From contraception to pregnancy planning: can oral contraceptives be used for folate supplementation?

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Impact of births complicated by neural tube defects (NTD)

Neural tube defects (NTDs) are congenital structural abnormalities of the brain and vertebral column caused by failure of neural tube closure [1]. They include anencephaly (a lethal malformation), encephalocele and spina bifida. Most pregnancies with anencephaly are terminated in the first trimester [2]. Spina bifida is usually compatible with life but typically causes substantial disability in survivors. Together with low birth weight, NTDs and other congenital anomalies (2–3% of all livebirths) are the leading cause of infant mortality and have remained so for nearly 80 years. Worldwide, NTDs affect more than 400,000 pregnancies a year and result in an estimated 41,000 deaths and 2.3 million disability-adjusted life years [3].

NTDs have a huge social and economic impact. It is estimated that the average total lifetime cost for each infant born with spina bifida is approximately USD 532,000, while estimated annual medical and surgical costs for those living with spina bifida in the United States exceed USD 200 million [4]. The accompanying emotional and social problems of those affected by spina bifida should not be underestimated.

Importance of folate

The aetiology of NTDs is multifactorial [5]. Adequate intake of folic acid by women a few months before pregnancy and during the first trimester can significantly reduce the risk of fetal NTDs in both healthy women and those at higher risk of having a child with an NTD (diabetics, obese women, smokers, alcohol consumers, antiepileptic drug users).

In 1991 the Medical Research Council Vitamin Study [6] reported that periconceptional intake of 0.4 g/day folic acid reduced the recurrence of offspring with non-syndromic NTDs by 72%. However, the majority of NTD pregnancies are first occurrences [7]. A randomized trial in Hungary showed that periconceptional folic acid supplementation of 0.8 mg/day significantly reduces first occurrence of NTDs [8]. Furthermore, there is increasing evidence that folic acid may also protect against other congenital anomalies, especially heart and orofacial defects [9].

The current worldwide accepted recommendations for preconceptional folic acid supplementation may be summarized as follows:

1. All women of childbearing age, if planning pregnancy, should consume 0.4 mg/day folate from supplements, fortified foods, or both, in addition to consuming food folate from a varied diet starting at least 1 month before conception and through the first 3 months of pregnancy.
2. Women at high risk of an NTD pregnancy (e.g. maternal NTD, previously affected pregnancy, type 1 diabetes, use of antiepileptic drugs) should consume 4 mg/day folic acid during the periconceptional period [10].

Traditional programmes for the prevention of poor pregnancy outcomes commence with the first prenatal visit. The course of many poor outcomes, however, is set before this first encounter. Organizations representing professionals and those working for the prevention of both maternal and perinatal morbidity

Table I: *Sources of folate supplementation in the periconceptional period [13–21].*

Folate source	Advantages	Disadvantages
Folate from unprocessed foods	Available in a variety of everyday foods	Low bioavailability Prone to oxygenation and food processing Large amounts are needed to meet daily folate requirements Inefficient in patients with malabsorption
Foods fortified with folic acid	Supplement to unprocessed foods	Only 10% of reproductive-age women consume a highly protective amount of folate Non-target population has long and unnecessary exposure to folate Available only in certain countries
Folic acid tablets	Cheap and available worldwide	Poor compliance Lack of awareness among women and health care providers
Oral contraceptives containing folate	Optimal folate concentration in periconceptional period that remains sufficient for several weeks after cessation of oral contraceptive Protective folate concentration in cases of accidental pregnancy due to contraceptive failure or poor compliance Suitable for both birth control and prevention of birth defects (pregnancy planning) Provides an opportunity to educate women during counselling about prevention of birth defects Suitable for a targeted population without exposing those not at risk	Suitable only for contraceptive pill users

and mortality in all developed countries now recognize that preconceptional health promotion is an important part of women's health care. During periods of rapid cell growth and division, such as embryogenesis and fetal development, maternal folate requirements increase dramatically.

By 56 days post-conception, any major structural anomalies of the forming fetus have already developed. Closure of the neural tube occurs within just 28 days of conception, when most women are still unaware of their pregnancy. Organogenesis in the human embryo may be disrupted by environmental factors, for example maternal habits (alcohol use and smoking), underlying maternal disease (diabetes), teratogenic drug exposure (vitamin A, antiepileptics) and maternal nutritional status (folate levels) [11].

Preconceptional counselling and family planning also help to prevent other poor pregnancy outcomes. For example, the benefits of smoking cessation before (or during) pregnancy for the prevention of low birth weight, prematurity and placental abruption have been well documented [12].

Currently, women of childbearing age can improve their periconceptional folate status by (1) eating unprocessed foods rich in natural folate, (2) eating foods fortified with folic acid, (3) taking tablets containing folic acid and (4) taking oral contraceptives with added folate *(Table I)*.

Sources of folate

Unprocessed foods rich in natural folate

Barely any woman of childbearing age gets the required daily amount of folate through unprocessed foods rich in folate. Furthermore, natural folate is heat-labile and prone to oxidative cleavage, such that it may be destroyed by storage, processing and cooking. The bioavailability of naturally occurring folate is relatively low.

Foods fortified with folic acid

In 1998, the United States implemented mandatory

fortification of bread, cereal, flour, corn meal, pasta, rice and other grain products with folic acid to reduce the occurrence of NTDs. Many countries followed suit, including Canada, Australia, Chile and some African and Asian countries. The rate of NTDs in the United States dropped by 25% [13], while in Canada food fortification has achieved a 46% reduction in the prevalence of NTDs [14]. However, in Europe no country has yet moved to compulsory food fortification due to concerns about possible health risks related to raising the folic acid intake of whole populations. Although food fortification in the United States increased the serum folate levels of women of childbearing age to an acceptable level, less than 10% of these women reached a red blood cell folate level (906 nmol/l) considered to be highly protective [15]. Therefore it is likely that women of childbearing age need to consume additional folic acid through tablet supplementation in order to reach protective red blood cell folate levels.

The Irish experience showed that voluntary food fortification can have a beneficial effect on public health but cannot serve as a reliable public health intervention. The Irish Food Safety Authority found an undesired high blood folate status in a substantial proportion of the population, especially among children and the elderly [16]. Recent scientific developments linking excessive folic acid intake to an increased risk of some developmental diseases, degenerative disorders and even cancer emphasize the need to ensure that individuals are not exposed to excessive folic acid levels in the food supply [17].

Tablets containing folic acid

Despite growing public awareness about the importance of taking folic acid supplements, it is estimated that a minority of women actually follow existing recommendations and take folic acid supplements during the advised period [18, 19]. There are several reasons for this: a substantial proportion of women are not aware of the recommendations, and in those who are, compliance is poor.

It is estimated that over 50% of pregnancies are unplanned. Once a pregnancy test is shown positive, there is nothing much that can be done to prevent an NTD, since the critical period of neurulation has already occurred. Health care providers have their own responsibility in this issue. Despite the fact that in the United States more than 50% of women aged 18–39 access preventive health services, for the majority a visit to the gynaecologist is no more than a PAP smear, pelvic examination, ultrasonography or new or repeat prescription of contraceptives. A recent study of nearly 600 obstetrician-gynaecologists and family physicians revealed that, in an annual well-woman examination for women of childbearing age, 42% of obstetrician-gynaecologists reported addressing multivitamin supplementation 'occasionally' or 'never' and 39% addressed the specific nutrient folic acid 'occasionally' or 'never'; the figures for family practitioners were 55% and 59%, respectively [20].

"Once a pregnancy test is shown positive, there is nothing much that can be done to prevent an NTD, since the critical period of neurulation has already occurred."

There are several possible explanations for the lack of attention to proven prevention strategies, such as inadequate education of clinicians about preconceptional health and pregnancy planning, poor appreciation of the incidence of unintended pregnancies and congenital anomalies, and possible lack of confidence that preconceptional health counselling can make a difference. Women who are not considering pregnancy are believed to be even less likely to consume folic acid on a regular basis, because their focus is on preventing pregnancy rather than preventing birth defects.

Adding folate to oral contraceptives: a new, targeted approach in the primary prevention of NTDs

Oral contraceptives are predominantly used for reversible contraception. An oral contraceptive with added folate is already available in the United States. At the end of September 2010 the US Food and Drug Administration approved Beyaz® tablets, a combined oral contraceptive that contains a folate (levomefolate calcium 0.451 mg) in addition to drospirenone and ethinylestradiol [21]. Beyaz® is based on the approved product YAZ®, which contains the same doses of estrogen and progestogen. Beyaz® is also approved for the secondary indication in women choosing to use an oral contraceptive as their method of contraception, to raise folate levels for the purpose of reducing the risk of NTDs in a pregnancy conceived while taking the product or shortly after discontinuing it. The primary efficacy study for Beyaz® was a multicentre double-blind randomized controlled US trial in 379 healthy women aged 18–40 who were treated with Beyaz® or YAZ® alone for up to 24 weeks. Beyaz® was found to increase folate levels in the study group. In a German study of Beyaz®, folate

levels remained elevated for several weeks following its discontinuation.

If all oral contraceptives were fortified with folate, they would provide the recommended minimum of 0.4 mg folate daily to the approximately 17 million women in the United States who use this form of birth control. Even if these women took their oral contraceptives along with daily multivitamins containing folic acid, there would be no concern about possible overdosing, because even 1 g/day folic acid is not considered an overdose.

"Adding folate to oral contraceptives is about preconceptional health promotion and changing pregnancy prevention into pregnancy planning."

Combining folate with an oral contraceptive is of essential importance for those with poor compliance, since roughly 1 million women a year become pregnant in the United States while taking birth control pills and half of these unintended pregnancies go to term. By using oral contraceptives with added folate, women would receive recommended protective doses of folate for the crucial period before conception and at the beginning of pregnancy; the risk of NTDs both in planned and unplanned pregnancies would therefore be substantially reduced. As one-fifth of women become pregnant within one cycle of stopping oral contraceptive use [22], a substantial proportion of women could not achieve protective folate levels even if they started folic acid supplementation immediately after stopping oral contraceptives.

Of course, when women decide to stop oral contraceptives and become pregnant, their health care provider has a responsibility to counsel them about folic acid supplementation. Adding folic acid to oral contraceptives has the potential to increase opportunities to educate providers about the importance of folic acid as an effective, cheap and safe medicine. Additionally, women would be exposed to messages about folic acid on the product packaging and possibly also from the pharmacist. Adding folate to oral contraceptives is about preconceptional health promotion and changing *pregnancy prevention* into *pregnancy planning*.

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