Prevention of neural tube defects

INTEGRATED MANAGEMENT OF PREGNANCY AND CHILDBIRTH **(IMPAC)**

The standard

All women, from the moment they begin trying to conceive until 12 weeks of gestation, should take a folic acid supplement. Women who have had a fetus diagnosed as affected by a neural tube defect (NTD) or have given birth to a baby with NTD should receive information on the risk of recurrence, be advised on the protective effect of periconceptional[1] folate supplementation and be offered high-dose supplementation.

Aim

To prevent NTDs and other congenital malformations in the fetus.

Requirements

- ☐ A national policy and locally adapted guidelines on folic acid supplementation are available and are correctly implemented.
- ☐ Health providers are competent in the following areas: the risk of folic acid deficiency; the benefits of folic acid supplementation before conception and during early pregnancy; correct supplement dosages; and the importance of advising pregnant women to take folic acid before conception and during the first trimester of pregnancy.
- ☐ Folic acid is available and affordable to women.
- ☐ A method to record the preventive treatment provided is in place.
- ☐ Health education activities are conducted to raise the awareness of women and of the community on the importance of taking folic acid supplements in the periconceptional period.

Applying the standard

Health providers in antenatal and family planning clinics must:

- Advise women trying to conceive to take a dose of 400 µg folic acid daily, starting two months before the planned pregnancy.
- Advise women who have not been supplementing their diet and who suspect themselves to be pregnant to begin taking 400 µg folic acid daily and to continue until they are 12 weeks pregnant.
- Counsel pregnant women who have previously had a baby with NTD or who have diabetes or who are under anticonvulsant treatment about the increased risk of a future baby being affected, and advise them to take 5 mg folic acid daily and increase their food intake of folate.
- Record the treatment given in the maternal card.
- Record cases of NTD, in accordance with local guidelines, in the logbook and in the woman's record.

[1] Before pregnancy and in the first three months of pregnancy.

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Audit

Input indicators

- Policy and local guidelines on folic acid supplementation are available in clinics.
- Training on folic acid supplementation and NTDs is provided to health staff of antenatal and family planning clinics.
- Information on the benefits of increasing folic acid intake is available and displayed in antenatal and family planning clinics.

Process and output indicators

- The proportion of ANC cards reporting whether or not a woman has taken folic acid prior to conception and/or during the first 12 weeks of pregnancy.
- The proportion of women reporting taking folic acid supplements during the periconceptional period.

Outcome indicators

- Incidence of neural tube defects in the newborn.

Rationale

Burden of suffering

NTDs represent one of the most common congenital malformations in neonates worldwide *(1)*. They constitute a heterogeneous group of disorders that occur during the first weeks of gestation, involving specific elements of the neural tube and its derivatives *(1,2)*. The incidence of NTDs in the general population varies from 1 per 1000 pregnancies in the USA to 12 per 1000 in parts of Ireland and Wales and among Indian Sikhs and certain ethnic groups in Egypt *(1,2)*.

The exact cause of NTDs is not known; over 95% occur in couples with a negative family history *(1,2)*. Nevertheless, the risk of recurrence is 1 in 33 couples with one affected pregnancy and 1 in 10 for those with two affected pregnancies *(1)*. Sisters of women with an affected child have a 1 in 100 risk and sisters of a man with an affected child have a 1 in 300 risk *(1)*. Folic acid and zinc deficiencies have been proposed as possible causes. Known factors associated with higher risk include maternal diabetes, alcohol abuse by the mother, aminopterin ingestion and antenatal X-irradiation *(1)*. Suspected contributing factors are anticonvulsant therapy, maternal hyperthermia, antenatal exposure to rubella and hallucinogen ingestion *(2)*.

Efficacy and effectiveness

Folic acid supplementation before conception and during the first trimester of pregnancy is one of the few public health interventions effective in reducing the risk of NTDs *(2–5)*. Controlled randomized clinical studies showed that folic acid supplementation during the perinatal period reduced the risk of recurrence in women who had previously borne a child with NTDs *(3)*. The evidence indicates that periconceptional folate supplementation reduces the incidence of NTDs in the general population *(2,4,5)*. The reduction is similar for first and recurrent cases of defects. Owing to the heterogeneous etiology of NTDs, however, the risk cannot be eliminated by this intervention.

Among other factors possibly associated with NTDs is a genetic mutation involving the methylenetetrahydrofolate reductase gene (the C677T allelic variant) *(6)*, but it is not clear if the occurrence of NTDs among the offspring of women with such a mutation is reduced by a higher intake of folate *(7)*. It is also unclear whether there is a link between vitamin B_{12} deficiency and NTDs *(8)*, but any future supplementation scheme could also include this vitamin *(4,9)*. Folate supplementation could be especially important in women undergoing folate-depleting treatment, such as with antiepileptic drugs *(2,10)*, aminopterin, methotrexate, sulfamethoxazole or pyrimethamine, but further research is needed to reach a firm conclusion.

Randomized trials, supported by many observational studies, indicate that periconceptional use of folic acid in multivitamin supplements reduces the overall risk of birth defects, even after excluding NTDs *(11)*. This overall reduction seems to be due to a reduced risk of cardiovascular anomalies (reduction of 34-58% in different studies), orofacial defects (reduction of

30%), limb deficiencies (reduction of 46-81%), urinary defects (reduction 40-83%), and onphalocele and imperforate anus.

Folate supplementation has been associated with a small increase in multiple gestation, but a recent systematic review does not support this finding *(3)*. No harmful effects of folate supplementation have been demonstrated, either in the short or the long term *(2,12)*. However, if an increase in multiple gestation is confirmed, it might be necessary to reconsider the benefits of folate supplementation. The effectiveness of the intervention, both in developed and in less developed countries, depends on informing women of childbearing age and on the ability to plan a pregnancy *(13)*. Possible alternatives or complements to giving folate supplements as pills could be information on changing the diet *(7,14)* and food fortification *(5)*, although these interventions alone are less effective in increasing plasma folate levels owing to lower bioavailability *(5,7,14)*. If food fortification is employed, it is recommended that a higher level of folate (350 µg/100 g food) be used *(15)*. In the North American setting, high-dosage fortification is considered to have a high benefit-to-cost ratio *(15)*. It is still unclear as to whether NTDs can be prevented by increasing the consumption of foods rich in folates. There is also uncertainty as to the benefits and risks for the whole population from fortification of basic foods with folate; this is linked mainly to the possibility of masking pernicious anaemia in elderly patients who receive folate supplementation *(4)*.

The table below summarizes the evidence from the most relevant studies. The level of evidence is presented using the NICE methodology which applies a coding from 1 (high level) to 4 (low level). For details, see also the *Introduction to the Standards for Maternal and Neonatal Care* and the *Process to develop the Standards for Maternal and Neonatal Care* on http://www.who.int/making_pregnancy_safer/publications/en. For an overview of a comprehensive list of evidence, please refer to the reference section of the standard.

Study (Type & Level of evidence)	Population & Setting	Objective & Intervention	Outcomes linked to the standard	Results	Comments
2. Lumley et al. 2004 Most recent substantive amendment April 2001 **Systematic review** **1++**	4 trials, 6425 women Australia, Canada, France, Hungary, Ireland, Israel, United Kingdom, countries of the former USSR Baseline risk of NTD – minimum 0.2% – maximum 7.8%	To assess the effects of periconceptional increased consumption of folate or multivitamins on the prevalence of NTD The dose of folate in the trials ranged from 0.36 to 4 mg/day	NTD incidence – minimum – maximum Miscarriage Stillbirth Multiple gestation	Folate + vitamin supplement vs control NNT [a] 694 (575–1190) NNT 18 (15–30) 4 studies, 6424 women NS [b] 3 studies, 7600 women NS 3 studies, 7600 women NS 3 studies, 6241 women	Two trials comparing folate alone vs vitamins alone showed that reduction in NTD is due to folate and not to vitamins
8. Ray & Blom 2003 **Systematic review of case control studies** **2++**	17 case-control studies were included, mean sample size 33 cases and 93 controls.	To investigate the association between low maternal B12 and increased risk of fetal NTD	NTD	Low level vs high level of serum vitamin B12 Odds ratio 0.9–13.3 (0.4–65.5)	There seems to be a moderate association between low maternal vitamin B12 status and the risk of fetal NTDs; no final conclusions can be drawn

[a] Number needed to treat [b] Non-significant

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Links and additional sources

I. *Auditable standards. Care after birth*. London, Royal College of Obstetricians and Gynaecologists, 1999.

II. *Pregnancy, childbirth, postpartum and newborn care: a guide for essential practice*. Geneva, World Health Organization, 2003 (http://whqlibdoc.who.int/publications/2003/924159084X.pdf, accessed 7 December 2004).

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