Prevention of Neural Tube Defects and proper folate periconceptional supplementation

Pietro Cavalli

Servizio di Genetica, Azienda Istituti Ospitalieri

Reprint requests to:
Pietro Cavalli
Servizio di Genetica, Azienda Istituti Ospitalieri
26100 Cremona, Italy

"Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community." (WHO, 1985).

The WHO statement on the rationale use of medicines, and the reasons why medicines are often used irrationally should be carefully considered even in the present days, as physician must face lack of knowledge, limited economic resources, and a plethora of therapeutic suggestions.
Neural tube defects (NTDs) are severe birth defects, occurring in 0.5 to 2 per 1000 pregnancies. The neural tube is the embryonic structure that develops into the brain and spinal cord: the defects arise from failure of embryonic neural tube closure by the fourth week of pregnancy (28th day after conception), causing malformations of the brain and spine, most commonly anencephaly and (myelo)meningocele or spina bifida, less frequently craniorachischisis (involving the posterior body axis) and encephalocele (involving the closure of the cranial neural tube).
Periconceptional folate intake can prevent about 70% of NTDs. However, correct NTDs prevention using periconceptional folate supplementation is rarely accomplished, as folinic acid (5-formyltetrahydrofolate) is commonly considered as an equivalent substitute of folic acid, while timing and dose of folate supplementation are often randomly approached.
Following the WHO recommendations, some simple and practical rules are reviewed hereafter, with the aim to improve the efficiency of folate supplementation in preventing NTDs.

Doses

Prevention up to 70% of NTDs can be achieved by supplementation with 4 mg/day of folic acid (1). However, two points should be emphasized: i) the preventive effect of folic acid is greater in women with lower serum folate, and ii) higher folate intake is related with higher risk reduction. Supplementation with 0.4 mg/day are associated with a 36% risk reduction (2). Higher risk reduction (up to 70%) can be obtained with a ten fold dosage of folic acid (4 mg daily).
However, a dose of more than 1 mg of folic acid daily might mask a clinical condition caused by vitamin B12 deficiency. For all those reasons, the recommended folic acid supplementation in the normal population is 400 mcgr (0,4 mg) daily.

> Every women in their reproductive years planning a pregnancy should undergo periconceptional supplementation with 0.4 mg (400 mcgr) folic acid daily.

In Italy, two pharmaceutical products (Folidex 400 mcg and Fertifol 400 mcgr) are labeled to prevent NTDs in the general population and are effective in reducing NTD occurrence risk.
However, reducing recurrence risk in women with a previous history of NTD requires a different approach. Those women are advised to take at least 4.0 mg folic acid daily, that is a tenfold dose of vitamin supplementation (3).

> Women with a previous history of NTDs are advised to undergo at least 4.0 mg folic acid supplementation daily.

In Italy, two pharmaceutical products (Folina 5 mg and Folico 5 mg) are available to prevent NTDs recurrence risk.

Timing

Neural tube closure is completed 28 days (four weeks) from conception, and the preventive effect of folic acid is not effective after that period. Moreover, highest serum folate levels require at least three weeks of treatment with folic acid (4).
Those are the reasons why folate supplementation should start al least one month before conception and continue until at least two months after conception.

> Folic acid supplementation should start at least one month and preferably two to three months prior to conception

Appropriateness

In Italy, the use of folates in preventing NTDs is a somewhat confusing task, and folinic acid is widely prescribed instead of folic acid. In particular, folinic acid (Calcium levofolinate: Folanemin, Levofolene) tablets are labeled “to mitigate side effects of cytosathic drugs”, and NTDs

prevention has never been claimed by Manufacturers.
It should be reminded that all data from scientific research in NTDs prevention are based on folic acid only, and folinic acid has never been cited in that field.
Moreover, folic acid and folinic acid supplementation achieve different effects in preventing NTDs in some experimental models (transgenic mice).
Also, no data are available on the exact dose of folinic acid that corresponds to the dose of folic acid before mentioned.
Furthermore, in Italy the lower dose of folinic acid tablests is 4.0 mg, that could be hardly justified in the general population.
Daily cost of folic acid use varies from Euro 0.05 (Folico tablets) to 0.12 (Folidex, Fertifol, Folina tablets), while daily cost of folinic acid is four to ninefold higher (Euro 0.30-0.45).

The use of folinic acid (calcium levofolinate) in preventing NTDs is inappropriate.

References

1. Prevention of neural tube defects: results of the Medical Research Council Vitamin Study. MRC Vitamin Study Research Group. Lancet 1991;338(8760):131-7.
2. Wald NJ, Law MR, Morris JK, Wald DS. Quantifying the effect of folic acid. Lancet 2001;358(9298):2069-73.
3. ACMG. American College of Medical Genetics Statement on Folic Acid: fortification and supplementation. Am J Med Genet 1998;78:381.
4. Truswell AS, Kounnavonq S. Quantitative response of serum folate to increasing intakes of folic acid in healthy women. Eur J Clin Nutr 1997;51(12):839-45.