Chapter 3

Folic and Folate Acid

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Additional information is available at the end of the chapter

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Abstract

Folate is a water-soluble B vitamin, also known as vitamin B9 or folacin. It is found naturally in a wide variety of foods, including vegetables, fruits, nuts, beans, dairy products, meats, eggs, seafood, and grains. However, only about 50% of the folate naturally present in food is bioavailable. Folate is critical in the metabolism of nucleic acid precursors and several amino acids, as well as in methylation reactions. Folic acid helps our bodies produce and maintain new cells, and it helps prevent DNA changes that may lead to cancer. Folate deficiency can cause anemia, insomnia, irritability, depression, Alzheimer's disease, cardiovascular disease, and more serious health problems. An inadequate folate status during early pregnancy increases the risk of congenital anomalies, such as neural tube defects (NTDs), which are life-threatening and cause life-long disabilities. Therefore, it has been recommended by the U.S. Public Health Service that even before becoming pregnant, women should consume 400 μg of synthetic folic acid daily, whether in the form of foods or supplements, as well as maintain a healthy diet of folate-rich foods to reduce NTD risk.

Keywords: folate, folic acid, homocysteine, health and outcomes, nutritional education

1. Introduction

Folate is a group of small water-soluble molecules that form one of the so-called B complex vitamins, also known as vitamin B9 or folacin. It is found naturally in a wide variety of foods, including vegetables, fruits, nuts, beans, dairy products, meats, eggs, seafood, and grains. However, only approximately 50% of the folate naturally present in food is bioavailable [1]. Folate is critical for the metabolism of nucleic acid precursors and several amino acids, as well as to methylation reactions. Folic acid helps our bodies produce and maintain new cells, and it helps prevent DNA changes that may lead to cancer. DNA methylation is an epigenetic mechanism that evidently plays a role in Alzheimer's disease [2]. An increase in the risks of

depression and cardiovascular disease was observed independent of folic acid and vitamin B12 status [3, 4]. In this review, we will discuss recent issues related to the impact of folate and folic acid on cognitive and reproductive functions.

2. Folate metabolism in humans

Folate metabolism is closely linked to homocysteine (Hcy) metabolism, where Hcy is as an important factor in arteriosclerosis and aging. After the discovery of Hcy in 1932, it was demonstrated to be an important intermediate in the metabolism of amino acids. The folate metabolite 5-methyltetrahydrofolate (5-MTHF) is a substrate of methionine synthase, which remethylates Hcy to form methionine and links the folate cycle with Hcy metabolism (**Figure 1**) [5].

The substrate 5-methultetrahydrofolate requires vitamin B12 as a cofactor of methionine synthase. The effect of vitamin B12 is diminished by the larger role of folate status in determining total Hcy. Pyridoxal phosphate, the active form of vitamin B, is a cofactor for enzymes involved in amino acid metabolism. These enzymes include cystathionine β-synthase, the first enzyme in the transsulfuration pathway that breaks down Hcy to sulfate.

2.1. Folate metabolism and neurodegenerative and neuropsychiatric diseases

Insufficient amounts of folate and vitamin B12 limit the conversion of Hcy into methionine, which is a direct precursor of S-adenosylmethionin (SAM). SAM plays an important role in the methylation of neurotransmitters involved in depression [6]. Lower concentrations of

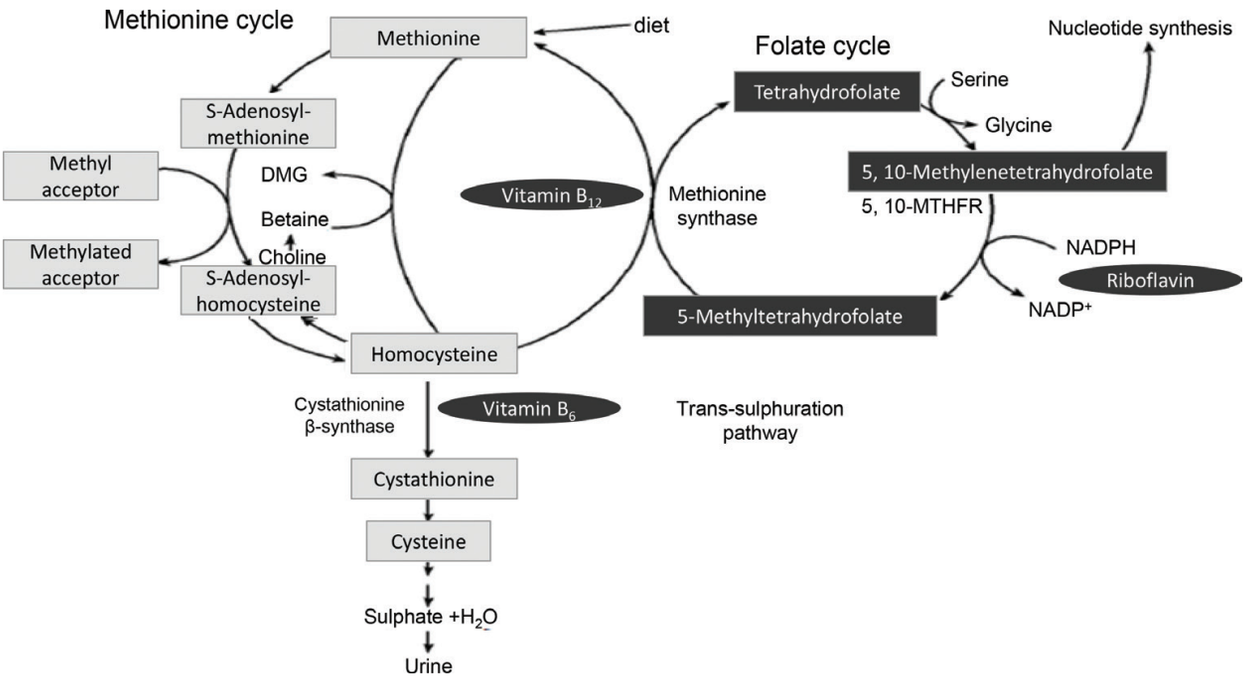

Figure 1. Pathways for the folate cycles and homocysteine metabolism. *Source*: Ref. [5].

SAM and monoamine neurotransmitter metabolites were observed in the cerebrospinal fluid of severely depressed patients with high Hcy levels, compared to similar patients with normal Hcy levels [7].

MTHF is able to cross the blood-brain barrier into the cerebrospinal fluid [8]. One important function of folate is its role in the one-carbon cycle. In this pathway, folate is converted by methylenetetrahydrofolate reductase into MTHF, which combines with the amino acid Hcy to produce eventually, with the help of vitamin B12, S-adenosylmethionine (SAMe). SAMe is important, because it functions as a methyl donor in a variety of biochemical reactions and has been suggested to be somehow involved in the synthesis of the three neurotransmitters in the brain: serotonin, epinephrine, and dopamine [9]. **Figure 1** illustrates the actions of 5-MTHF and SAMe in methylation and neurotransmitter synthesis [10]. Thus, a folate deficiency could result in a deficiency of these neurotransmitters.

According to epidemiological and biological evidence, depressive disorders among individuals with epilepsy or neurological and psychiatric problems and the elderly could be caused by low folate [11, 12]. Folic acid affects the rate of the synthesis of the neurotransmitters dopamine, norepinephrine, and serotonin and it acts as a cofactor in the hydroxylation of phenylalanine and tryptophan [13]. Biogenic amine metabolism disturbances may lead to various psychiatric disorders, and a deficiency in folic acid may exacerbate neuropsychiatric disorders such as mental confusion, memory changes, cognitive slowing, and mood disorders.

Measurements of folate levels in plasma, serum, and erythrocytes are the most widely used biochemical indices of folate status, in addition to measurements of dietary folate intake. In a previous study of 883 elderly Latina women aged 60–93, the adjusted odds ratio for increased depressive symptoms in women in the lowest tertile of plasma folate was 2.04, which was significantly different from that in women in the highest tertile of folate [3]. Gilbody et al. reported that subjects with low serum levels, red blood cell (RBC) folate levels, and low folate intake had 1.4 times increased risk of depressive symptoms, compared with those with a high folate status [14]. On the other hand, in the Women's Health and Aging Study, serum homocysteine and folic acid levels were not associated with depression status among physically disabled women with a mean age of 77.3 years [15].

The elderly are of particular concern because of age-related declines in vitamin absorption and the extraction of vitamin B12 from protein [16] and age-related increases in autoimmunity against intrinsic factor or the gastric parietal cells that produce it [17]. Elevated plasma Hcy concentrations are common in older age [18]. With advanced age, the prevalence of a low vitamin B12 status increases from 5% at age 65 to 20% at age 80 years [19]. The reviews of population-based studies found that a low folate status is associated with mild cognitive impairment, Alzheimer's disease, and depression in healthy and neuropsychiatric diseased older people [20].

2.2. Folic metabolism and cancer

Several epidemiological studies have suggested an inverse association between folate status and the risk of cancer, including colorectal, lung, pancreatic, esophageal, stomach, cervical,

ovarian, and breast cancers [21]. Folic acid helps our bodies produce and maintain new cells, and it helps prevent DNA changes. Folate plays an essential role in one-carbon transfer involving the remethylation of Hcy to methionine, thereby ensuring the provision of SAMe, the primary methyl group donor for most biological methylation reactions. Folic acid linked with conjugating agents only enters cells through the folate receptor (FR) [22], a cell surface glycosylphosphatidylinositol-anchored glycoprotein in humans [23]. Folate might influence the development of cancer through its role in one-carbon metabolism and its subsequent effects on DNA replication and cell division [24]. However, research has not established the precise nature of folate's effect on carcinogenesis.

2.3. Folate metabolism and reproductive function

Maternal nutrition, especially folate, is critical for optimizing pregnancy outcomes. The increase in folate required during pregnancy is due to the growth of the fetus and uteroplacental organs. The demand for folate is increased to support both the normal physiological changes of mothers and the optimal growth and development of the fetus and offspring [25]. Impaired placental perfusion due to hyperhomocysteinemia is implicated in having a negative effect on pregnancy outcomes. Inadequate folate intake before conception and early pregnancy increases the risk of congenital malformations of the brain and spinal cord, such as anencephaly, spina bifida, and neural tube defects (NTDs). NTDs are the most common and severe congenital malformations of the central nervous system, occurring secondary to lack of closure of the neural tube and leading to long-term morbidity. Neurulation, the process of neural tube formation, is completed 28 days after conception, as many women do not realize that they are pregnant at this stage [26]. Das et al. found in the systematic review that folate fortification had a significant impact on reducing neural tube defects (risk ratio; RR: 0.57 (95% CI: 0.45, 0.73)), spina bifida (RR: 0.64 (95% CI: 0.57, 0.71)), and anencephaly (RR: 0.80 (95% CI: 0.73, 0.87)). Folate fortification significantly reduced the incidence of congenital abnormalities [27].

3. Recommended dietary intake of folate in humans

Folate deficiency can cause anemia, insomnia, irritability, and far more serious health problems. In 2000, the D-A-CH societies (Germany [D], Austria [A], and Switzerland [CH]) initiated a recommendation of 400 μg of folate daily among adults [28], a value agreed to by the USA, Canada [29], Australia, and New Zealand [30]. The World Health Organization (WHO) and the Food and Agriculture Organization (FAO) of the United Nations [30] also agreed, setting an estimated average requirement (EAR) of 320 μg of dietary folate equivalents (DFE)/day and a recommended dietary allowance (RDA) of 400 μg DFE/day for adults. **Table 1** indicates the various recommendations. By combining RBC folate, plasma total Hcy, and plasma or serum folate, the Institute of Medicine concluded an EAR for adults with a focus on adequate quantities of folate, via food or food plus folic acid and consumed under controlled conditions, to maintain normal blood concentrations of these indicators [31].

Each country issues an RDA as the mean of estimated requirements for pregnant women that must be increased to meet the demands of increasing maternal tissues, fetal growth, fat store

	Adults		Pregnant women	
	EAR (μg/day)	**RDA (μg/day)**	**EAR (μg/day)**	**RDA (μg/day)**
WHO/FAO[1]	320	400	370–470	600
USA, Canada[2]	320	400		600
Australia and New Zealand[3]	320	400	520	600
Japan[4]	200	240	400	440

Notes: EAR, estimated average requirement (average daily level of intake estimated to meet the requirements of 50% of healthy individuals); RDA, recommended dietary allowance (average daily level of intake sufficient to meet the nutrient requirements of nearly all (97–98%) healthy individuals).

[1] *Source:* The WHO/Food and Agriculture Organization of the United Nations at the Institute of Medicine (IOM) of the National Academies [31].

[2] *Source:* IOM [29].

[3] *Source:* Australian National Health and Medical Research Council and New Zealand Ministry of Health [30].

[4] *Source:* Overview of Dietary Reference Intakes for Japanese by the Minister of Health, Labour and Welfare [59].

Table 1. Reference values for folate/folate equivalents for adults from different international societies and organizations.

growth, and the increase in basal metabolic rate. In 1992, the U.S. Public Health Service recommended that all women of reproductive age in the USA capable of becoming pregnant should consume 400 μg of synthetic folic acid daily from fortified foods or supplements. In addition, they should consume a balanced, healthy diet of folate-rich food to prevent two common and serious birth defects: spina bifida and anencephaly [32, 33]. All women between 15 and 45 years of age should consume folic acid daily because half of U.S. pregnancies are unplanned and because these birth defects occur early in pregnancy (3–4 weeks after conception), before most women know they are pregnant. The Food and Drug Administration mandated the addition of folic acid to all enriched cereal grain products by January 1998 [34]. Experimental and epidemiological evidence has shown that periconceptional dietary supplementation with folic acid can result in an estimated 50–70% decrease in the prevalence of NTDs [35].

4. Global strategies of folic acid fortification for reproductive-age women

In 2009, the U.S. Preventive Services Task Force published updated guidelines reinforcing these recommendations [36]. Recently, the National Institute for Health and Clinical Excellence [37] reinforced this focus on the periconceptional period. The best-known recommendation for women who are planning a pregnancy is to take 400 μg of folic acid a day in supplements to prevent NTDs. As of July 2015, almost 80 countries had fortified their wheat flour with folic acid, and health agencies in many countries have officially recommended the periconceptional consumption of folic acid in the range of 400–500 μg by young women capable of conceiving or planning to conceive [37].

Fortification leads to a decrease in the prevalence of serum deficiency from 30% to less than 1% and a decrease in the prevalence of an RBC folate deficiency from 6% to no measureable

deficiency [38]. The number of cases of spina bifida and anencephaly among deliveries occurring during 1995–2011 in 19 population-based birth defect surveillance programs in the US was reported by the Centers for Disease Control and Prevention (**Figure 2**) [39]. Overall, a 28% reduction in prevalence was observed for anencephaly and spinal bifida. The mandatory fortification of standardized enriched cereal grain products in the US has resulted in a substantial increase in blood folate concentrations. In a study based on data from a National Health and Nutrition Examination Survey, the mean serum folate concentration for women aged 15–44 years who did not use supplements increased from 10.7 to 28.6 nmol/L shortly after initiating fortification in the USA, an almost threefold increase [40].

The incidence rate of NTDs was reported to be 0.97 per 1000 births in some European countries [41]. The reported NTD prevalence ranges and medians for each region were: Africa (5.2–75.4; 11.7 per 10,000 births), Eastern Mediterranean (2.1–124.1; 21.9 per 10,000 births), Europe (1.3–35.9; 9.0 per 10,000 births), Americas (3.3–27.9; 11.5 per 10,000 births), South-East Asia (1.9–66.2; 15.8 per 10,000 births), and Western Pacific (0.3–199.4; 6.9 per 10,000 births) [42]. According to the Morbidity and Mortality Weekly Report, if 50–70% of NTDs can be prevented by consuming 400 μg of folic acid per day, assuming a prevalence of 300,000 NTDs per year, worldwide folic acid fortification could prevent 150,000–210,000 NTDs annually [35].

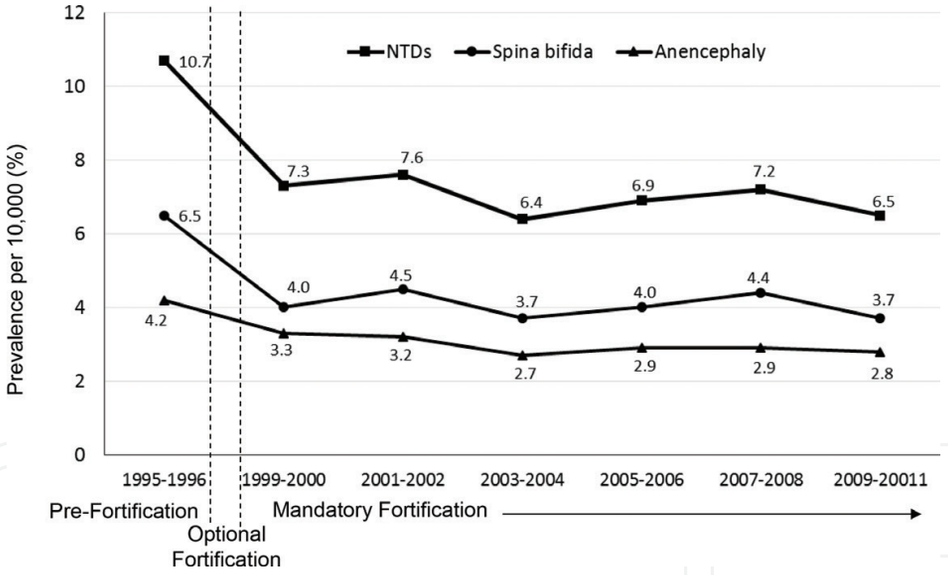

Figure 2. Prevalence of spina bifida and anencephaly in the USA, 1995–2011. *NTDs: Spina bifida + anencephaly. *Source*: Neural tube defect ascertainment project of the National Birth Defects Prevention Network at Centers for Disease Control and Prevention [39].

5. Current trends of worldwide folic acid food fortification

Figure 3 shows the world's industrially milled flour and rice fortification legislation with at least iron and folic acid, from March 2017. According to the food fortification initiative, globally, 86 countries have initiated legislation to mandate the fortification of wheat flour

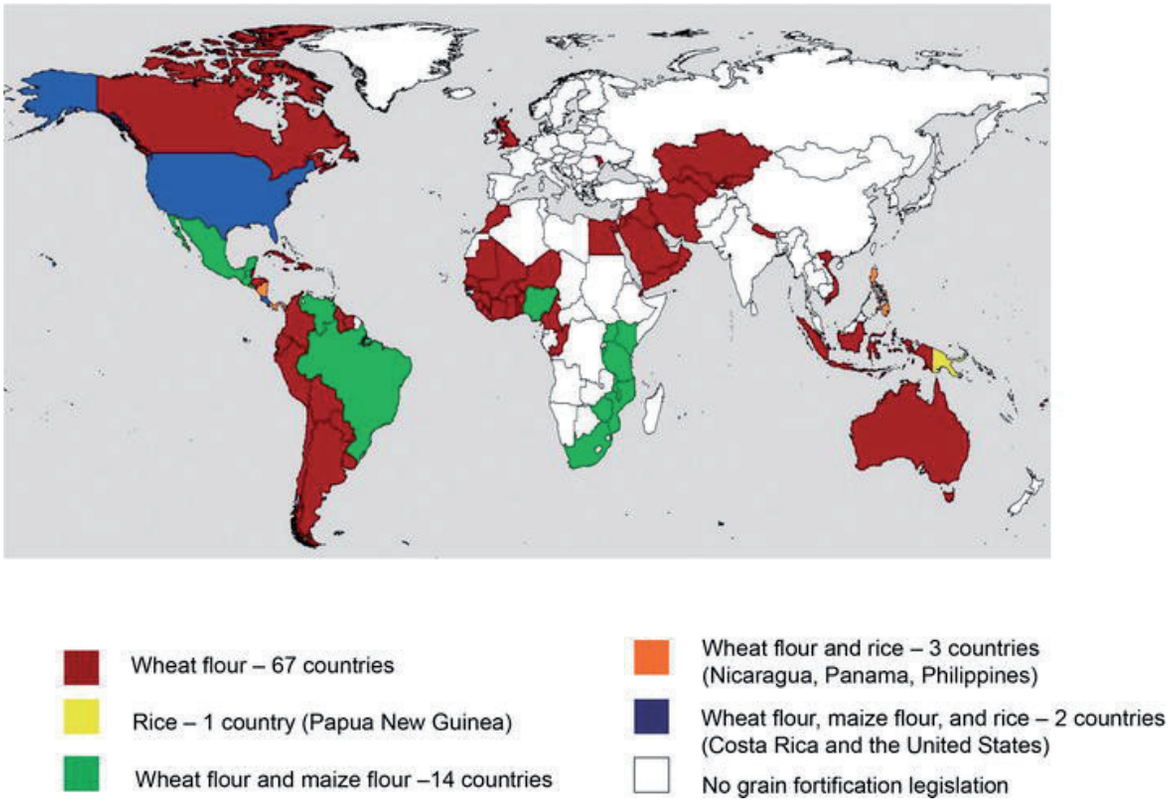

Figure 3. World's map of industrially milled flour and rice fortification with at least iron or folic acid. *Source*: Food fortification initiative in March 2017 [43].

alone or in combination with other grains, while over 100 countries have not introduced mandatory folic acid fortification, including the EU, China, and Japan [43].

The U.S. program adds 140 μg of folic acid per 100 g of enriched cereal grain product and it has been estimated to provide 100–200 μg of folic acid per day to women of childbearing age [44]. In Canada, it is mandatory to fortify white-wheat flour and enriched cornmeal with 150 μg of folic acid/100 g and enriched pasta with 200–270 μg of folic acid/100 g [45]. Berry et al. estimated that in the USA and Canada, the additional intake of about 100–150 μg/day of folic acid through food fortification has been effective in reducing the prevalence of NTDs at birth and in increasing blood folate concentrations in both countries [46].

In Ireland, all bread, including white, wholemeal, and brown, manufactured or marketed in Ireland, with the exception of minor bread products, should be fortified on a mandatory basis with folic acid at a level that provides 120 μg per 100 g of bread consumed. The voluntary folic acid fortification of foods, for example, cereal bars, yogurt, or juice, is permitted [47].

In Australia, all plain, fancy and sweet breads, rolls, and buns, including bagels, focaccia, English muffins made with yeast and flour mixes or flour for domestic bread making must contain folic acid. Organic bread is not required to contain folic acid. Some manufacturers also voluntarily choose to fortify other foods with folic acid, for example, breakfast cereal. Manufacturers must list folic acid in the ingredients list on the labels of foods fortified with folic acid. Currently, some cereals and cereal products, bread, and fruit juice have folic acid voluntarily added by food manufacturers [48].

5.1. Benefits of folic acid supplementation

Folate requirements can be affected by bioavailability, nutrient interactions, and smoking. The bioavailability of folates in food is about 50–60%, whereas that of the folic acid used to fortify foods or as a supplement is about 85% [1]. Folic acid as a supplement is almost 100% bioavailable on an empty stomach. Among 2919 older adults with elevated Hcy concentrations of ≥12 μmol/L, participants received either 500 μg of vitamin B12 and 400 μg of folic acid daily or a placebo for 2 years. Depressive symptoms were measured with the Geriatric Depression Scale-15. However, 2-year supplementation with vitamin B12 and folic acid in older adults with hyperhomocysteinemia showed that lowering Hcy concentrations does not reduce depressive symptoms, but it may have a small positive effect on health-related quality of life [49]. A study by Lachner et al. suggested a supplementation dose of at least 1000 μg/day might be more effective in reducing depressive symptoms [50]. Okereke et al. reported that long-term, high-dose, daily supplementation with folic acid and vitamins B6 and B12 did not reduce overall depression risk in 4331 older women (mean age 63.6 years), without prior depression [51].

Nguyen et al. [52] conducted a randomized controlled trial designed to assess the impact of supplementation in Guatemala. In total, 459 women aged 15–49 years were assigned to four groups at random to receive weekly (5000 or 2800 μg) or daily (400 or 200 μg) folic acid plus iron, zinc, and vitamin B12 for 12 weeks. Depression was measured using the Center for Epidemiologic Studies Depression Scale. Women in the lowest tertile of RBC folate were 1.7 times more likely to be depressed than those were in the highest tertile (OR = 1.71; 95%CI: 0.91, 3.18) at baseline. However, this relationship disappeared after adjustments for potential confounding factors. Mean depression scores and the prevalence of depression decreased postintervention, with no differences in the degree of improvement by group. It is difficult to evaluate the effect of supplementation on depressive symptoms, because this study had no placebo control group. This is because a number of reports have suggested that folate supplementation may enhance the effectiveness of certain antidepressant regimens [53, 54].

6. Education and technical consultation on folate deficiency

The nutritional intake of reproductive-age women appears inadequate during the preconceptional period. Among almost all women, folate intake is less than the RDA. Promoting women's health during preconception is a key public health strategy. Thiele et al. [55] observed in Germany that better educated women had higher indices of qualitatively beneficial diets than did lesser educated women. Adolescents at universities and colleges are potentially important targets for the promotion of healthy lifestyles, including physical, psychological, and eating habits. However, little is known about nutritional and health-related behaviors.

Questions arise as to how pregnant women show concern for their consumed diets and whether pregnant women get appropriate nutrient information during their routine antenatal checkups. Bookari et al. [56] reported that 65% of pregnant women were not familiar with the healthy eating recommendations. Nearly 80% of pregnant women would have liked education about nutrition and dietary advice [57], but Anya et al. [58] reported that women spend

3 min or less with their antenatal care providers and less than 40% had been informed or educated about diet and nutrition. These results suggest pregnant women lack opportunities to receive adequate and appropriate nutrition education during antenatal care. Most women expect advice on general dietary improvements, with the remainder seeking advice on how to promote the quality and quantity of nutritional intake. A critical goal for women should be to make behavior changes to ensure a good nutritional status before, during, and beyond pregnancy, which may lead to improved birth outcomes. More effective education campaigns should be set up by health care providers to improve women's awareness. Health care providers should educate reproductive-age women about careful food selection and meal planning and preparation at clinics, schools, or offices through mass media.

7. Conclusion

Folate deficiency impairs DNA replication and cell division, which adversely affects rapidly proliferating tissues, such as bone marrow, and results in the production of unusually large macrocytic cells with poorly differentiated nuclei. An increase in the risks of anemia, depression, and cancer was observed independent of folic acid. As the world is aging rapidly, attention on aging-related mental disorders has increased. Malnutrition is common among people aged 65 years and older. In addition, despite the abundance of information concerning folic acid, many women of reproductive age either are still unaware of its importance or do not value this information. The RDA guidelines have not worked effectively to appeal to the public. More effective education campaigns should be set up by health care providers to improve women's awareness.

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