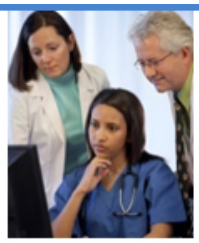

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Topic: Prenatal Care

Case #1106

FOLIC ACID IN WOMEN'S HEALTH

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Learning Objectives for this **periFACTS®** Case: Upon completion, the learner will be able to:

- Discuss how folic acid functions in the body.
- List sources of folic acid in the diet and the role of food fortification in the prevention of birth defects.
- Identify recommended supplementation levels of folic acid.

INTRODUCTION

You might wonder why we need to revisit the topic of folic acid use during pregnancy. "Hasn't this issue long since been resolved?" you might ask. Scientifically, the answer is yes, but the importance of folic acid must be kept at the forefront of obstetric practice, because it is easy to take it for granted despite being one of the simplest ways known to reduce the incidence of certain serious birth defects. Folic acid can prevent nearly all cases of *folic acid-preventable* spina bifida and anencephaly. In addition, some studies associate folic acid supplementation with a reduction in cardiovascular defects and cleft palate as well. Folic acid is the only known vitamin in

which supplementation prior to conception and in early pregnancy prevents birth defects.* The medical community can play an important role in communicating the importance of preconception folic acid usage to prevent birth defects in women of reproductive age.

Table 1. Fortified Foods and Other Food Products High in Folic Acid

Green Leafy Vegetables	Other Vegetables	Meat	Fruit and Fruit Juices	Others	Fortified Flour Products
Spinach	Okra	Beef Liver	Bananas	Mushrooms	Breads
Broccoli	Asparagus	Beef Kidney	Lemons	Yeast	Cold Cereals
Lettuce	Beans		Melons		Pasta
			Tomato Juice		Crackers
			Orange Juice		Cookies
					Baked Goods

FOLIC ACID

Folic acid, also known as (2S)-2-[(4-{[(2-amino-4-hydroxypteridin-6-yl)methyl]amino} phenyl)formamido]pentanedioic acid—is a water-soluble, essential B vitamin that is particularly important for deoxyribonucleic acid (DNA) synthesis. The human body does not make folic acid and, therefore, relies on dietary folate to maintain adequate concentrations. Fortunately, folic acid is found in a variety of foods (Table 1) or can be taken as a supplement. In societies in which nutrition is suboptimal and supplements are impractical, low-cost dietary interventions can be effective mechanisms to improve health and reduce birth defects. Because over-the-counter supplements require active intent (purchase and then remembering to take), an effective population-based approach is to fortify common foods with vitamins to increase average daily intake. The best example has been the fortification of grain flour with folic acid in the United States (U.S.) (CDC, 2004). *S*ince 1998, the FDA has required that folic acid be added to "enriched" cereal grains such as flour, breads, pasta, bakery items, cookies, rice, and crackers. This fortification has been undertaken specifically to prevent folic acid-preventable neural tube defects; however, the fortification with folic acid has been important in the treatment of other illnesses associated with folic acid deficiency (See Table 2). Mandatory folic acid fortification in the U.S. also has prevented almost all of folic acid-preventable spina bifida and anencephaly as well as folate deficiency anemia (Mosley, 2009, and Odewole, 2013). Folic acid also has been voluntarily added to many brands of cold breakfast cereals by the manufacturer.

* There are concerns that vitamin A and D deficiency may be associated with higher rates of certain birth defects, too, but the evidence is tentative at this point, and whether supplementation is preventive is unclear (Emmett, 2014; Murguria-Peniche, 2013; Downing, 2012; and Kabir, 2014).

Table 2. Folic Acid – The Many Reported Uses

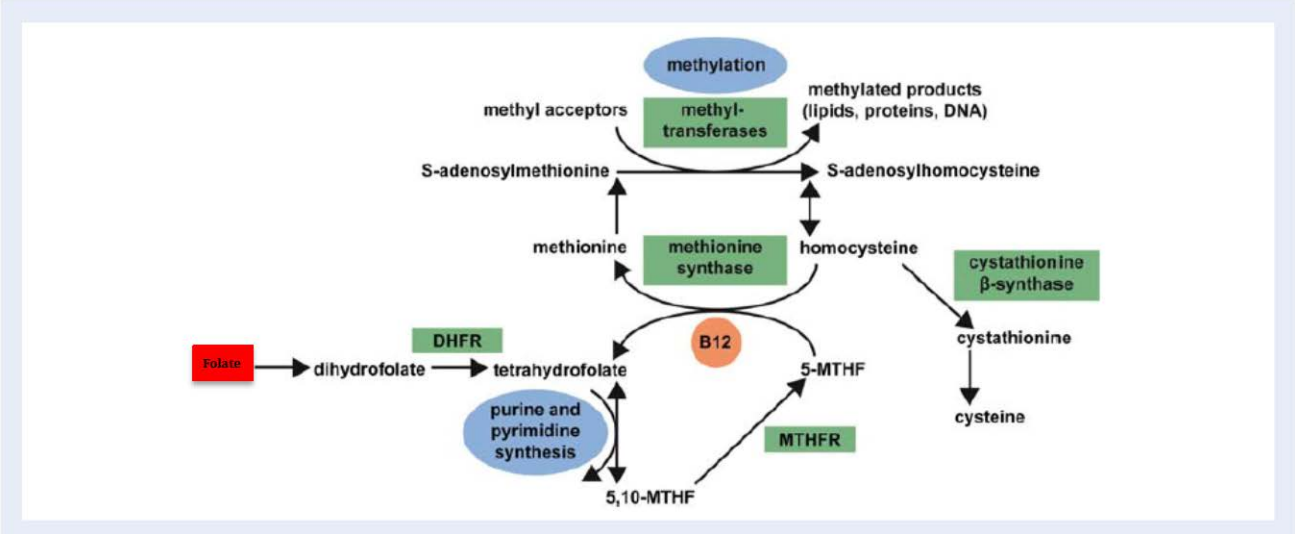
Anemia	Alzheimer's disease
Gastrointestinal malabsorption	Age-related hearing loss
Ulcerative colitis	Macular degeneration
Liver disease	Restless leg syndrome
Alcoholism	Osteoporosis
Renal dialysis	Sleep problems
Colon cancer	Nerve pain
Cervical cancer	Vitiligo (skin disease)
Prevention of heart disease and stroke	Fragile X syndrome
Reduce blood levels of homocysteine	Gum disease
Memory loss	Reduce adverse effects of certain chemotherapeutic agents

*** Not all of these reported benefits have been proven.**

HOW DOES FOLIC ACID WORK, AND WHAT IS THE DAILY INTAKE REQUIREMENT?

Once in the body, folic acid is metabolized to folinic acid, the biologically active form, first by reduction to dihydrofolate and then to the active compound tetrahydrofolate. A number of genetic alterations in key enzymes (dihydrofolate reductase, methylhydrofolate reductase) can alter the effectiveness of folic acid. Tetrahydrofolate's primary function is to transfer methyl groups to nucleic acids that are used to make

Figure 1. Folate—homocysteine—methionine metabolism. B12, vitamin B_{12}: DHFR, dihydrofolate reductase; MTHF, methyltetrahydrofolate; MTHFR, methyltetrahydrofolate reductase.



Adapted from Van Gelder M, van Rooij I, Miller RK, Zielhuis GA, Lolkje TW, van den Berg D, and Roeleveld N (2010). Teratogenic mechanisms of medical drugs. Human Reproduction Update, 16(4):378-394.

DNA, a process that also requires vitamin B_{12}. Lack of folate (or of B_{12}) leads to impaired DNA synthesis and hinders cell division. Rapidly growing cells are vulnerable to folate deficiency; in the adult, the hematopoietic system is one of the most sensitive, with suppressed red blood cell production leading to anemia. With a balanced diet, mild folic acid deficiency usually is well tolerated, but in rare cases of marked deficiency, a severe macrocytic anemia may follow.[*] Folate also maintains normal homocysteine levels by recycling it to the amino acid, methionine. Figure 1 depicts the folic acid-methionine–homocysteine metabolic pathway. Note also the importance of vitamin B_{12} in this pathway.

FOLIC ACID AND NEURAL TUBE BIRTH DEFECTS

In 1965, Hubbard reported an association between a relative maternal folic acid deficiency and an increased rate of neural tube defects (NTDs), in particular open spina bifida and anencephaly (Hubbard, 1965). In 1980, Smithells reported a non-randomized trial that suggested a multivitamin with 360 micrograms of folic acid would prevent 70% of spina bifida and anencephaly cases. In 1991, Wald and colleagues (MRC, 1991, Lancet) reported a randomized controlled trial providing evidence that folic acid would prevent spina bifida and anencephaly among high-risk women. The rate went down by 72%. Czeizel (1992) followed up with a randomized trial that suggested that a multivitamin with 800 micrograms would prevent all spina bifida and anencephaly cases in women with no known increased risk. Based on these and other studies, the CDC published recommendations for high-risk women: 4,000 micrograms a day while planning pregnancy and 400 micrograms at other times. In 1992, the CDC published the United States Public Health Service Recommendations that all women who could become pregnant consume 400 micrograms of folic acid daily.

Following these recommendations, the U.S. Food and Drug Administration required that enriched cereal grains have folic acid added that has resulted in each adult woman consuming 150 micrograms of folic acid a day. The Canadian government made the same requirement. There have been remarkable decreases in spina bifida levels in both countries with spina bifida and anencephaly rates approaching 5 per 10,000.

FOLIC ACID FOOD FORTIFICATION AND SUPPLEMENTATION SUCCESS

For women not at apparent increased NTD risk, lesser degrees of folate intake suffice. In the U.S., the Food and Drug Administration (FDA) began requiring fortification of grain-based products with 1.4 mg/kg folic acid in January 1998. Such fortification also has been mandated in Canada (1.5 mg/kg flour), in Chile and Costa Rica (2.2 mg/kg flour). Folic acid fortification of food, however, is not practiced in the United Kingdom or any country in Europe. These countries have chosen to rely on health campaigns to encourage women of reproductive age to consume folic acid supplement pills. As a

[*] Immature, underdeveloped red blood cells are large and, thus, are called macrocytes.

result, only about 20% of women who become pregnant in the United Kingdom were taking folic acid supplements when they became pregnant. Clinicians living in these countries should be vigilant in recommending folic acid supplement pills to their patients at all times. Because over 50% of pregnancies in the U.S. are unplanned, the recommendation should apply to all women of reproductive age, not just those who are planning a pregnancy.

Debate continues about whether a balanced diet provides sufficient folic acid. Although eating a good diet is encouraged, the randomized trials showing that folic acid prevents spina bifida included women who took a folic acid supplement pill in addition to eating their usual diet.

Compliance with dietary folic acid supplementation, even with the many public health initiatives, requires renewed public and provider awareness. Following impressive success, behaviors sometimes slip back into old patterns. The most recent evidence available in the U.S. demonstrates that fewer than 60% of women are taking folic acid before pregnancy (Khodr, 2014). Part of this is a result of the high unplanned pregnancy rate and the fact that many women do not seek care until their pregnancy has been established, making preconception counseling impossible. Some providers also do not discuss the importance of folic acid in the preconception period during routine office visits. Yet, information on folic acid to prevent birth defects should be given to all women, regardless of ethnicity/race, education, or age. At the same time, it must be recognized that folate should not "be promoted as a teratologic panacea" (Källén, 2002), but as an important step in minimizing not only NTDs, but also some cardiac and facial clefting defects. Aside from the negligible risk of masking B_{12} deficiency or the possible interference of folate with sulfa-related malaria treatment in pregnant women, it nearly is risk-free (Ouma, 2006).

FOLIC ACID IN MULTIVITAMINS AND PRENATAL VITAMINS IN LOW-RISK WOMEN

Currently in the U.S., prenatal vitamins contain 800 micrograms or more of folic acid in each tablet, and they often are recommended by healthcare providers for women who are not at apparent increased risk for birth defects. The U.S. Public Health Service recommendation is for all women of reproductive age to consume 400 micrograms of folic acid a day. A usual multivitamin is the most common form of supplement taken. Women who have previously had a pregnancy affected by anencephaly or spina bifida and are planning a pregnancy should be taking 4,000 micrograms a day in folic acid pills.

FOLIC ACID SUPPLEMENTATION AND COUNSELING IN YOUR OBSTETRIC PRACTICE

In summary, there is unequivocal evidence that folic acid taken before and during the early weeks of pregnancy prevents a high proportion of spina bifida and anencephaly cases. Mandatory folic acid fortification of a centrally processed and widely eaten

food such as flour has been found to be a highly effective way to prevent these severe birth defects. Were mandatory fortification programs required and implemented in all countries, there would be few, if any, cases of folic acid-preventable spina bifida and anencephaly. Care providers can be most effective in preventing these birth defects by successfully advocating for required folic acid fortification in their country. In those countries without required folic acid fortification, clinicians should recommend that all women of reproductive age consume 400 micrograms of folic acid a day unless they have previously had a pregnancy affected by spina bifida or anencephaly. These women should be encouraged to take 400 micrograms a day if they are not planning a pregnancy, but 4,000 micrograms a day if they are planning a pregnancy.

For additional information and assistance concerning folic acid usage or for assistance with medication, occupational, and environmental exposures when planning or during pregnancy, call (1-866-626-6847) or contact www.MotherToBaby.org.

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For additional reading on this important topic, one can review the chapter on vitamins, minerals, and trace elements in the 3rd Edition of *Drugs during Pregnancy and Lactation: Treatment Options and Risk Assessment* (Miller and Peters, 2014).

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