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CURRENT STATUS OF FOLIC ACID FORTIFICATION IN ROMANIA

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Abstract

Among other benefits, folic acid has proven its role in preventing neural tube defects in the fertile female population. The neural tube defect prevalence is 21.9 in 10.000 births in the Eastern Mediterranean, while in the United States of America, the majority is from 5.5 to 6.5 in 10.000 births. This difference, in favor of the United States, is probably due to the folic acid food fortification program. In Romania, the importance of periconceptional care is still underestimated; women from disadvantaged areas do not seek medical advice before pregnancy, during pregnancy, or even postpartum, and an obstetrician does not monitor most pregnancies. Folic acid supplementation periconceptionally remains a neglected subject in the Romanian population, which could benefit from folic acid food fortification.

Keywords: *folic acid, folate, food fortification, neural tube defects, cardiovascular disease, stroke*

Introduction

Folic acid is a well-known essential nutrient that plays a crucial role in RNA and DNA synthesis, hematopoiesis, and DNA methylation. Another possible part could be in normal neuronal function, as folic acid is most frequently used to prevent the occurrence or reoccurrence of neural tube defects (1). Although healthcare workers and patients generally use folic acid, folic acid represents the synthetic form found in prenatal supplements or multivitamins. At the same time, folate, or vitamin B9, is the form of folic acid naturally found in food (2). The three folic acid sources are natural sources (vegetables like cowpeas, spinach, asparagus, white rice, green peas, broccoli, peanuts, lettuce, fruits like orange, papaya, banana, avocado, and oher origin aliments like beef liver, eggs, bread), pharmacological sources (multivitamins, prenatal vitamins, some oral estrogen-progestin pills, some iron-folate supplements) and food fortification (fortified breakfast cereal, fortified grain products). The folic acid food fortification program was introduced in the United States of America (USA) 1998 to prevent neural tube defects. It included fortifying all cereal grain products with folic acid (3). This public health measure has decreased the prevalence of newborns with neural tube defects by 35% every year; in other words, due to folic acid food fortification, 1300 babies born yearly in the USA do not have neural tube defects (3). Unfortunately, folic acid food fortification was not globally embraced. In Europe, there is heterogeneity regarding folic acid food fortification: the United Kingdom has incorporated this program into the health policies, while other European countries have been a skeptic regarding the safety and possible long-term effects (the possibility of masking a deficiency in vitamin B12, a potential role in cancer) (4).

A recent comprehensive narrative review published by Ismail et al. in 2023 (5) analyzing intended and unintended consequences of folic acid food fortification revealed that, besides the famous role

in neural tube defects prophylaxis, folic acid fortification played a role in the metabolism of homocysteine, preventing hyperhomocysteinemia, which is present as a risk factor in 60% of cases of cardiovascular disease, resulting in lower rates of cardiovascular disease. With the decrease in cardiovascular disease, a reduction in stroke cases was also observed (RR: 0.9; 95% CI: 0.84, 0.97; p = 0.005) (6). Concerning mental health and depression, besides folic acid fortification, folic acid supplements in 6-year-old children with mothers diagnosed with epilepsy and receiving anti-seizure medication, there was a statistically significant increase in the children's IQ (7); in addition, adolescents exposed to folic acid have a lower risk of psychosis spectrum symptoms (8). The risk of cognitive impairment in the elderly population is still debated, as cognitive function is more associated with vitamin B12 deficiency rather than folate excess. Regarding depression, although there are no studies regarding the association with folic acid fortification, there has been a low folic acid serum level in patients with depression. This fact could suggest that folic acid fortification or supplementation could aid in the fight against depression (9). Folic acid deficiency is linked to macrocytic anemia, which can cause red blood cell macrocytosis; current evidence is heterogeneous, with the need to further investigate the response of folic acid fortification on macrocytic anemia (5). Furthermore, folic acid supplementation has proven certain benefits in type 2 diabetes mellitus, specifically in reducing glycosylated hemoglobin, insulin resistance, fasting blood glucose, or homocystinuria (10). The main consequences of folic acid fortification are summarized in Table 1.

Table 1. *Consequences of folic acid fortification*

Effects of folic acid fortification
Neural tube defects prophylaxis up to 66-93% of cases
Prevention of hyperhomocysteinemia
Preventing cardiovascular disease
Preventing stroke (RR: 0.9; 95% CI: 0.84, 0.97; *p* = 0.005)
Lower risk of psychosis spectrum symptoms in adolescents
Higher IQs in 6-year-old children with epileptic mothers treated with antiseizure medication and folic acid
Reducing glycosylated hemoglobin in type 2 diabetes mellitus
Reducing insulin resistance in type 2 diabetes mellitus
Reducing fasting blood glucose in type 2 diabetes mellitus
Reducing homocystinuria in type 2 diabetes mellitus

In Romania, the current guideline, the Pregnancy Monitoring Methodology (11) provided by the Romanian Society of Obstetrics and Gynaecology since 2021, includes a recommendation for neural tube defects prophylaxis consisting of folic acid or other folic acid derivatives administration to a pregnant patient before eight gestational weeks. In current practice, this recommendation can be confusing, as information about the dosing or which type of folic acid should be used is not specified; the timing is also unspecified: should we use it preconceptionally, how long before the pregnancy or after the confirmation of the pregnancy? Are there conditions that could limit the absorption of folic acid or conditions that require an elevated supplementation of folic acid? The World Health Organization (WHO) recommends that every woman trying to conceive be administered 400 µg folic acid supplement daily, and supplementation should be continued until 12 gestational weeks. In addition, WHO recommends that pregnant women with a previous baby with a neural tube defect or a history of a fetus diagnosed with a neural tube defect should receive high-dose supplementation consisting of 5 mg folic acid daily (12).

Conditions associated with folate deficiency are represented by anorexia nervosa, a low intake of fortified food (low-carbohydrate diets with absent bread or pasta intake), treatments that may interfere with the metabolism of folic acid (trimethoprim, sulfasalazine, methotrexate, phenytoin), inflammatory bowel disease, intestinal bypass, intestinal resection, renal failure with dialysis, celiac disease, ethanol consumption, obesity, methylenetetrahydrofolate reductase (MTHFR) polymorphisms, the presence of folate receptor autoantibodies or chronic hemolytic anemia or exfoliative dermatitis, pathologies that require increased amounts of folic acid (13).

Regarding low-risk pregnancies, The American College of Obstetricians and Gynecologists (ACOG) (14) and the Centers for Disease Control and Prevention (15) recommend a 0.4 mg daily dose of folic acid at least one month preconceptionally and for at least the first 12 weeks during pregnancy. For patients presenting a moderate risk of developing neural tube defects (gastrointestinal malabsorption, type I and type II diabetes, severe liver disease, alcohol use, renal disease with dialysis, family history of neural tube disease, congenital folic acid pathologies), the Society of Obstetricians and Gynecologists of Canada (SOGC) recommends 1 mg folic acid daily three months preconceptionally and at least the first trimester of pregnancy (16). Patients at high risk of having pregnancies complicated by neural tube defects include couples that have cases of open neural tube defects in their personal history or have first degree relatives with this pathology; SOGC and ACOG recommend a 4 mg folic acid supplementation 3 months preconceptionally and during the first 12 weeks (14,16). The universal recommendation is to administer multivitamins including folic acid throughout pregnancy and lactation.

Conclusions

In conclusion, the Romanian population could benefit from folic acid fortification, as it has proven certain benefits, more specifically, the fertile population eager to procreate in order to prevent neural tube defects with its most spectacular and representative complications, spina bifida and acrania. While folic acid food fortification has yet to be promoted or integrated into national health policies, there is a real need for proper folic acid supplementation guidelines, which should be personalized depending on the individual risk of having a fetus with neural tube disease. In the meanwhile, women who seek periconceptional care should be advised by healthcare providers to introduce folic acid supplementation to ensure a minimal risk of neural tube defects occurrence.

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