the folic acid, so this vitamin must be supplied with food or supplemented [12]. Folates

Figure 3. Structural formula of folic acid [1].

are present in food of both vegetable and animal origin. It occurs as reduced multiglutamic folic acid derivatives, mainly tetrahydrofolate (FH₄) or dihydrofolate (FH₂), containing up to 9 glutamic acid residues in the γ -peptide bond. Polyglutamine conjugates (mainly derived from vegetables) constitute in the food consumed about 3/4 of the total content of folate, 1/3 are monoglutaminofolates, mainly derived from cereal and meat products.

Folates are deconstructed in the gastrointestinal tract to monoglutamine forms, which is a necessary condition for their absorption and use. This process is activated by zinc pteroinoglutamic hydrolase. In the monoglutamine form, folates are absorbed into the cells of the gut mucosa, where most of them are reduced to di- and tetrahydrofolates. A two-step folic acid reduction reaction, first to DHF followed by tetrahydrofolate, is catalysed by dihydrofolate reductase (DHFR) [4, 13]. Folates are also reduced in the liver, primarily to the form of 5-methyl-tetrahydrofolate. They are then transported to tissues and transformed into polyglutamates by adding 4-8 glutamic acid residues that form long side chains. Folates reach the highest concentrations in blood after 30-60 min. The plasma half-life is about 3-3.5 hours [1].

The role of folates in many metabolic processes ensures the proper functioning of all body cells. Tetrahydrofolic acid is a coenzyme involved in the transfer of single-carbon fragments: $-\text{CH}_3$, $=\text{CH}_2$, $=\text{CH}-$, $-\text{CH}=\text{O}$, $-\text{CH}=\text{NH}$. Folates are not closely related to one apoenzyme, they participate as mobile cofactors in many key enzyme reactions. As a result, they are cosubstrates for the reactions in which they participate [12]. The polyglutaminization that occurs in cells significantly increases the affinity of folates, both as substrates of certain enzymes and as selective inhibitors of other enzymes in the folic acid pathway [12]. For this reason, folic acid is involved in the synthesis of purine and pyrimidine bases, nucleotide

synthesis and protein synthesis. Moreover, it participates in the conversion of histidine into glutamic acid, in the methionine cycle, in which 1-carbon units, as methyl groups, are necessary for the methylation of homocysteine to methionine, as well as S-adenosylmethionine, which is a donor of methyl residues, in the synthesis of phospholipids and in methylation processes of proteins and DNA [14, 15]. An additional function of cellular folates as a regulating molecule is to exert an allosteric effect on several enzymes in the folate and methionine cycles, such as methylenetetrahydrofolate reductase (MTHFR), glycine N-methyltransferase (GNMT) or serine hydroxymethyltransferase (SHTM). The regulatory role of folates is not well understood, but it is influenced not only by the similarity of folates to enzymes but also by the level of cell folates [12]. Although the concentration of folates in cells is subject to many regulatory processes, the concentration in serum has a pronounced effect on their concentration in the cell.

Occurrence of folic acid in food

Among the products of plant origin, the largest amounts of folates are contained in raw or short-cooked green leafy vegetables (spinach, lettuce), as well as in broccoli, brussels sprouts, asparagus and kale (Figure 4). Legume seeds, as well as cereal grains and wheat germs, peas, soybeans and beans, contain significant amounts of folate. Its content varies in the range of 150-200 $\mu\text{g}/100\text{ g}$. Vegetables and fruits rich in vitamin C or β -carotene are a very good source of folic acid. Nuts are also a valuable source of folic acid - from 66 $\mu\text{g}/100\text{ g}$ (Italian) to 110 $\mu\text{g}/100\text{ g}$ (arachis) [14].

Among the products of animal origin, a high content of folate is found in yeasts and organ meats, including

Figure 4: Folate content in selected food [Fig. own 16].

mainly the liver (200–580 µg/100 g). The content of folate in milk is low (about 5 µg/100 g). In turn, milk fermented beverages - buttermilk and yoghurt, contain more folic acid (7–10 µg/100 g) resulting from the action of lactic acid bacteria. Hard ripened cheeses contain 10–40 µg/100 g of these compounds, ripening soft (brie, camembert) contain 60–100 µg/100 g of folate, and curd has about 30 µg/100 g. Eggs also have a high content of this vitamin - 65 µg/100 g, with the majority of folic acid in the yolk. Among fish, the best source of folic acid is salmon, containing 26 µg/100 g [16, 17].

The folates present in food products are sensitive to environmental factors, such as high temperature, UV radiation, metal ions (copper, iron) or pH changes. During long-term storage of food, folic acid is oxidized to less available derivatives. Technological processing, including thermal processes, and especially long-term heating, reduce the content of this vitamin by as much as 50–80% [15, 18].

Absorption of folic acid

The bioavailability of natural folates depends on the type of food products, the forms of folates in these products, their sensitivity to digestive processes, or the presence of other food ingredients that may interfere with digestion and the use of folic acid. In some plant raw materials (cabbage, oranges, tomatoes and beans), there are

inhibitors of intestinal enzymes (conjugates) that reduce the absorption of this vitamin [4].

The use of folic acid in the body is affected not only by its total content in the daily food ration, but also by the chemical form. Currently, more and more food products, such as breakfast cereals, juices, non-alcoholic beverages are enriched with synthetic folic acid (pteroyl-glutamic acid), which is a form not found naturally in nature [10]. It differs from folates naturally found in the diet because it is in the oxidized state and contains only one glutamate residue. Natural folates, used as coenzymes and regulatory molecules in the body, have a reduced form (tetrahydrofolates, THF), and above all are polyglutamine forms. It is assumed that the bioavailability of naturally occurring folates in food is lower than the synthetic form of folic acid, and 30–80% is absorbed, depending on the food product [16]. Up to 100% of synthetic folic acid is absorbed, because as a monoglutamate form it does not require hydrolysis [13].

Many external and intracorporeal factors affect the absorption and use of folates. The most important reasons for deficiency of this vitamin include: low intake of folate-containing products, increased demand for this vitamin (especially during pregnancy and lactation) and deficiency of ingredients affecting the transformation of folate, especially iron, zinc, cobalamin, ascorbic acid or methionine [16]. Deficiency of folic acid is also present in structural and functional disorders of the body, such as celiac disease, Crohn's disease, intestinal inflammation,

liver disease, partial resection of the stomach or jejunum [4]. The use of stimulants is also one of the factors that reduce the absorption of folates. Alcohol abuse inhibits their absorption in the small intestine, transport to tissues and storage in the liver, also blocks the release of folic acid from hepatocytes and inhibits DNA methyltransferase.

Absorption of folic acid reduces the availability of drugs, e.g., antidiabetic action metformin, non-steroidal anti-inflammatory drugs, preparations affecting the acidity of the gastrointestinal tract (aluminum and magnesium preparations), anti-tuberculosis drugs, or antiepileptic phenytoin, which accelerates the breakdown of folic acid. Folate management is also disrupted by oral hormonal contraceptives and folic acid antagonists from the group of sulfonamides or cytostatic agents [4]. Long-term exposure to solar UV radiation may also cause a decrease in the content of folates in the blood serum [18].

When properly fed, the content of folic acid in the serum ranges from 6-20 ng/ml, and in erythrocytes 160-640 ng/ml. Determination of serum folate concentration is a good indicator of current consumption, while the determination of erythrocyte content indicates systemic stores, stored for 120 days, i.e. during the survival of erythrocytes. Proper folate intake should ensure that the folic acid concentration in erythrocytes is maintained above 340 nmol/L. With a total deficit in food, systemic folic acid reserves are exhausted after 3-4 months [1].

The demand and intake of folic acid

In the light of the latest nutritional recommendations, the daily requirement for folate is 400 µg [19]. Women of childbearing age, as well as in the first trimester of pregnancy should take 600 µg of folic acid daily as a primary prophylaxis of neural tube defects. Also during the lactation period, the demand is increased to 500 µg/day. For women who have had offspring with a neural tube defect, higher doses of folic acid, up to 4 mg/day, are recommended. According to Scientific Opinion on Dietary Reference Values for folate recommendations range from 120 µg DFE/day for 1-3 year old children to 330 µg DFE/day for boys and girls aged 15-17 years. For pregnant women, an AI of 600 µg DFE/day is derived based on a study on the maintenance of serum and red blood cell folate concentrations in pregnancy. For lactating women, an additional intake of 130 µg DFE/day is considered to cover folate losses via breast milk; this figure is added to the AR for non-lactating women and a PRI (Population Reference Intake) of 500 µg DFE/day is derived [20].

Deficiency of folic acid is one of the most frequently occurring nutritional deficiencies in Poland. It was shown that only 27% of pregnant women used folic acid supplementation. It was shown that the average consumption of folates among women of childbearing age covered only 70% of the recommended standard [21]. Studies carried out by Sicińska and Bojarska [22] showed that young women consumed on average 127-315 µg of folate per day. Low consumption of folates is also observed among the elderly, through eating too little fresh vegetables and fruits, in Poland on average 155 - 283 µg/day is consumed.

Due to the common shortages of folic acid, attention should be paid to increasing the consumption of foods naturally rich in these compounds, as well as food products enriched with this vitamin. In Poland fortification with folic acid is not obligatory, but only voluntary. In 2011 there were over 200 products enriched with folic acid on the Polish market [21, 22]. The most numerous group were cereal products, mainly breakfast cereals, as well as juices, drinks and sweets. Due to the losses occurring during the food preparation process, the maximum permitted amount of folic acid added is no more than 100% of the recommended daily intake per 100 g (100 ml) or a portion of the food product [16, 21]. It was shown that the highest content of folic acid is found in some sweets (up to 800 µg/100 g) and margarine (up to 500 µg/100 g of product), and the lowest in fruit drinks (up to 40 µg/100 ml). Nevertheless, the consumption of fortified foods does not provide a complete coverage of the demand for folic acid. Sicińska and Bojarska [22] conducted a study among students on the intake of supplements and food products enriched with folic acid. The authors showed that folic acid uptake from enriched products covered only 35% of the daily requirement for this vitamin. In the United States, where fortification with folic acid cereal products has been compulsory since 1998, the addition of folic acid is 0.14 mg/100 g of flour and other cereal products. Similarly, in Great Britain 0.24 mg of folic acid is added for every 100 g of flour. In these countries, a marked reduction in the number of births of children with neural tube defects has been observed, as well as a reduction in the number of ischemic stroke cases in the elderly. Flour was selected as a carrier of folic acid due to the relatively low price and the widespread consumption, and thus the possibility of large-scale prophylaxis. The relatively small amounts of added folic acid result from fears of excessive intake of this vitamin, which may, among others, result in masking the symptoms of vitamin B12 deficiency in the elderly [12-15, 21-22]. Due to the important role of folates in metabolic processes, even small deficiencies of this

vitamin can have a significant impact on the functioning of our body.

Overdosing of folic acid may cover neurologic symptoms in people with vitamin B12 deficiency and may interact with anticonvulsants. A daily intake of 15 mg of folic acid may cause nervous and digestive system disorders, and allergic skin reactions may also occur [16].

Effects of folic acid deficiency

Folic acid is present in many metabolic processes in the body. Its deficiency in the diet primarily results in the formation of severe fetal disorders (neural tube defects), megaloblastic anemia, increased homocysteine level in the blood, slowed down synthesis of DNA and replication (division) of cells, impaired function of the nervous system (hyperactivity and difficulty in falling asleep), inhibiting the growth and restoration of cells in the body, feelings of exhaustion, problems with concentration, as well as states of anxiety and anxiety, depression, insomnia, memory problems and digestive disorders [23-27].

Appropriate supply of folic acid in the diet prevents the development of atherosclerosis. It is a disease in which homocysteine plays an important role in etiopathogenesis. It is a sulfuric amino acid formed transiently as a result of the metabolism of methionine - an exogenous amino acid present in proteins of animal origin, supplied from food [25, 28]. In healthy subjects, the majority of homocysteine is transformed (through transsulfuration) to cystathionine and then to cysteine or by remethylation to methionine. The essential substrate in this process is folic acid. It serves as a donor of the methylene group of dihydromethyltransferase, an enzyme responsible for the methylation of homocysteine [27, 28]. In the case of metabolic disorders or metabolic abnormalities in homocysteine metabolism, excess blood accumulates in the blood. The increase in homocysteine level in blood plasma is one of the many causes of atherosclerotic changes in the cardiovascular system, leading to increased collagen production and remodeling of the vessel wall. Hyperhomocysteinemia also leads to damage to the connective tissue of the arteries, may increase the adhesion of platelets to the endothelium, as well as stimulate coagulation processes [28, 29]. In pregnant women, hyperhomocysteinemia is additionally a risk factor for hypertension and neural tube defects in the fetus [4, 25, 30].

Many studies have shown an inverse correlation between folate and homocysteine levels in the blood - supplementation with folic acid decreases homocysteine

concentration [28, 31]. Meanwhile, studies carried out in Poland showed that 26% of men and 16% of women have an elevated level of this amino acid in blood [31].

The correct concentration of folic acid can also be a homocysteine-independent agent for the prevention of coronary heart disease. It was shown that an increase of its plasma concentration by 4 ng/l was associated with a nearly 2-fold reduction in the risk of coronary heart disease [32]. At the same time, there are studies showing that supplementation with folic acid, despite lowering homocysteine, does not reduce the number of cardiovascular events in high-risk populations of this type of event. In the studies of Liem et al. [33] 300 patients with stable coronary heart disease received 0.5 mg of folic acid daily. They observed a decrease in homocysteine levels by 18%, while in the control group this level did not change. However, no significant differences were observed between the patients of both groups in the number of endpoints (vascular incidents, deaths). Other studies of this type also showed no beneficial outflow of supplements with B vitamins (including folic acid) on the risk of cardiovascular diseases [269-33].

In recent years, there are more and more data suggesting the important role of folic acid in the functioning of the nervous system. Its beneficial effect on the functions of this system is related to its contribution to the formation of neurostimulants in the body, such as dopamine, noradrenaline, adrenaline. With significant deficiencies of this component, depression may occur [1]. In clinical and epidemiological studies, it has been shown that adequate folate intake in the diet also reduces the risk of other neuro-psychiatric disorders (e.g. psychosis, dementia, epilepsy). These effects are the subject of further research, but it can be concluded that in proper folate intake in the body it prevents elevation of homocysteine in the blood, which protects against disorders such as dementia, cognitive disorders, mood disorders and others [1].

Due to the large role of folic acid in the metabolism of nucleic acids, it is necessary for the proper production of red blood cells. Its deficiency is (along with vitamin B12) one of the factors of the formation of megaloblastic anemia. If the amount of folic acid is insufficient, erythrocyte production is impaired, its volume is increased, the survival time is reduced and premature destruction occurs in the bone marrow. There is also leukopenia and thrombocytopenia. The main causes of megaloblastic anemia are disorders of nucleic acid synthesis, and folic acid deficiency results in disturbances in the synthesis of purine precursors [23]. Megaloblastic anemia usually accompanies: states of increased consumption of folic

acid, e.g. in pregnancy, impaired absorption e.g. in lipid diarrhea. On the other hand, secondary haemolysis and chronic haemolytic anemia, congenital gastrointestinal defects, anticonvulsants, cytostatic agents. The most vulnerable to this type of anemia are pregnant women, especially after 30 years of age. Treatment consists of administering large amounts of folic acid (1-5 mg), in the case of malabsorption of folic acid this dose can be increased to 15 mg [23]. In exceptional cases, even blood transfusion may be necessary. Megaloblastic anemia in children usually occurs between 2 and 17 months of age. The baby is born with a high concentration of folic acid, but the reserves obtained from the mother are enough for 8-10 weeks. The folate deficiency is more common in premature babies and twins who have received less vitamin A from their mother.

Epidemiological and experimental studies involving humans and animals indicate that the condition of folate nutrition modulates the risk of cancer in some tissues [33-34]. Folic acid prevents damage to the structure of chromosomes, making the cells more resistant to carcinogenic factors. The reduced level of folic acid leads to an increased activity of proto-oncogenes and the induction of neoplastic transformation of cells. Folic acid and its metabolites are co-oxidants of DNA methylation [21]. The results of epidemiological studies suggest an inverse relationship between folate consumption and the risk of occurrence of, among others, lung, pancreatic, esophageal, stomach, cervical, breast or leukemia cancers [35]. Most data concern the role of folic acid in the prevention of colon cancer. An inverse relationship between folate intake, blood folates and risk of cancer and colon adenoma has been shown [34-35].

One of the best-known functions of folic acid is to prevent the formation of neural tube defects in the fetus. Fetal development is a process in which - due to the intensive division of cells - the production of DNA acids increases, which significantly increases the need for folate. Adequate supply of folic acid is of particular importance in the period preceding pregnancy and in the first weeks of pregnancy. Many scientific studies have shown that women taking folic acid during this period may reduce the risk of some congenital malformations in newborns. Of particular importance is the effect of folic acid on reducing the risk of having a baby with a neural tube defect. Taking folic acid in the periconceptional period can also be effective in the prevention of other congenital malformations, including defects of the heart, limbs, urinary tract and craniofacial clefts [4].

Insufficient nutritional status of folate in pregnant women increases the frequency of miscarriages and

pregnancy complications, and reduces the birth weight of the newborn. A serious effect of folic acid deficiency in the diet of pregnant women are fetal neural tube defects. The moment of shaping of the neural tube, from which the brain and spinal cord of the child develops, is particularly important. Failure to close the neural tube leads to developmental defects of diverse clinical forms. This happens in the first two months of fetal life. This disorder is characterized by deformations of the skull and spine, which lead to the death of a newborn child immediately after birth or permanent disability [4, 36]. The most widespread and the most serious defects of the neural tube are anencephaly and spina bifida. They are the result of a defect in the process of the formation of the central nervous system (CNS). These defects occur when the part of the neural tube, which later develops the spinal cord and the brain, does not close. The closure takes place about 24 days after the insemination, i.e. at the time when the woman only finds out that she is pregnant. Anencephaly is a lethal disorder. The consequence of the remaining neural tube defects are premature deaths or permanent disability [2].

The incidence of these defects in the world ranges from 0.5 to 8, and in Poland 2-3, per 1000 live births [21-22]. Poland is among the countries with the highest infant mortality in Europe due to congenital neural tube defects. In 2001, congenital malformations accounted for 34% of all deaths. At the same time, this is the second most frequent cause of infant death due to birth defects in infants in Poland. Prevention of the aforementioned defects is possible thanks to the use of folic acid supplementation, which reduces the probability of appearance of these defects by 58 to 100% [30, 35-38]. Neural tube defects may be genetically determined, but they may also be the result of environmental impacts. The birth of a child with a defect qualifies the given family to an increased genetic risk group. The risk of a defect in another child is about 4% and increases to over 10% in the case of earlier birth of two children with neural tube defects [23]. Due to very unfavorable prognosis for children born with neural tube defects prevention is of fundamental importance here.

There is a large body of literature demonstrating the deficiency of maternal folic acid intake in preventing birth defects, as well as investigations into potential adverse consequences of consuming folic acid above the upper intake level (UL). Recently, two authoritative bodies convened expert panels to assess risks from high intakes of folic acid: the U.S. National Toxicology Program and the UK Scientific Advisory Committee on Nutrition. Overall, the totality of the evidence examined by these panels, as well as studies published since the release of their reports,

have not established risks for adverse consequences resulting from existing mandatory folic acid fortification programs that have been implemented in many countries. Current folic acid fortification programs have been shown to support public health in populations, and the exposure levels are informed by and adherent to the precautionary principle. Additional research is needed to assess the health effects of folic acid supplement use when the current upper limit for folic acid is exceeded [39].

Due to the important roles of this vitamin in the body, in order to prevent folic acid deficiency it is important to pay attention to the consumption of products naturally rich in B vitamins and folic acid or enriched with this vitamin. In the case of some population groups, in particular for pregnant women and during childbearing period, it is also advisable to supplement the daily food ration with a synthetic form of folic acid. Too high doses of folic acid supplements may mask neurological symptoms in people with vitamin B12 deficiency and interact with anticonvulsants [25]. Daily ingestion 15 mg of folic acid may cause disorders of the nervous and digestive systems, also allergic skin reactions may occur. However, folic acid in doses slightly exceeding the physiological demand of folic acid is a safe vitamin.

Conclusion

The increasing pool of evidence supporting the health-promoting effects of folic acid suggests the possibility of its future role in the prevention and the treatment of diseases. Folic acid is used as a supplement in most cases but is increasingly being used as medication especially in trials as an anti-cancer medication [40]. Although the effect of folic acid supplementation during the pre-conception period to reduce the incidence of neural tube defects (NTDs) is well established, its effect on other diseases yielded many contradictory results. Therefore, effects of folic acid supplementation appear worth being investigated in more detail by prospective studies.

Most of the published studies were observational studies and a lesser proportion were conducted on cell lines and animals. Supplementation and medicinal benefits of folic acid in some diseases should only be recommended when its beneficial effects are well established in humans.

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