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Awareness and use of folic acid in the Netherlands

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Summary

Neural tube defects (NTDs) and some other severe congenital anomalies are partly preventable by the periconceptional use of folic acid. This thesis describes how scientific knowledge about folic acid was implemented in Dutch policy and analyses the effect of this policy.

Chapter 1 describes the results with respect to NTD prevalence (first part), and with respect to the prevalence of other birth defects (second part) of controlled clinical trials and observational studies related to the use of folic acid supplements. All but one study showed that the risk of having a child with an NTD can be reduced by at least 50% if folic acid supplements are taken periconceptionally. Most studies were recurrence studies using different doses of multivitamins containing folic acid. The efficacy of 4 mg of folic acid in women with a recurrence risk was conclusively demonstrated by the MRC trial in the UK. The Hungarian trial of Czeizel showed the same preventive effect for first occurrences with folic acid (800 µg) taken as part of a multivitamin. In a study on Chinese women, Berry showed in 1999 a highly protective effect of 400 µg of folic acid alone on the NTD occurrence risk.

The Hungarian study of Czeizel not only showed a protective effect on the occurrence of NTDs but also on the occurrence of other birth defects. The second part of Chapter 1 describes studies on possible protective effects of folic acid on the occurrence of orofacial clefts, cardiac defects, urinary tract defects, and limb reduction defects. The majority of these studies show a preventive effect of multivitamins containing folic acid.

Chapter 2 describes how this scientific knowledge was implemented in the Dutch situation. Two official reports on this topic were published in 1992 and 1993. Only women with a prior NTD pregnancy (recurrence group) were advised to take 4 mg folic acid pills per day. Women with a higher than normal risk because of exposure to risk factors, such as diabetes mellitus or epilepsy, were advised to take the same dose as advised for women with a normal population risk; that is 400 µg of folic acid per day. Since the consumption of folic acid-rich food is not enough to reach, at population level, a sufficient level of folic acid during pregnancy, the report advised to consume foods fortified with folic acid. Regulations in the Netherlands, however, do prohibit such a fortification. An effect of food fortification with folic acid could be masking pernicious anaemia, thus delaying the diagnosis of a vitamin B₁₂ deficiency. Although the report concluded that there were no specific groups in the Dutch population who would be at extra risk for a vitamin B₁₂ deficiency if food were fortified with folic acid, food fortification was not a real option at that time. Instead, all women of childbearing age were advised to take a 0.5 mg folic acid pill. The main problem with folic acid supplementation is to reach the target group sufficiently in time to take folic acid for at least four weeks before conception. Therefore, the Ministry of Health, Welfare, and

Sports initiated a campaign in 1995 to reach and inform this target group. Apart from the national campaign, there was also a regional campaign, in which extra attention was given to reach women with a lower socio-economic status, because they are more difficult to reach and because NTDs are more prevalent among them.

Chapter 3 describes the method and results of the campaign in two national surveys. Pregnant women at their first or second antenatal visit to the obstetrician, general practitioner or midwife were asked to fill out a questionnaire. Level of education was used as an indicator of socio-economic status. Before the campaign, an increase of knowledge so as to match the level of knowledge of adverse effects of alcohol and smoking was considered adequate -that is, 70% of women planning a pregnancy should know about the advice and 65% of these women should use folic acid appropriately. After the campaign, awareness and use of folic acid had increased considerably, both for lower and for higher educated women. The results of the surveys show that the knowledge criterion is met (in 1996, 77% had heard about folic acid before pregnancy), but this is not the case for the use criterion (in 1996, 21% took folic acid in the advised period). However, socio-economic differences in awareness and use of folic acid have not significantly decreased. The effort made in the additional campaign to reach in particular lower educated women, did not result in reducing the differences between groups of different socio-economic status. To the contrary of its target, media attention focused on the lower educated group benefited the higher educated group more. Reasons for not taking folic acid were either not thinking about it or a too late awareness to be able to start in time.

In 1998 and 2000, two follow-up studies were performed in the Northern Netherlands. Chapter 4 describes the results. Since the level of knowledge (before pregnancy) was already high in the survey of 1996, it was not surprising that this remained constant at about 75% in later years. In 1998, the socio-economic differences in knowledge with respect to the advised period for taking folic acid had increased. In 2000, the percentage of women who knew this advised period decreased. Media was the most important source for obtaining information about folic acid. In the follow-up studies, the use of folic acid in the advised period increased to 36% for both studies while socio-economic differences remaining stable. The four surveys show that appropriate use of folic acid never exceeds 50%, not even for higher educated women. This is unexpected especially since the Netherlands is a country with a very high percentage of planned pregnancies. The conclusion is that in order to reduce the NTD risk for all women fortification of food with folic acid should be investigated. This in combination with a structural campaign promoting folic acid and informing women about the right period to take it.

Chapter 5 deals with the final goal of the folic acid public campaign, namely the reduction of the prevalence of NTDs and possible other birth defects. The Northern

Netherlands (NNL) EUROCAT registry was used to investigate this. In Chapter 5.1 a methodological exercise is described attempting to estimate the expected prevalence of defects had the supplementation of folic acid never been introduced. A model was built to estimate the prevalence of NTDs and other folic acid sensitive defects (FASDs). FASDs are defined as NTDs and orofacial clefts, conotruncal heart defects, urinary tract defects and limb reduction defects. The total prevalence over the years 1981-1995 was used as the base-line prevalence to estimate the prevalence for the years 1996-1999. The results of the model show to be dependent on the used cut-off point i.e. the last year included in the model. This is mainly due to insufficient informative years. As a consequence, the model may be unstable. However, it is clear from the results in chapter 5.1 that in the Northern Netherlands with 20,000 newborns per year and 35% of women taking folic acid, it is very difficult to detect a significant decrease of a rare birth defect such as NTD. For FASDs this detection will be easier since the prevalence is higher and does not fluctuate as much as the NTD prevalence.

This is the reason why in chapter 5.2 a case control study analysis is performed using the EUROCAT NNL data to investigate the possible preventive effect of folic acid in the FASD group. The study showed a significant reduction in risk of heart defects and a strong indication for a reduction in the prevalence of urinary tract defects.

Finally, chapter 6 discusses further implementation of strategies to improve folic acid intake. The results of the surveys described in this thesis imply socio-economic differences with respect to the prevalence of NTDs and the intake of folic acid. There are three possible pathways to increase the amount of folic acid. Firstly, by eating more folic acid rich-foods. However, several studies have shown that this is a relatively ineffective way compared with food fortified with folic acid. This is probably due to the fact that the synthetic form of the vitamin is more stable and more bioavailable. It is estimated that the bioavailability of natural food folate is approximately 50%. The second pathway is by supplementation; this is the current strategy in the Netherlands. This thesis shows that it is not enough to have a high percentage of planned pregnancies and a positive attitude towards folic acid to make this strategy a success. The last option is to fortify food with folic acid. This is common practice in most European countries where mostly cereal grain products are fortified. In the USA, enriched flour is fortified with 140 μg folic acid per 100 g since 1998. In the UK, the government is advised to follow the same strategy but with a higher amount of folic acid: 240 $\mu\text{g}/100$ g. A risk of excessive intake of folic acid is that it may mask pernicious anaemia, a vitamin B₁₂ deficiency. But nowadays, this anaemia can be diagnosed by determination of B₁₂ in serum. Apart from helping to prevent serious birth defects, food fortified with folic acid may also help to reduce arteriosclerotic vascular disease by reducing homocysteine levels. However, there are no studies that directly relate dietary folate to the occurrence of vascular disease.

Since this thesis shows that socio-economic differences with respect to the use of folic acid are increasing, the option of fortification must be seriously considered. It is

therefore disappointing that a recent report of the Dutch Health Council concludes to only fortify products especially aimed at women who want to become pregnant. Nothing is said about what kind of products to think of, or the amount of folic acid to be added. If food fortification is not feasible in the nearby future, then the information on folic acid to all women of childbearing age has to be intensified and has to be structural. The media are important, but this thesis showed that health care professionals play an important role as well. In particular lower educated women are relying on the advice of their general practitioner. The right time to start with folic acid, at least four weeks before conception, should be stressed more. Finally, since the sensitive period in embryonic development for some birth defects is longer than for NTDs, this thesis recommends extending the postconceptional period of taking folic acid to at least three months of pregnancy.