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# Folic acid for the prevention of neural tube defects

## *Ácido fólico na prevenção dos defeitos do tubo neural*

Editorial

Neural tube defects (NTDs) are among the most common birth defects, which include anencephaly, spina bifida, and encephalocele. These serious birth defects of the brain and spine are preventable and are significant causes of infant death and childhood disability. It is estimated that there are more than 300,000 NTDs worldwide each year, many of these occurring in low-resource countries. They happen in approximately 1 of 1,000 births in the United States[1,2].

In Brazil, there is no reliable data regarding general incidence of spina bifida and other NTDs, except for reports of series in specific areas of the country. In the Brazilian Northeastern region, in a tertiary level hospital, the prevalence was five cases for every 1,000 births[3]. A population review for a 14-year period in the South of the country revealed a prevalence of approximately six cases per 10,000 births[4] and in the Southeast, it was 1.13 per 1,000 live birth[5].

Results of randomized controlled trials[6-8] and several observational studies[9,10] showed that 50 to 85% of NTDs can be prevented if women consume a folic acid — containing supplement before and during the early weeks of pregnancy in addition to the folate in their diet. Moreover, the Technical Committee and Multidisciplinary Update of the National List of Essential Medicines from the Brazilian Health Ministry recommend for the primary prevention of NTDs daily doses of 400 to 800 mcg, at least 30 days before planning to get pregnant and continue throughout the first trimester of pregnancy. In order to provide appropriate pharmaceutical form and concentration for the primary prevention of NTDs, an oral solution of 0.2 mg/mL folic acid was included in the National List of Essential Medicines[11].

The recommendations were developed through the collaborative efforts of the fetal and perinatology committee branch of the Brazilian Federation of Gynecology and Obstetrics (FEBRASGO) and external reviewers[12]. Due to the evidence that the prevention of NTDs by folic acid supplementation evolved over time, there are two separate recommendations: one for women at low risk-groups, who are mainly those with no previous history of a NTD-affected pregnancy, and one for females who have had a previous one and are considered at high risk-group for recurrence.

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Of all the children with a NTD, 95% were born to couples with either no family history of these defects or others risk factors. Evidence to date suggests that a supplement of 400 mcg (0.4 mg) of folic acid prevents the occurrence from 60 to 85% of NTDs, when it is taken before conception and continued throughout the first 30 days of pregnancy[6,7,9,12-16].

The working group recommends that all women of childbearing age who are capable of becoming pregnant take 400 mcg of folic acid daily, at least 30 days before planning to become pregnant and continue throughout the first trimester of pregnancy. In addition, women in reproductive age should be counseled on the benefits of folic acid supplementation during any gynecological appointment, such as at the time of their pap smear test, especially if the pregnancy is being planned. Considering the high rate of unplanned pregnancies in Brazil, the group reassures all efforts of public agencies towards the development of comprehensive programs to fortify food and do periodical follow-up of these programs.

## High-risk group for neural tube defects

among couples who had a child with a NTD, the recurrence risk is from 2 to 3% in subsequent pregnancies[1]. In 1991, the Medical Research Council (MRC) Vitamin Study Group[7] reported the results of a well-designed, prospective, randomized trial of folic acid supplementation for the prevention of NTDs in pregnancies of women who had a previous child with a NTD, and the CDC published its daily dose recommendations of 4,000 mcg (4 mg) of folic acid.

The results of the MRC study conclusively demonstrated that a daily dosage of 4,000 mcg of folic acid, in addition to folate in the diet, before and during early pregnancy, resulted in a 71% recurrence reduction of NTDs. The addition of other vitamins to the daily folic acid dose did not reduce the risk further. Use of multivitamins without folic acid did not result in a reduced risk for NTDs. The MRC study did not explore the possible benefit of a dosage lower than 4,000 mcg of folic acid. However, an earlier non-randomized study conducted in the United Kingdom suggested that a lower dosage, 360 mg daily, resulted in a comparable recurrence reduction of NTDs[17].

The working group recommends that women in the high-risk group who are planning to becoming pregnant take 4,000 mcg of folic acid daily, at least 30 days before and continue throughout the first trimester of pregnancy. In addition, pregnant women should be discouraged from using high doses of folic acid. Particularly, avoiding to take larger doses those that the one defined by the manufacturer, once this could induce an overdose of other vitamins and/or macro or micronutrient, being harmful to maternal and fetal health.

There is no rule for the prevention of other high-risk factors beyond previous history of NTD and patients with seizure disorders, being treated with valproic acid or carbamazepine (risk is approximately 1%). Nevertheless, those who are planning to become pregnant, and have a relative (as the brother, nephew or niece) with NTD (risk is approximately 0.3 to 1.0%), have type 1 diabetes mellitus (risk is approximately 1 %), or their partner has a NTD (risk may be 2–3%), should discuss with their physician the potential risk of having an affected child, as well as the advantages and disadvantages of increasing the intake of folic acid daily preconcepcional 400 mcg to 4000 mcg[13].

Implementing this recommendation may provide the opportunity for primary prevention of over than 70% of these serious disabling birth defects. Regular and ongoing ingestions of folic acid by women of childbearing age is necessary due to the fact that half of the pregnancies are unplanned, and NTDs occur during the first four weeks of gestation.

Despite the worldwide recommendation, only 16% of childbearing age women take folic acid and (only about) 5% of low risk-group take the correct dose of 400 mcg.

Hence, this piece of advice should be followed by the implementation of an educational program to prevent NTDs throughout the use of 400 mcg of folic acid supplementation, fortified foods, or a combination of both.

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