Klotz

Acid folic and pregnancy: A mandatory supplementation

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Abstract

Neural tube defects (NTD) occur in 0.5 to 2 per 1000 pregnancies with various handicaps for the affected child. It is now well established that folic acid deficiency (absolute or relative) is a predisposing factor to this type of malformation. Several randomized controlled trials showed that high-dose folic acid (4 mg) is an essential factor for prevention of neural tube defects recurrence and significantly prevents the first occurrence of neural tube defects with a lower dose (0.4 mg). Other etiologies can favor the occurrence of NTD such as MTHFR polymorphism, some antiepileptic therapies, obesity and pregestational mellitus diabetes. Necessity of a preconception folic acid supplementation or at least folate nutritional status evaluation should be known for all of us including patients and public.

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Keywords: Neural tube defects; Folic acid; Pregnancy; Folates

Résumé

Les anomalies du tube neural (ATN) touchent 0.5 à 2 grossesses pour 1000 et entraînent divers handicaps chez l’enfant atteint. Il est aujourd’hui bien établi qu’une carence en acide folique (absolue ou relative) est un facteur de prédisposition à ce type de malformation. Plusieurs essais contrôlés randomisés ont montré que l’acide folique à haute dose (4 mg) était un facteur essentiel pour la prévention de la récidive des anomalies du tube neural et empêchait de manière significative leur première apparition avec une dose plus faible (0,4 mg). D’autres étiologies peuvent favoriser l’apparition des ATN, tels le polymorphisme de la MTHFR, certaines thérapies antéépileptiques, l’obésité et le diabète prégestationnel. La nécessité d’une supplémentation préconceptionnelle en acide folique ou, tout au moins, d’une évaluation des apports nutritionnels en folates, devrait être considérée par l’ensemble du corps médical, divulguée aux patientes et le grand public.

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Mots clés : Anomalies du tube neural ; Acide folique ; Grossesse ; Folates

In France, about half of the women of childbearing age have a folate deficiency. In most cases, this deficiency remains undiagnosed. The origins of this deficiency are multiple:

- a poor nutrition lacking fruits or fresh vegetables;
- inadequate energy intakes;
- frequent restricting diets without medical control.

The oral contraceptive pill, an excessive consumption of alcohol and tobacco also increase the risk of deficiency, as well as some medical treatments (anticonvulsant).

A fundamental difference exists between folic acid and folate. Folic acid is a synthetic compound that does not exist as such in nature. It has to be metabolized after absorption into biologically active folate metabolites. Folate (vitamin B9) is naturally found in food compounds. The B9 vitamin is essential for the embryologic development. Its protective effects are also involved in the prevention of Alzheimer’s disease, cardiovascular diseases and even in some cancers. In the literature, folate deficiency is
associated with low birth weight, premature delivery, miscarriage, congenital malformation and preeclampsia spectrum.

Neural tube defects (NTDs) affect an average of 1 in every 1000 established pregnancies world wide, although variations in NTD prevalence have been reported from 0.2–10 per 1000 in specific geographical locations (1). The anglo-saxon countries have one of the highest prevalence (8.05 per 10,000) with the north region of China. The total prevalence and live birth prevalence of NTD in Europe can be found by using data from EUROCAT registries and website for the period 1991–2011 ([www.eurocatnetwork.eu/ABOUTUS/MemberRegistries/MembersAndRegistryDescriptions/AllMembers].

We must care also about the precarious patients for which the deficiency can be easily attributed to food factor.

Folate (vitamin B9), present in large quantities in green fruits and vegetables, plays a fundamental role in growth and cell division [1]. Folic acid and its metabolites are important for the synthesis of purine and pyrimidine (Fig. 1). A folate deficiency causes a disturbance of the synthesis and methylation of DNA and hyperhomocysteinemia. Many studies have demonstrated a significantly increased risk of damage (as miscarriage, or thrombosis) in case of polymorphism of some of the genes involved in folate metabolism: MTHFR and MTHFD1 [2,3]. Patients carrying these genetic variants present difficulties to synthesize the active form of folate from folic acid. For 15% of the homozygous genetic variants patients for MTHFR, there is a decrease in the enzymatic activity of 75% and for the 35% heterozygous a decrease of 40% is described. About 50% of women do not transform correctly their folic acid. The alternative suggested by some studies to overcome this resistance, would be the administration of the 5methyltetrahydrofolate (5-méthylTHF) molecule that does not need to be metabolized [3].

1. Impact on the neural tube

The neural tube defects (Fig. 2) are the most frequent foetal abnormalities after the heart defects. These neural tube defects appear between the 22nd and the 26th day of gestation and occurs for 0.5 to 2 for 1000 pregnancies with various geographic and ethnic disparities [1].

The symptomaticology depends on the location and extent of the lesion. As showed on Fig. 2, a prenatal diagnosis can be done by an ultrasound examination (Fig. 2A). The seriousness of the condition can lead to the option of a medical termination of pregnancy (Fig. 2B). Over the past 15 years, the in utero surgery has developed in the antenatal management of spina bifida. A randomized trial in the US: Management of myelomingocele Study (MOMS) showed encouraging short-term results for children with a 50% reduction of hydrocephalus and improved mental and motor function at 30 months of life but with an increasing rate of prematurity. The long-term results are not yet known [1]. The PRIUM test, which tries to repair myelomingocele in utero is underway in France. However, before talking about surgery repair, it is necessary to consider prevention.

EUROCAT, the European register, showed a decrease in the prevalence of spinal dysraphism between the eighties and the nineties of the XX century. This prevalence then stabilized around 0.5/1000 pregnancies. In Paris in 2011, the prevalence of spina bifida was 3.79 per 10,000 pregnancies and 1.14 per 10,000 live births. This decrease is related to the introduction of dietary supplementation with folic acid in some countries, notably Ireland, but also found in the United States and Canada with a decrease of 34 and 50% respectively since the policy of systematic enrichment of certain foods conducted since 1998 and
currently underway in over 53 countries [4]. In 1991, a double blind randomized trial (The Medical Research Council Vitamin Study) on over 1000 patients demonstrated that high-dose folic acid (4 mg) was the main protective factor of the recurrence risk of neural tube defects (i.e. to prevent a second case of NTD in case of a first baby with the disease), with a decreased risk of recurrence of 3.5 to 1% in case of supplementation. In the US, before food fortification policy, the recurrence risk was estimated in the order of 2 to 5% [2]. A randomized trial in Hungary has also shown that administration of folic acid (0.8 mg) significantly reduced the initial occurrence of neural tube defects. Many studies have showed that low maternal levels of folic acid would be a promoting factor of neural tube defects [2]. Thus, in preconception, serum folate levels should be higher than 16 nmol/L. The optimum rate to an adequate prevention would be 50 nmol/L [3]. However, a recent study by Khoshnood et al. pointed out that in the absence of mandatory fortification, the prevalence of NTD had not decreased in Europe despite long-standing recommendations aimed at promoting periconceptional folic acid supplementation and existence of voluntary folic acid fortification [5]. An explanation can be found in the study by Luton et al. showing that despite broad communication, among 400 pregnant patients in France only 20% declared having had a pre or periconceptional supplementation [6].

2. Impact on other types of fetal abnormalities

In addition to being involved in the genesis of neural tube defects, folate deficiency increases the risk of prematurity, low birth weight and preeclampsia. Maternal folic acid supplementation appears to be ($OR = 0.45; 95\% CI, 0.29–0.71)$ significantly associated with a decreased risk of esophageal atresia, conotruncal heart defect, cleft palate, urinary malformations and omphalocoele.

It seems that folate levels can also have an impact on the psycho-affective development of the child. Some studies have shown that maternal folate levels can promote the development of the child and reduce the risk of hyperactivity [7].

3. Some possible sides effects to care about?

Acid folic supplementation also has its controversies. A possible promoting factor has been suggested for colorectal and breast cancer. An excessive intake of folate has been also associated with an exacerbation of B12 deficiency symptoms.

Recent studies have not confirmed any connection between folic acid supplementation and risk of colorectal adenoma, breast cancer, risk of twins, or with the risk of masking a vitamin B12 deficiency in a relatively young and healthy population of pregnant women. But this outcome could be of concern in other type of population (probably older). However, some authors recommend the administration of folic acid in a multivitamin supplement containing vitamin B12 [3,8]. A slightly increased risk of respiratory infection and children’s asthma was described with high doses of folic acid (5 mg) by some authors but deserve to be confirmed by other studies [8].

4. The importance of the developmental origin of health and adult diseases (DOHAD)

The necessity of folate prevention is now well established and prevention before and during pregnancy is now better understood. In the past three decades, association between early life exposures and the risk of diseases has been studied. These new theories and their scientific basis studies are most commonly called the DOHAD: developmental origin of health and adult diseases. The earliest periods of development are the most critical. The sensitivity of the epigenetic system to environmental factors occurs primarily during the period of developmental plasticity because this is the time when epigenetic marks undergo critical modifications [8]. Once a tissue or system is fully developed, while still somewhat plastic, it is less sensitive to alterations by environmental stimuli. The most sensitive window for epigenetic effects is different for each tissue and may extend into early childhood and perhaps into puberty or beyond for some tissues such as the brain and the reproductive system. These subtle functional changes, in many cases, are due to altered gene expression leading to altered cell proteins and in some cases altered numbers and/or location of cells.

In Gambia, Domínguez-Salas et al. [9] showed that the global methylation level in child was associated with the preconceptional and nutritional status of the mother by comparing some lymphocytes child cells and during the dry or wet season. The preconceptional and nutritional status is linked with the vitamin B12, B6, homocysteine and cysteine level. An enriched nutritional intake, including folate, can have a direct impact on the epigenome of the fetus and on his future capacities of adaptation or diseases (physical or psychological fragility). It seems that even the preconceptional status of the father has a significant part on the epigenome of the fetus.

5. Acid folic and diabetes

Offspring of women with pregestational diabetes mellitus have an increased risk of congenital anomalies, including NTDs. In animal models, folic acid supplementation reduces glucose-induced congenital anomalies with a threshold effect. In experimental work, administration of inositol, arachidonic acid and several antioxidant compounds, as well as folic acid, to the embryo, has proven to attenuate the teratogenic effects of a diabetic environment. Future therapeutic efforts may include supplementation with antioxidants or micronutrients, such as folic acid, to the pregnant diabetic woman, although exact compounds and doses need to be determined [10]. Some studies report a certain reduction in maternal teratogenic effect of DM-1 after folic acid supplementation during pregnancy, but the explanation of this effect requires further study [11]. In recent years, several academic societies have recommended high doses of folic acid (4–5 mg/day) to diabetic pregnant women, based on their risk of congenital malformations. When using high doses, we must take into account that they are in the pharmacological range, that there is no evidence of their benefit as a primary prevention strategy in diabetic pregnancy and those side effects are potentially serious [12]. The first effort must be done with a
good primary prevention with a dose of 0.4 mg, and if possible a prepregnancy counselling. If the dose of 5 mg was recommended for diabetic pregnant women, it would also be important to design follow up studies to detect potential side effects of such a policy.

6. Conclusion

A periconceptional folic acid supplementation is recommended in Europe and in many parts of our World. However, since 10 years, these measures did not allow a universal reduction in the rate of neural tube defects probably because these measures did not consist in fortifying current food everywhere. In a European survey published in 2013, only 17% of patients were aware of the role of folic acid in preventing spinal dysraphism [13]. It is well established that these lesions are multifactorial. However, folate deficiency, a treatable condition, remains a public health concern and recommendation on periconceptional supplementation. It should be known by all that 0.4 mg/day of folic acid started 4 weeks before and up to 12 weeks of pregnancy is efficient in primary prevention and that 5 mg/day for 4 weeks in anticonceptional to 12 weeks of pregnancy in the presence of history but also when taking certain antiepileptic drugs.

Disclosure of interest

The authors declare that they have no competing interest.

References