



Integrated Nursing, Nutritional, and Health Information Perspectives on Folic Acid Deficiency: An Updated Review

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Abstract

Background: Folic acid (Vitamin B9) is a water-soluble micronutrient essential for DNA synthesis, erythropoiesis, and one-carbon metabolism. Deficiency disrupts these processes, leading to clinical consequences such as megaloblastic anemia, elevated homocysteine levels, and, critically, neural tube defects (NTDs) in developing fetuses. Despite public health measures like food fortification, deficiency remains a significant global health concern, particularly in vulnerable populations.

Aim: This review aims to provide an integrated, multidisciplinary perspective on folic acid deficiency, synthesizing its etiology, pathophysiology, clinical manifestations, and management strategies from nursing, nutritional, and medical viewpoints to guide comprehensive patient care and public health initiatives.

Methods: The approach is a comprehensive literature review and clinical synthesis. It details the diagnostic evaluation, including clinical assessment, complete blood count analysis, and biochemical testing (serum/red blood cell folate, homocysteine, and methylmalonic acid levels). Management strategies, from oral and parenteral supplementation to dietary modification and public health fortification, are examined.

Results: Folic acid deficiency has a multifactorial etiology, including inadequate dietary intake, malabsorption syndromes, medications, and increased physiological demand. Diagnosis is confirmed through characteristic macrocytic anemia and low folate levels. Treatment with oral folic acid (1-5 mg/day) is highly effective, leading to hematological recovery within weeks. Public health fortification programs have successfully reduced the prevalence of deficiency and NTDs in many countries.

Conclusion: A collaborative, interprofessional approach is fundamental to the effective prevention, diagnosis, and management of folic acid deficiency. Integrating medical treatment, nursing care, nutritional counseling, and public health strategies is essential to mitigate its hematological, neurological, and developmental consequences.

Keywords: Folic Acid Deficiency, Megaloblastic Anemia, Neural Tube Defects, Nutritional Supplementation, Interprofessional Care.

1. Introduction

Folate deficiency denotes a state in which circulating or erythrocytic concentrations of folate fall below thresholds established to indicate inadequate

status. Diagnostic cutoffs vary across laboratories and studies, reflecting differences in assay methods and interpretative criteria; nevertheless, the defining feature remains subnormal folate in serum, plasma, or

red blood cells. Folate, also identified as vitamin B9 or folacin, is a water-soluble micronutrient integral to fundamental cellular processes. It participates directly in nucleotide biosynthesis, supports erythropoiesis, and sustains metabolic pathways that underlie cell proliferation and tissue maintenance. Dietary folate occurs naturally in green leafy vegetables, legumes, selected fruits, and organ meats such as liver, forming the principal source of the vitamin in unfortified diets [1]. Folic acid, the synthetic and oxidized form of folate, is employed extensively in fortified foods and as a component of nutritional supplements because it exhibits favorable stability and absorption characteristics relative to many naturally occurring folate derivatives. Public health policy in multiple jurisdictions has adopted folic acid fortification of staple grains to reduce the incidence of neural tube defects and other folate-responsive outcomes. This measure reflects the vitamin's established role in early embryogenesis and in neural tube closure; mandatory fortification has been implemented in numerous countries, including the United States, as a preventative strategy. [1]

At the biochemical level, folate serves as a coenzyme within one-carbon metabolism, a network of reactions that transfers single-carbon units for biosynthetic and methylation processes. These one-carbon transfers enable the *de novo* synthesis of purine and pyrimidine nucleotides, thereby providing the raw material for DNA and RNA assembly required for cell replication and repair. [2][3] Folate-dependent reactions also supply methyl groups for methylation reactions that regulate amino acid interconversions and influence epigenetic mechanisms governing gene expression. Because folate-dependent pathways support nucleic acid synthesis and methylation, tissues with high rates of cell turnover—most notably the hematopoietic compartment and the developing embryo—exhibit pronounced demand for adequate folate supply. Deficiency in this vitamin therefore disrupts DNA replication and cell division, producing characteristic cellular and clinical consequences [2][3]. Clinically, insufficient folate availability impairs normal erythroid maturation and leads to megaloblastic anemia. This hematological disorder is characterized by enlarged, immature red cell precursors and reduced effective erythropoiesis. Beyond hematology, folate insufficiency has been implicated in neuropsychiatric manifestations and cognitive alterations, reflecting the vitamin's roles in neural function and neurotransmitter metabolism. Folate deficiency also produces biochemical perturbations observable as elevated plasma homocysteine concentrations. Hyperhomocysteinemia, in turn, has been associated with increased risk for atherosclerotic vascular disease and other cardiovascular endpoints in epidemiological and mechanistic studies. [4] For clinicians and scholars seeking a concise clinical overview, StatPearls offers a companion resource titled "Folic

Acid" that summarizes diagnostic and management considerations [3][4].

Contemporary research has extended the scope of inquiry into folate status beyond classical hematological and congenital outcomes. Epidemiological and mechanistic studies have explored links between folate insufficiency and cerebrovascular events, neurodevelopmental disorders, certain pediatric malignancies such as childhood leukemia, and alterations in lipid metabolism. These investigations suggest that folate influences diverse biological systems and that its status may modulate risk across a spectrum of conditions. [5][6] Such associations remain the subject of ongoing study to clarify causality, effect magnitude, and the influence of confounding variables. At the same time, population-level interventions emphasizing supplementation and fortification have delivered measurable benefits in reducing neural tube defects and ameliorating clinical folate deficiency. Nevertheless, attention has turned to the potential consequences of excessive folic acid intake, as supraphysiological exposure raises theoretical and observed concerns regarding long-term cancer risk and the masking of other micronutrient deficiencies. These complexities underscore the need for balanced policies that maximize preventive benefits while minimizing unintended harms [5][6].

From a clinical nutrition and public health perspective, it is essential to calibrate intake recommendations to physiological needs across the life course. Recommended daily folate intake is expressed in dietary folate equivalents to account for differences in bioavailability between natural food folates and synthetic folic acid. Intake recommendations vary by age and physiological state, with infant requirements beginning at approximately 65 micrograms dietary folate equivalents and adult recommendations typically set at 400 micrograms per day. Requirements increase markedly during periods of rapid growth and heightened metabolic demand; pregnant individuals are advised higher intake to support fetal development, commonly recommended at 600 micrograms per day, and lactating individuals at approximately 500 micrograms per day. [7] These guidelines aim to preserve nucleic acid synthesis, support erythropoiesis, and prevent the clinical and subclinical consequences of deficiency, particularly during gestation when maternal folate status has direct implications for embryonic development. Collectively, the biochemical functions, clinical manifestations, and public health implications of folate and folic acid position this nutrient as a central focus in maternal-child health, hematology, and preventive nutrition. Ongoing research seeks to delineate the broader ramifications of folate status for chronic disease risk and to refine recommendations that balance efficacy, safety, and population-level impact [7].

Etiology

Folic acid deficiency arises from multiple interacting mechanisms that reduce folate intake, impair intestinal absorption, compromise intracellular metabolism, or increase physiological demand. The pathways to deficiency are heterogeneous and include altered requirements during physiological states, genetic variants that perturb folate processing, disorders that limit gastrointestinal uptake, pharmacological antagonism or enhanced catabolism, inadequate dietary supply, toxic exposures that disrupt folate handling, and rare inherited enzyme defects. Understanding these diverse etiologies clarifies clinical risk stratification and informs targeted prevention and treatment strategies [8]. Periods of increased physiological demand constitute a prominent category of causes. Pregnancy imposes a marked increase in one-carbon metabolic flux to support rapid cell proliferation and organogenesis, producing substantially higher folate turnover and requirement. Lactation maintains elevated maternal demand to supply folate to milk and sustain maternal tissue replacement. Childhood and adolescent growth spurts similarly elevate needs because of accelerated DNA synthesis and expansion of lean tissue. Chronic hemolytic states increase erythropoietic activity and thus folate consumption through continuous production of red blood cells. Extensive epidermal regeneration, as occurs with severe burns or exfoliative dermatologic conditions, raises systemic folate turnover through heightened mitotic activity in skin. Renal replacement therapies such as hemodialysis can cause net folate loss while also increasing metabolic stress and requirement, thereby necessitating augmented intake in affected patients. [8]

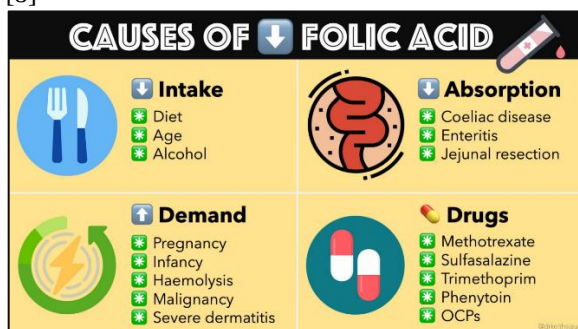


Figure-1: Folic Acid Deficiency Causes.

Genetic variation modifies folate metabolism and can predispose individuals to functional deficiency despite apparently adequate intake. Polymorphisms in the methylenetetrahydrofolate reductase gene, notably the C677T variant, diminish enzymatic activity involved in conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a key methyl donor for homocysteine remethylation. Such variants alter intracellular folate distribution and methylation capacity and thereby increase the propensity for biochemical and clinical folate insufficiency in some

populations. Disorders of intestinal integrity and function reduce folate absorption and represent a second major etiologic domain. Enteropathies that damage small intestinal mucosa, including celiac disease, tropical sprue, and inflammatory bowel disease, impair folate uptake by decreasing functional absorptive surface. Surgical resections that shorten absorptive length, as in short bowel syndrome or certain bariatric procedures, remove the mucosal regions specialized for folate transport and thus reduce bioavailability. Hypochlorhydria and achlorhydria diminish gastric acid driven processes that facilitate folate liberation from food matrices and subsequent absorption. Postoperative alterations in gastrointestinal anatomy such as those that follow Roux-en-Y gastric bypass further compromise oral folate uptake and predispose to deficiency if not corrected by supplementation [8].

Pharmacological agents can interfere directly with folate utilization or increase its breakdown. Antifolate chemotherapeutic drugs such as methotrexate inhibit dihydrofolate reductase and disrupt nucleotide biosynthesis. Anticonvulsants including phenytoin induce hepatic enzymes and alter folate metabolism. Antimicrobials such as trimethoprim impair bacterial and host folate pathways. Sulfasalazine and other agents that affect mucosal function can reduce folate absorption. Chronic exposure to these drugs may produce progressive depletion of folate pools and manifest as hematologic or neuropsychiatric sequelae if unrecognized. Dietary insufficiency remains a frequent and remediable cause of deficiency at the population level. Diets that provide limited quantities of folate rich foods, including green leafy vegetables, legumes, and fortified grains, fail to sustain tissue stores. Food preparation practices involve prolonged heating accelerate folate degradation because reduced folates are heat sensitive and labile during cooking. Cultural, economic, or behavioral patterns that constrain dietary diversity exacerbate risk and concentrate deficiency among vulnerable groups. Alcohol exerts multiple deleterious effects on folate status. Chronic alcohol intake impairs intestinal absorption, reduces hepatic storage capacity, and alters folate metabolism by modifying enzymatic activity. Alcohol related nutritional neglect compounds these effects, making alcoholism a major contributor to folate insufficiency in clinical settings [8].

Interactions with vitamin B12 status produce a functional folate deficit through biochemical sequestration. Vitamin B12 deficiency impairs methionine synthase activity, halting the conversion of homocysteine to methionine and causing accumulation of methyl-tetrahydrofolate in a form unavailable for nucleotide synthesis. The resulting "folate trap" reduces the pool of folate cofactors needed for DNA replication and leads to megaloblastic

changes despite total body folate content that may appear normal. Congenital enzyme defects in folate metabolism, although rare, produce profound derangements in folate handling. Inborn errors such as dihydrofolate reductase deficiency and other enzymopathies in the one-carbon pathway compromise conversion steps essential to regenerating tetrahydrofolate and its derivatives. Affected individuals may present in infancy or childhood with severe hematologic and neurologic manifestations refractory to standard dietary interventions, and they often require specialized metabolic management. In many clinical scenarios more than one factor contributes to folate depletion. For example, an individual with a marginal diet who undergoes bariatric surgery and receives anticonvulsant therapy faces additive risks. Socioeconomic determinants that limit food access can interact with medication exposures and genetic predispositions to amplify deficiency prevalence within communities. Recognition of this multifactorial architecture is critical for clinicians assessing etiology in individual patients and for public health planners designing preventive interventions [8].

Etiologic clarity informs preventive measures. Where increased demand is predictable, targeted supplementation and peripartum fortification programs reduce incidence of deficiency related outcomes. Where malabsorption or drug interference predominates, therapeutic strategies include higher oral doses, parenteral administration when needed, and modification of offending medications when feasible. Inherited metabolic disorders require tailored biochemical and genetic approaches. Comprehensive etiologic assessment thus guides effective, individualized management and population strategies to mitigate the health burden of folic acid deficiency [8].

Epidemiology

Folic acid deficiency has a markedly uneven global distribution. In high-income settings that implemented mandatory folic acid fortification of staple foods, deficiency prevalence has fallen to low single digits. In contrast, low- and middle-income countries continue to report substantial burdens, particularly among women of reproductive age and populations without reliable access to fortified foods or supplements. Cross-national comparisons attribute most of this disparity to differences in national fortification policy, supplement uptake, dietary patterns, and health system capacity for preventive care. [9][10] Population surveys and representative studies illustrate the scale of the problem in regions without effective fortification or where socioeconomic constraints limit dietary diversity. In many low-income countries the prevalence of biochemical folate deficiency among women of reproductive age exceeds 20 percent, and indicators of folate insufficiency adequate to prevent neural tube defects affect over 40 percent of women globally. These figures reflect both

absolute lack of intake of folate-rich foods and failure of periconceptional supplementation programs to reach the women at highest risk. The public health implication is persistent preventable perinatal morbidity despite well-established preventive measures. [11] National surveillance in high-income settings reveals residual pockets of risk even after fortification. Data from the United States National Health and Nutrition Examination Survey identify subgroups with disproportionately low folate status. Among nonpregnant women aged 12 to 49 years, a substantial minority demonstrated suboptimal red blood cell folate levels, with elevated risk concentrated among racial and ethnic minority groups, women who do not use dietary supplements, those who rely solely on fortified grains, and current smokers. These patterns indicate that fortification alone does not guarantee adequate status at the individual level when behavioral, cultural, and access barriers persist. [12]

Country-level analyses reinforce the role of age, socioeconomic position, and public health policy in shaping folate status. In Korea a national sample of women aged 15 to 49 returned a mean serum folate value near 9.1 ng/mL, while prevalence estimates varied with the diagnostic threshold applied. Using a conservative cutoff of less than 3 ng/mL yielded a deficiency prevalence of 6.2 percent, and a less stringent threshold of less than 4 ng/mL increased prevalence to 14.9 percent. Younger women, particularly those aged 15 to 24, demonstrated the highest rates of low serum folate, with more than 30 percent falling below the 4 ng/mL threshold. Age-specific vulnerability may reflect dietary transitions, contraceptive and pregnancy patterns, and differential supplement use among younger cohorts. [13] The effect of mandatory fortification on deficiency prevalence is among the clearest successes in nutrition policy. Australian experience documents large declines in folate deficiency following the introduction of mandatory folic acid fortification of bread and other staples. Between 2004 and 2008 remote and indigenous communities experienced elevated rates of deficiency; subsequent fortification reduced prevalence from 12.2 percent to 1.5 percent in the period 2010 to 2015, representing a relative risk reduction of approximately 88 percent. The strongest absolute and relative gains occurred in remote and indigenous populations, yet urban and non-indigenous groups also recorded meaningful declines. These outcomes demonstrate that well designed, population-level interventions can rapidly narrow disparities when implementation reaches marginalized groups. [14] Global comparisons emphasize the contrast between countries with mandatory fortification and those without. In jurisdictions where fortification programs are established, population prevalence of folate deficiency can be as low as 1.7 percent. By contrast, countries lacking fortification report rates that approach or exceed 20 to 24 percent in some

surveys. The policy landscape in Europe illustrates an intermediate pattern: many countries recommend periconceptional supplementation but stop short of mandatory fortification, creating heterogeneity in population status and persistent windows of preventable risk. [15]

Epidemiological risk concentrates in defined demographic groups. Women of reproductive age remain the priority population because maternal folate status directly determines risk of neural tube defects in offspring. Other vulnerable groups include people with low socioeconomic status, institutionalized older adults, and individuals with cognitive impairment who have restricted diets and limited access to preventive health services. These populations often face multiple barriers to adequate intake, including food insecurity, limited health literacy, and reduced contact with primary prevention programs. In addition, medical subgroups such as patients with malabsorptive disorders, those taking folate-antagonist medications, and individuals undergoing hemodialysis display elevated clinical risk irrespective of population-level fortification. Surveillance methods and diagnostic thresholds influence reported prevalence and complicate cross-study comparisons. Studies differ in whether they use serum folate, red blood cell folate, or functional biomarkers such as homocysteine. The choice of cutoff alters measured prevalence and the interpretation of population risk for specific outcomes, notably neural tube defect prevention. Consequently, harmonization of laboratory methods and consensus on threshold values would improve comparability and guide more precise public health action [15].

Epidemiologic evidence informs program priorities. Where deficiency remains common, integrated strategies combining mandatory fortification, targeted supplement distribution for women of reproductive age, and public education yield the most reliable reductions in prevalence. Where fortification is established but disparities persist, surveillance should focus on subgroups with low supplement use and restricted diets, and on monitoring potential unintended effects of high folic acid exposure. Cost-effectiveness analyses from multiple countries consistently show that fortification and periconceptional supplementation produce substantial reductions in neural tube defects at low incremental cost, supporting continued investment in these interventions. Gaps remain in global surveillance and program reach. Data scarcity is most acute in low-resource settings where routine biochemical monitoring is limited. In such contexts national estimates of folate deficiency may underrepresent regional variation and fail to capture high-risk populations. Strengthening laboratory capacity, integrating folate indicators into existing nutritional surveillance platforms, and prioritizing epidemiologic studies in underserved areas are necessary steps to close knowledge gaps and to tailor interventions where

they are most needed. In sum, the epidemiology of folic acid deficiency reflects a clear policy signal: where population-level fortification and accessible supplementation exist, deficiency becomes rare; where structural barriers persist, significant prevalence endures. Epidemiologic surveillance, targeted program design, and sustained policy commitment are the foundations for reducing the global burden of folic acid deficiency and its preventable sequelae [15].

Pathophysiology

Folate functions as an indispensable cofactor in cellular one-carbon metabolism with direct involvement in nucleotide biosynthesis, methyl group transfer, and erythroid maturation. Dietary folate is absorbed predominantly in the proximal small intestine where specialized transporters mediate vectorial uptake across the apical membrane of enterocytes. The principal carriers responsible for intestinal absorption include the proton-coupled folate transporter and the reduced folate carrier. These systems operate most efficiently at a slightly acidic luminal pH and provide the entry point for dietary reduced folates and for the synthetic analogue folic acid, which is converted to active forms following intestinal uptake. Once translocated into enterocytes and subsequently into the circulation, folate undergoes a stepwise enzymatic reduction to dihydrofolate and then to tetrahydrofolate. Tetrahydrofolate then accepts one-carbon units to form derivatives such as 5,10-methylene tetrahydrofolate and L-5-methyl tetrahydrofolate, the latter representing the dominant circulating species. [16][17] Intracellular recycling of L-5-methyl tetrahydrofolate back to tetrahydrofolate is contingent upon functional cobalamin dependent methionine synthase. In the absence of vitamin B12, remethylation of homocysteine to methionine fails and 5-methyl tetrahydrofolate accumulates within cells, effectively sequestering folate in a metabolically inactive pool. This biochemical sequestration yields a functional folate deficiency that impairs de novo nucleotide synthesis despite normal total folate measurements in plasma or erythrocytes. The molecular consequence is reduced availability of tetrahydrofolate cofactors required for transfer of one-carbon units in the synthesis of purines and thymidylate. The resulting deficit in nucleotide supply produces stalled DNA replication forks, replicative stress, and faulty chromosomal segregation in rapidly dividing cell populations [16][17].

The restricted size of total body folate reserves combined with daily losses and the magnitude of physiologic demand predispose individuals to relatively rapid onset of deficiency when intake or absorption is inadequate. Total stores are small on the scale of milligrams and daily requirements approximate several hundred micrograms. Under conditions of inadequate intake, impaired absorption, or heightened metabolic demand the reservoir of

active folate declines over a matter of weeks to months. Reduced tetrahydrofolate availability impairs nucleotide synthesis and yields characteristic defects in hematopoiesis. Megaloblastic anemia emerges as a principal clinical manifestation because erythroid precursors require sustained nucleotide supply for normal DNA replication and cell division. The marrow displays ineffective erythropoiesis, nuclear cytoplasmic asynchrony, and release of macrocytic red cells with shortened survival. Concomitant cytopenias and bone marrow dysplasia may occur because other rapidly proliferating lineages also depend on folate dependent nucleotide synthesis [18][19]. Beyond nucleic acid synthesis, folate occupies a central node in methylation biology. One-carbon metabolism couples folate mediated transfer of methyl groups to formation of S-adenosylmethionine, the universal methyl donor for methylation of DNA histones and small molecules. Folate depletion reduces flux through methyl donor pathways and produces global and locus specific hypomethylation of genomic DNA. Hypomethylation alters transcriptional control at genes crucial for development cell cycle regulation and immune function. Experimental models demonstrate that deficiency induced hypomethylation modifies expression of developmental regulators and morphogens and can perturb patterns of tissue differentiation. These epigenetic consequences link folate status to developmental outcomes and to long term changes in gene expression that persist beyond the period of acute deficiency. [20]

Homocysteine metabolism represents a sensitive functional readout of impaired folate dependent remethylation pathways. With insufficient folate mediated provision of methyl groups homocysteine accumulates in plasma. Hyperhomocysteinemia exerts multiple pathophysiologic effects including endothelial dysfunction oxidative stress and promotion of prothrombotic states. Elevated homocysteine interferes with nitric oxide mediated vasodilation and enhances susceptibility to vascular injury, mechanisms that have been implicated in increased cardiovascular risk associated with low folate status. The accumulation of homocysteine also reflects reduced synthesis of downstream metabolites required for redox homeostasis and for the maintenance of one-carbon cofactor pools. [21] Compensatory molecular responses occur in chronic folate depletion. Cells upregulate expression of transport proteins such as the proton-coupled folate transporter and the reduced folate carrier in an attempt to increase import of available folate. While this adaptive response may partially restore intracellular folate levels in mild deficiency it does not substitute for adequate systemic supply when dietary intake or absorption remains inadequate. At the transcriptional level folate deficiency modulates expression of genes governing chromatin remodeling and DNA repair including histone deacetylases and other epigenetic modulators.

Changes in chromatin regulatory machinery both reflect and amplify the epigenetic instability induced by inadequate methyl donor availability and propagate defects in cellular repair pathways. [18][19][22]

Cellular outcomes of folate insufficiency include both increased programmed cell death and decreased proliferative capacity. Experimental systems reveal enhanced apoptotic signaling in progenitor cell compartments and reduced cell cycle progression in tissues with high mitotic indices. These cellular responses compromise tissue maintenance and regenerative capacity and contribute to organ specific dysfunction. In the developing embryo, impaired proliferation and increased apoptosis within neural folds and other structures can culminate in morphologic defects such as neural tube closure failure. In adult tissues cumulative deficits in cell renewal and increased cell loss can impair mucosal integrity hematologic competence and neurocognitive function. Interactions with xenobiotics and genetic variants further modulate pathophysiology. Drugs that antagonize folate pathways such as antifolates and some anticonvulsants produce direct enzymatic blockade of essential conversion steps and can precipitate clinical deficiency even when intake is sufficient. Genetic polymorphisms in enzymes of one-carbon metabolism alter intracellular distribution of folate derivatives and modify susceptibility to functional deficiency and to the epigenetic effects of low folate. These interactions create heterogeneity in clinical presentation and in response to supplementation [18][19][22].

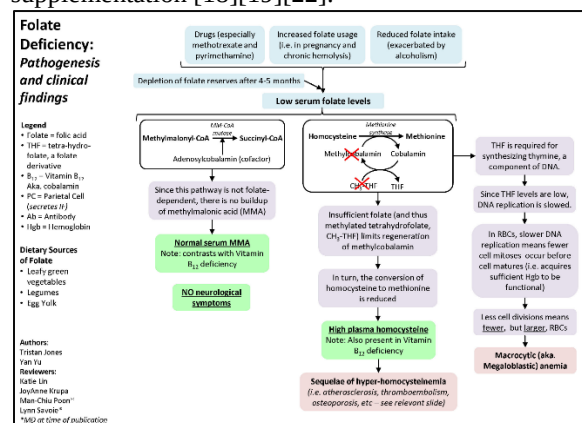


Figure-2: Pathogenesis of folic acid deficiency.

The clinical manifestations of folate deficiency therefore reflect a cascade that begins at molecular disruption of one-carbon transfers progresses through impaired nucleotide availability and altered methylation and culminates in defective cell division increased apoptosis and organ dysfunction. Hematologic abnormalities are the most readily observed phenotype, but vascular neural and developmental consequences arise from common underlying mechanisms. The temporal dynamics of deficiency depend on the balance between intake absorption of metabolic demand and compensatory adaptations. Rapidly proliferating tissues manifest

earliest and most severe dysfunction while chronic deficiency exerts cumulative effects on epigenetic regulation vascular biology and neurodevelopment. Therapeutic interventions that restore folate supply reverse many of the biochemical abnormalities and ameliorate hematologic signs provided irreversible organ damage has not occurred. Repletion restores tetrahydrofolate pools normalizes methyl donor flux and reduces homocysteine concentration. Understanding the molecular cascade linking folate to nucleotide synthesis methylation and cellular survival clarifies why preventive measures such as periconceptional supplementation and population level fortification are effective in reducing developmentally mediated structural defects and in preventing hematologic disease [18][19][22].

History and Physical

A focused and systematic history is the cornerstone for identifying the etiology of folic acid deficiency and for guiding subsequent diagnostic testing and management. Begin by quantifying dietary intake with attention to habitual consumption of folate-rich foods such as dark leafy vegetables, legumes, citrus fruits, and fortified grain products. Elicit changes in diet over the preceding months, including food insecurity, recent weight loss, restrictive diets, or cultural practices that limit access to fresh produce. Ask specifically about food preparation methods because prolonged cooking and repeated reheating diminish folate content and may transform an adequate food supply into a marginal one. Document use of vitamin supplements and fortified foods, the dose and frequency of intake, and the timing relative to conception for women of reproductive age. Capture pregnancy history including current gestational age, prior pregnancies, outcomes, and any preconception supplementation; periconceptional folate status has direct implications for neural tube defect risk and shapes the urgency of intervention [23]. Medication exposure is a critical domain of the history. Record prescription and over-the-counter agents with potential antifolate effects including methotrexate, trimethoprim, sulfasalazine, and certain anticonvulsants such as phenytoin. Ask about recent or long term antibiotic use, antiretroviral therapy, and any chemotherapeutic agents. Explore adherence patterns and whether medications have been started, stopped, or dose-adjusted recently. Include herbal supplements and alternative medicines because some preparations may interact with folate metabolism or with other prescribed drugs. Obtain a complete surgical history with emphasis on bariatric procedures, small bowel resections, or gastric surgeries that alter gastrointestinal anatomy and reduce absorptive surface. Prior radiation to the abdomen or pelvis and past episodes of intestinal ischemia or severe enteritis should be noted [23].

Assessment of gastrointestinal symptoms directs attention to malabsorption syndromes. Ask

about chronic or recurrent diarrhea, steatorrhea, weight loss, bloating, and symptoms triggered by gluten or lactose. Screen for established diagnoses such as celiac disease, inflammatory bowel disease, tropical sprue, and chronic pancreatitis. Investigate prior intestinal biopsies or investigations such as serologic testing and endoscopic findings. A history of achlorhydria or long term proton pump inhibitor use is relevant because reduced gastric acidity impairs folate release from food matrices and hampers subsequent absorption [23]. Quantify alcohol intake with precision. Determine pattern, quantity, duration, and recent changes in consumption. Chronic heavy drinking produces multifactorial impairment of folate status through reduced intake, impaired absorption, diminished hepatic storage, and altered enzymatic handling. Explore social determinants that may underlie alcohol misuse, including housing instability, psychiatric comorbidity, and social isolation, because these factors also increase the likelihood of nutritional deficiencies and reduce access to preventive care. Document states of increased physiological demand. Ask about current pregnancy and lactation, recent or ongoing hemolytic processes, chronic inflammatory dermatoses with extensive epidermal turnover, and periods of rapid growth such as infancy and adolescence. Inquire about chronic hemolytic disorders and transfusion history because increased erythropoietic activity accelerates folate consumption. Health behaviors that raise metabolic demand, such as smoking and uncontrolled chronic illness, also influence folate kinetics and should be recorded [23].

A careful neurologic history helps distinguish folate deficiency from cobalamin deficiency. Explore sensory disturbances, paresthesias, gait instability, loss of vibration and proprioception, and cognitive changes. Neurological deficits that include posterior column dysfunction or progressive neuropathy suggest vitamin B12 deficiency or combined deficiency and warrant immediate biochemical differentiation. Ask about mood changes, memory difficulties, irritability, and sleep disturbances; these neuropsychiatric manifestations can occur with folate deficiency, particularly in older adults, though severe sensorimotor deficits are more characteristic of cobalamin deficiency [23]. Family history and genetic background should be included. Elicit relatives with known inborn errors of folate metabolism, early childhood developmental anomalies, or recurrent pregnancy losses. Enquire about ethnic or geographic origins associated with higher prevalence of specific enzyme polymorphisms that modulate folate handling. Social history should address socioeconomic factors, educational attainment, and food access because these variables are strong determinants of dietary diversity and supplement uptake. Physical examination must be directed yet thorough. Inspect the oral cavity for glossitis characterized by a smooth, swollen, erythematous tongue and for mucosal ulcerations.

Measure conjunctival and palmar pallor, tachycardia, and signs of exertional intolerance indicative of anemia. Evaluate for mild jaundice or scleral icterus that can result from ineffective erythropoiesis and intramedullary hemolysis of fragile megaloblastic erythrocytes. Palpate for splenomegaly, which may accompany hemolytic states or chronic hematologic stress. Perform a focused neurologic examination assessing vibration, proprioception, light touch, and deep tendon reflexes. Assess coordination and gait to detect subtle cerebellar or sensory ataxia. Conduct a cognitive screen when indicated, documenting attention, short term memory, and executive function because folate deficiency may present with subtle neuropsychiatric changes in older adults [23].

Include a targeted abdominal examination for signs of chronic liver disease or malabsorption and an assessment of nutritional status including body mass index, muscle wasting, and signs of micronutrient deficiencies. Examine the skin for evidence of exfoliative disorders, chronic wounds, or burns that increase folate demand. In women of reproductive age, perform a focused obstetric and gynecologic assessment when appropriate, documenting uterine size, fetal heart tones, and any complications that could influence maternal folate requirements. Integrate historical and physical findings to prioritize differential diagnosis and testing. Distinguish dietary insufficiency from malabsorption by correlating history of intake with gastrointestinal symptoms, surgical history, and response to prior supplementation if any. Suspect medication induced deficiency when antifolate or enzyme inducing drugs are present and symptoms progress despite adequate dietary intake. Consider combined deficiencies, particularly cobalamin deficiency, when neurologic signs are evident; do not initiate folate repletion before excluding or treating B12 deficiency because masking of hematologic signs may delay recognition of irreversible neurologic injury. A comprehensive history and physical examination identify modifiable contributors, clarify urgency, and guide appropriate laboratory evaluation and referral. Early recognition of risk factors enables timely supplementation, modification of offending agents, and targeted referral to dietetic, gastroenterological, or addiction services. In pregnancy, prompt identification and correction of maternal folate insufficiency mitigate risk for congenital anomalies and other adverse developmental outcomes, which underscores the clinical priority of this assessment in women of reproductive age. [23]

Evaluation

Evaluation of folic acid deficiency begins with clinical assessment and proceeds to targeted laboratory testing. The goal is to confirm deficiency. The goal is to identify the cause. The goal is to assess severity and to exclude other diagnoses that require different therapy. Start with a focused clinical evaluation. Review diet history. Ask about supplement use and fortified food intake. Review medication

history for agents that interfere with folate pathways. Screen for alcohol use. Check for signs of malabsorption and for conditions that raise folate demand such as pregnancy hemolysis and extensive skin loss. Perform a focused physical exam to look for pallor glossitis jaundice and neurologic findings. Use clinical information to direct laboratory testing and imaging when indicated. Laboratory evaluation begins with a complete blood count and peripheral smear. A CBC often shows macrocytic anemia with mean corpuscular volume greater than 100 fL. Hemoglobin and hematocrit are reduced in symptomatic patients. Mean corpuscular hemoglobin may be normal or slightly high. Mild reductions in leukocyte and platelet counts sometimes appear. The peripheral smear commonly shows macrocytic red blood cells hypersegmented neutrophils and occasional megaloblasts. A reticulocyte count is often low and indicates ineffective erythropoiesis. Measure serum folate and vitamin B12 at the same time. Both deficiencies produce megaloblastic changes, and both must be assessed before treatment. Serum folate less than 2 ng per mL indicates deficiency. Levels between 2 and 4 ng per mL are borderline. Values above 4 ng per mL are generally considered normal. Interpret serum folate in clinical context because serum levels reflect recent intake and may miss chronic depletion [24].

Red blood cell folate gives a measure of long term folate status. Low RBC folate indicates chronic deficiency. RBC folate correlates with tissue stores and with risk of folate responsive outcomes such as neural tube defects [24]. Assess functional biomarkers to improve diagnostic accuracy. Measure plasma homocysteine and methylmalonic acid. Elevated homocysteine with normal methylmalonic acid and normal B12 suggests folate deficiency. When both homocysteine and methylmalonic acid are raised and B12 is low the pattern supports vitamin B12 deficiency. Use both markers when initial serum assays are equivocal or when clinical signs are unclear. Composite diagnostic scores that combine hematologic indices and biochemical markers can increase diagnostic precision. Such scoring systems have reported sensitivities and specificities that exceed 90 percent in validation studies. Use these tools when laboratory resources allow and when the clinical picture is complex. Consider advanced analytic methods in specialized settings. Microbiological assays for serum folate provide a biological measure of folate activity and remain a reference standard in some laboratories. Liquid chromatography tandem mass spectrometry allows precise quantification of different folate forms including L 5 methyl THF and unmetabolized folic acid. These methods are useful in research and in cases where detailed metabolic profiling will change management . [24][25][26][27].

Bone marrow examination is not required for routine diagnosis. Reserve bone marrow biopsy for cases in which hematologic malignancy marrow

failure or unexplained cytopenias are suspected. A marrow in folate deficiency shows hypercellularity macrocytosis and megaloblastic changes with nuclear cytoplasmic asynchrony. These findings support ineffective hematopoiesis but do not replace biochemical testing. Use marrow findings to exclude alternative marrow processes rather than to confirm simple folate depletion. [24][25][26][27] Interpret laboratory results with attention to confounders. Recent intake of folate containing supplements or fortified foods can normalize serum folate while tissue stores remain low. Chronic alcohol use liver disease and renal failure alter folate homeostasis and may shift biomarker relationships. Hemolytic states and recent transfusion change measured values. Certain medications cause false normal or abnormal results and therefore complicate interpretation. Use a stepwise diagnostic approach in pregnant patients. Assess RBC folate early in pregnancy when possible. Quantify supplement exposure. If serum or RBC folate is low begin replacement promptly given the risk to the embryo. When B12 status is unclear measure MMA because failing to identify B12 deficiency prior to folate repletion can leave neurologic injury unaddressed. Investigate malabsorption when history or symptoms suggest impaired intestinal uptake. Order celiac serology small bowel imaging and consider endoscopy with duodenal biopsy when indicated. Test for achlorhydria and consider review of bariatric surgery records. When malabsorption is confirmed plan for higher oral doses or for parenteral replacement. Screen for drug induced deficiency when patients use antifolates enzyme inducers or medications known to impair folate absorption. If possible modify the offending agent or arrange for prophylactic folate when therapies cannot be stopped. Coordinate with prescribing clinicians to balance therapeutic needs and nutritional risk [24][25][26][27].

Follow response to therapy with serial laboratory monitoring. Repeat CBC within two weeks to document rising reticulocyte count and clinical improvement. Normalize hemoglobin and MCV over four to eight weeks in most cases. Recheck folate and functional markers after clinical stabilization to confirm repletion and to guide maintenance dosing. In cases of ongoing loss or malabsorption plan long term monitoring. Integrate evaluation findings into a management plan. Confirm the diagnosis by combining clinical signs dietary history and laboratory evidence. Identify and treat underlying causes. Provide targeted supplementation and consider public health measures such as fortified foods or community programs for high risk groups. Document follow up and adjust testing when the clinical context changes. A structured evaluation clarifies diagnosis supports targeted therapy and reduces the risk of recurrent deficiency and its complications. Use clinical judgment to tailor testing in resource limited settings

and to escalate diagnostics when the initial workup is inconclusive or when the patient fails to respond to standard therapy [24][25][26][27].

Treatment / Management

The management of folic acid deficiency centers on restoring folate levels, correcting associated hematologic abnormalities, and addressing underlying causes that impair intake, absorption, or utilization. Oral supplementation with folic acid remains the standard therapeutic approach for most patients, as it is safe, inexpensive, and effective in replenishing folate stores. The usual oral dosage ranges from 1 to 5 mg per day, adjusted according to the degree of deficiency and the clinical setting. Mild cases, particularly those due to dietary insufficiency, often respond to 1 mg daily. Higher doses may be indicated for patients with chronic conditions such as hemolytic anemia, exfoliative skin disorders, or prolonged use of medications that interfere with folate metabolism. Treatment typically continues for four to six weeks or until hematologic recovery is complete, although longer therapy may be required in chronic disease states or persistent risk conditions. Parenteral administration is reserved for specific clinical scenarios where oral absorption is inadequate. This includes patients with malabsorption syndromes, short bowel syndrome, severe inflammatory bowel disease, or postoperative gastrointestinal dysfunction. Intramuscular or subcutaneous folic acid can be administered when enteral routes fail to maintain therapeutic levels. Dosing varies depending on clinical response and the underlying disorder, as no universal protocol has been standardized. Parenteral therapy is generally transitioned to oral maintenance dosing once absorption improves and deficiency is corrected [28][29].

When vitamin B12 deficiency coexists, both nutrients must be replaced concurrently. Folic acid alone will correct anemia but does not address the neurological manifestations of B12 deficiency. Moreover, isolated folate repletion can worsen neurologic symptoms by promoting hematologic recovery while masking the true underlying deficiency. Therefore, B12 supplementation should begin before or alongside folate replacement to ensure comprehensive correction of metabolic abnormalities. The duration of treatment depends on the etiology of deficiency. For reversible causes such as poor dietary intake, temporary supplementation for one to two months may suffice once diet improves. For chronic or irreversible causes—including alcoholism, celiac disease, inflammatory bowel disease, and long-term use of antifolate drugs—lifelong supplementation may be necessary to maintain adequate folate status. Ongoing monitoring of hematologic indices and serum folate levels is recommended to guide therapy and ensure sustained response [28][29]. In pregnancy, management carries specific clinical importance. Folate requirements increase significantly due to fetal

growth and maternal tissue expansion. Women diagnosed with deficiency during pregnancy are typically prescribed 500 micrograms to 5 mg of folic acid three times daily until laboratory normalization is achieved. Preventive supplementation is also essential. Women of reproductive age should consume at least 0.4 mg daily starting before conception and continuing throughout gestation. Those at high risk—such as individuals with a previous pregnancy affected by neural tube defects, those on antiepileptic medications, or those with diabetes—require higher prophylactic doses ranging from 4 to 5 mg daily. These recommendations are supported by strong evidence linking maternal folate status to reduced rates of neural tube defects and improved pregnancy outcomes. [30]

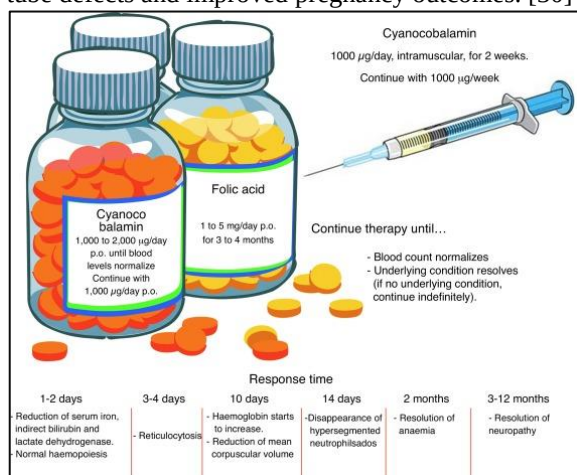


Figure-3: Treatment and management of Folic acid deficiency.

Adjunctive management focuses on dietary modification and lifestyle correction. Patients should be counseled to increase consumption of natural folate sources, including dark green vegetables such as spinach and kale, legumes such as lentils and chickpeas, and fruits such as oranges and papaya. Liver and fortified grain products are also rich in folate and should be integrated into daily meals when feasible. Counseling should also address alcohol reduction or cessation, as chronic alcohol intake impairs folate absorption and hepatic metabolism. Public health strategies play an essential role in preventing deficiency at the population level. Mandatory fortification of staple foods, such as wheat flour or rice, has led to significant declines in folate deficiency and related congenital disorders in many countries. Fortification ensures broad access to folate among vulnerable populations, including women of reproductive age, low-income groups, and communities with limited dietary diversity. In settings without mandatory fortification, targeted supplementation programs remain an effective alternative. Monitoring treatment efficacy involves serial laboratory testing and clinical assessment. Improvement in reticulocyte count within 7 to 10 days indicates effective erythropoiesis. Hemoglobin and hematocrit levels generally normalize within one to

two months. Persistent macrocytosis or anemia after adequate supplementation should prompt evaluation for concurrent vitamin B12 deficiency, ongoing blood loss, or bone marrow disorders [28][29].

Patient education is an integral component of management. Individuals should understand the importance of adherence to supplementation, especially in pregnancy and chronic disease. They should also recognize symptoms of recurrent deficiency such as fatigue, glossitis, and pallor to seek early reassessment. For patients on long-term medications that antagonize folate metabolism—such as methotrexate or phenytoin—regular monitoring and prophylactic folate supplementation are recommended to prevent recurrence. Treatment of folic acid deficiency is effective when approached comprehensively—through pharmacologic repletion, nutritional optimization, and correction of underlying risk factors. Regular follow-up and continued education sustain long-term health and reduce recurrence. By integrating supplementation with dietary and public health interventions, clinicians can prevent deficiency-related complications and support overall metabolic and hematologic health across populations [28][29][30].

Differential Diagnosis:

The differential diagnosis of folic acid deficiency centers on identifying other conditions that produce macrocytic or megaloblastic anemia. Since folate deficiency and vitamin B12 deficiency share overlapping hematologic findings, careful evaluation of clinical context and biochemical markers is essential to distinguish among possible causes. Vitamin B12 deficiency is the most important condition to differentiate, as both disorders cause megaloblastic anemia through impaired DNA synthesis. However, neurological symptoms such as paresthesias, ataxia, memory loss, and loss of proprioception are characteristic of vitamin B12 deficiency and absent in isolated folate deficiency. Elevated methylmalonic acid and homocysteine levels are typical in B12 deficiency, whereas only homocysteine is raised in folate deficiency. Alcoholic liver disease frequently presents macrocytosis due to direct toxicity of alcohol on erythroid precursors, altered lipid composition of red cell membranes, and secondary nutritional deficiencies. Chronic alcohol use may also coexist with folate deficiency because of impaired intestinal absorption and poor diet, complicating differentiation. Hypothyroidism causes non-megaloblastic macrocytosis due to reduced erythropoietic activity. Measurement of thyroid-stimulating hormone (TSH) helps identify this cause in patients with unexplained macrocytosis. Myelodysplastic syndromes and aplastic anemia are bone marrow disorders that can mimic folate deficiency by producing macrocytic or normocytic anemia with low reticulocyte counts. Bone marrow biopsy and cytogenetic studies help confirm these diagnoses. Drug-induced macrocytosis is another

consideration. Agents such as methotrexate, phenytoin, zidovudine, and hydroxyurea impair folate metabolism or DNA synthesis and may lead to megaloblastic changes. Hemolytic anemias and copper deficiency can also present with macrocytosis. Reticulocyte count, bilirubin levels, and copper assays help clarify these causes. Comprehensive evaluation of laboratory and clinical data ensures accurate distinction and appropriate management [30].

Prognosis

Appropriate folate repletion yields restoration of biochemical homeostasis and reversal of hematologic dysfunction in most affected individuals. Serum folate rises within approximately 17 days of supplementation, and population studies report reduction in the incidence of megaloblastic anemia by as much as 79 percent following corrective therapy. Hematologic recovery follows a consistent temporal sequence. Markers of intramedullary hemolysis decline within 24 to 48 hours of effective treatment. Bone marrow response appears as a surge in reticulocyte production by days three to four, signaling restoration of erythropoietic activity. Hemoglobin concentration and hematocrit begin to ascend within one to two weeks and reach normalization in the majority of cases within four to eight weeks. Morphologic abnormalities in circulating leukocytes resolve on a predictable timetable; hypersegmented neutrophils dissipate by days ten to fourteen, and associated cytopenias of leukocytes and platelets correct over a period of two to four weeks as marrow output stabilizes. Metabolic indices respond in parallel with hematologic parameters. Elevated plasma homocysteine declines after folate administration, reflecting reestablishment of one-carbon transfer and remethylation pathways. Reduction in homocysteine accompanies improvement in cellular methylation capacity and correlates with resolution of biochemical markers of folate insufficiency. When vitamin B12 deficiency coexists, coordinated repletion of both cofactors is required to prevent persistence of neurologic dysfunction and to secure full reversal of metabolic derangements [31].

Clinical recovery depends on prompt identification of underlying cause and on removal or mitigation of ongoing insults. Reversible etiologies such as isolated dietary shortfall respond to finite courses of supplementation and dietary modification. Chronic causes that impair absorption or sustain increased demand may require indefinite maintenance therapy and longitudinal monitoring to prevent relapse. Failure to identify concurrent cobalamin deficiency or to address malabsorptive states reduces the likelihood of complete recovery and raises the risk of long term morbidity. Beyond correction of hematology and metabolic indices, folate repletion exerts favorable effects on cardiovascular risk markers in some cohorts. Low dose folic acid has been associated with reductions in total cholesterol and low

density lipoprotein cholesterol and with increases in apolipoprotein A I. These lipid changes may contribute to modest declines in cardiovascular risk, particularly among individuals with hyperhomocysteinemia or metabolic syndrome. [31] Overall, when diagnosis is timely and therapy is appropriate, prognosis is good. Persistent or progressive deficits indicate unresolved underlying disease, treatment failure, or concurrent pathology and warrant further investigation [31].

Complications

Untreated folic acid deficiency produces a spectrum of adverse outcomes across hematologic, mucocutaneous, neuropsychiatric, obstetric, and vascular domains. Hematologically, sustained folate paucity precipitates ineffective erythropoiesis with resultant megaloblastic anemia. Progressive impairment of DNA synthesis may extend beyond erythroid precursors to involve multiple marrow lineages, producing leukopenia, thrombocytopenia, and in severe cases pancytopenia. These cytopenias increase susceptibility to infection, bleeding, and exertional intolerance and may mimic primary marrow disorders, complicating diagnostic pathways. Mucocutaneous and gastrointestinal manifestations reflect high turnover of epithelial tissues under conditions of nucleotide insufficiency. Glossitis typically presents as a smooth, erythematous, and tender tongue, frequently accompanied by angular stomatitis and oral ulceration. Gastrointestinal complaints may include anorexia, weight loss, and nonspecific dyspeptic symptoms that further impair nutritional intake and compound deficiency. Cutaneous findings and poor wound healing may be apparent in cases with concomitant exfoliative disorders that both increase folate demand and reveal underlying depletion. Neuropsychiatric sequelae encompass a broad array of cognitive and affective disturbances. Patients may develop fatigue, insomnia, irritability, and depressive symptoms, and some progress to frank cognitive decline or psychotic features when deficiency is protracted. Although classical posterior column dysfunction and sensory ataxia typify vitamin B12 deficiency, folate insufficiency has been associated with a reversible folate-responsive neuropathy in some reports; such neuropathies have demonstrated improvement with high-dose folate regimens (10 mg three times daily) in selected cases [32][33][34][35].

In pregnancy, maternal folate deficiency carries well-documented teratogenic and adverse perinatal risks. Insufficient folate during the periconceptional and early gestational periods increases the risk of neural tube defects. Beyond structural neural defects, observational data link maternal folate deficiency to higher rates of preterm delivery, fetal growth restriction, spontaneous abortion, and placental complications such as abruption. Neurodevelopmental sequelae have also

been described, including delays in language acquisition and other developmental domains among exposed offspring. Reported effect sizes for some outcomes include substantial absolute and relative increases in risk, reinforcing the preventive rationale for periconceptional supplementation [36]. Disruption of one-carbon metabolism in folate deficiency leads to accumulation of homocysteine and perturbation of methylation reactions. Hyperhomocysteinemia contributes to endothelial dysfunction, oxidative stress, and prothrombotic milieu, thereby linking folate deficiency mechanistically to elevated cardiovascular risk. These vascular consequences may be both direct, via endothelial injury, and indirect, via modulation of lipid and inflammatory pathways. Excessive folic acid intake also poses clinical concerns, particularly in older adults. High circulating folate can mask hematologic indicators of vitamin B12 deficiency and thereby delay recognition of cobalamin-associated neurologic injury. The relationship between folate and carcinogenesis is complex and appears context dependent; while adequate folate sufficiency likely protects against initiation of neoplastic lesions, supraphysiological folic acid exposure may, in some settings, accelerate progression of established neoplasms, notably within the colorectum. Epidemiologic and mechanistic data remain mixed, and this duality informs cautious approaches to high-dose supplementation in populations at increased cancer risk [37]. Overall, the complications of folic acid deficiency span reversible hematologic and mucosal pathology to potentially irreversible neurologic and developmental harm when diagnosis and treatment are delayed. Clinical vigilance, timely biochemical assessment, and appropriate replacement strategies mitigate most risks, whereas failure to identify concurrent cobalamin deficiency or ongoing causative factors increases the likelihood of persistent morbidity [37].

Consultations

Effective management of folic acid deficiency often requires a multidisciplinary approach that integrates medical, nutritional, and pharmacologic expertise. Consultation with relevant specialists is indicated in complex, refractory, or recurrent cases, as well as when deficiency arises from multifactorial causes such as malabsorption, chronic illness, or medication-induced interference with folate metabolism. Early specialist engagement supports comprehensive evaluation and minimizes the risk of diagnostic delay or incomplete correction of underlying factors. The primary care provider remains central in the coordination of care, overseeing diagnostic evaluation, initiation of supplementation, and follow-up of hematologic and biochemical response. This clinician also identifies when specialist input is warranted, particularly in patients who fail to respond adequately to standard therapy or present with concurrent systemic disorders. Dietitians and clinical nutritionists are essential contributors to long-term

management. They perform detailed dietary assessments, evaluate folate intake from natural food sources and fortified products, and design individualized nutrition plans that emphasize sustainable folate sufficiency. Their role extends to patient education on food preparation and selection strategies that preserve folate bioavailability, which is particularly valuable in populations with limited access to fortified foods [37].

For women of reproductive age, obstetricians and gynecologists provide critical preventive care by ensuring optimal folate status before and during pregnancy. Their involvement helps reduce the risk of neural tube defects, preterm labor, and other pregnancy-related complications linked to deficiency. Preconception counseling and adherence monitoring further enhance preventive outcomes in high-risk groups. Hematologists are consulted when the patient exhibits severe anemia, pancytopenia, or macrocytosis of uncertain origin. They guide advanced diagnostic evaluation, including bone marrow studies or molecular testing, to exclude alternative or coexisting hematologic disorders. In refractory cases, they assist in determining whether combined deficiencies or marrow pathology contribute to suboptimal treatment response. Pharmacists play an important role in identifying and managing drug interactions that impair folate absorption or metabolism, such as those associated with anticonvulsants, methotrexate, or sulfasalazine. They provide dosing guidance, ensure therapeutic compatibility, and recommend appropriate supplementation regimens based on concurrent therapies. Collaborative consultation across these disciplines promotes accurate diagnosis, effective treatment, and sustained remission. This integrated model of care not only restores hematologic function but also supports nutritional adequacy, reproductive health, and long-term metabolic stability in patients with folic acid deficiency [37].

Patient Education

Patient education plays a central role in preventing and managing folic acid deficiency. Patients should be informed about dietary sources, cooking practices, and supplementation strategies that maintain adequate folate levels. Emphasis should be placed on consuming a diet abundant in natural folate sources, including green leafy vegetables such as spinach and kale, legumes like lentils and chickpeas, citrus fruits, and fortified grains. Patients should also be advised to use low-heat cooking methods such as steaming or light sautéing, as excessive heat destroys folate and reduces its nutritional value. High-risk individuals require specific counseling on consistent supplementation and dietary adherence. A daily oral dose of 1 mg of folic acid is generally sufficient for preventing deficiency in groups with increased metabolic needs or impaired absorption, including those with a history of bariatric surgery, chronic alcohol consumption, malnutrition, chronic hemolytic anemia, or conditions involving rapid cell turnover.

Educating these patients on the consequences of untreated deficiency—such as anemia, cognitive decline, or pregnancy complications—can improve adherence to treatment and preventive regimens. Women of reproductive age require focused education on the preventive role of folic acid in fetal neural tube development. They should begin supplementation with at least 0.4 mg daily before conception and continue throughout pregnancy. Those with higher risk, such as previous neural tube defect-affected pregnancies or ongoing anticonvulsant therapy, should take increased doses of 4–5 mg daily under medical supervision to reduce recurrence risk and optimize fetal development [38].

Patients should also understand that routine supplementation is not required for all individuals but should be tailored to personal risk factors, lifestyle, and medical history. Counseling should address the impact of alcohol use, gastrointestinal diseases, and long-term medications on folate absorption. Reinforcing the importance of follow-up blood tests ensures proper monitoring of folate levels and response to treatment. Education must focus on building lifelong dietary habits, promoting food diversity, and encouraging regular medical checkups to detect early signs of deficiency. Effective patient education not only prevents recurrence but also reduces the long-term health burden associated with folate-related hematological and neurological disorders [38].

Other Issues

Folic acid deficiency remains a major nutritional and clinical concern with diverse systemic effects. Folate, or vitamin B9, serves as a coenzyme in several fundamental biochemical processes, including DNA and RNA synthesis, methylation reactions, and amino acid metabolism. Through its active tetrahydrofolate (THF) derivatives, folate participates in one-carbon transfer reactions essential for purine and thymidylate synthesis. This function underpins its critical role in erythropoiesis and cellular replication, particularly in rapidly dividing tissues such as bone marrow, gastrointestinal mucosa, and the developing fetus [39]. Folate operates in close metabolic coordination with vitamin B12 within the one-carbon cycle. The interdependence between these vitamins becomes evident in the “folate trap” phenomenon, in which a deficiency of vitamin B12 prevents the conversion of methyl-tetrahydrofolate (methyl-THF) back to THF, thereby rendering folate metabolically inactive. This biochemical block explains why vitamin B12 deficiency can manifest with features resembling folate deficiency and why concurrent assessment of both vitamins is essential before initiating therapy. Dietary sources of folate include leafy green vegetables such as spinach and kale, legumes, citrus fruits, and organ meats such as liver. However, folate is highly sensitive to heat and alcohol, both of which degrade its bioavailability. The nutrient is primarily

absorbed in the jejunum via carrier-mediated transport mechanisms that function optimally in a slightly acidic environment. Consequently, any pathology that disrupts jejunal integrity, such as celiac disease or inflammatory bowel disease, can impair folate absorption and precipitate deficiency [39].

The major etiological factors contributing to folate deficiency include inadequate dietary intake, chronic alcohol use, gastrointestinal malabsorption, prolonged use of medications such as methotrexate, phenytoin, or trimethoprim, and increased physiological demand as observed during pregnancy, hemolytic anemia, or rapid growth periods. Clinically, patients may present with nonspecific symptoms such as fatigue, pallor, weakness, and glossitis. Oral manifestations such as angular stomatitis and mucosal ulcers are frequent findings. Neurological manifestations, which are characteristic of vitamin B12 deficiency, are typically absent in isolated folate deficiency. However, subtle neuropsychiatric changes, including depression, irritability, or cognitive impairment, may still occur [39]. Laboratory findings form the cornerstone of diagnosis. A complete blood count commonly reveals macrocytic anemia, with a mean corpuscular volume (MCV) exceeding 100 fL. Peripheral smears typically show hypersegmented neutrophils and macroovalocytes. Biochemical testing demonstrates low serum folate levels (<2 ng/mL), while levels between 2 and 4 ng/mL are considered borderline. Elevated plasma homocysteine levels with normal methylmalonic acid (MMA) concentrations further support a diagnosis of folate deficiency, distinguishing it from vitamin B12 deficiency, in which both markers are elevated. Red blood cell folate levels offer a more accurate reflection of long-term folate status. Treatment primarily involves oral folic acid supplementation, typically administered in doses ranging from 1 to 5 mg per day, depending on severity and cause. For pregnant women, daily supplementation of at least 0.4 mg is recommended to prevent neural tube defects, with doses increased to 4–5 mg daily for high-risk individuals. Vitamin B12 status must always be evaluated before initiating folic acid therapy, as treating folate deficiency alone can mask hematologic signs of vitamin B12 deficiency while allowing neurological damage to progress. Following treatment initiation, reticulocytosis generally appears within three to four days, anemia begins to improve within one to two weeks, and full hematologic recovery occurs over four to eight weeks [39].

Untreated folic acid deficiency can lead to serious complications, including megaloblastic anemia, pancytopenia, and elevated homocysteine levels associated with increased cardiovascular risk. In pregnancy, deficiency significantly raises the risk of fetal neural tube defects, preterm delivery, and impaired fetal growth. Epidemiological studies show that deficiency is most prevalent among individuals

with chronic alcohol use, older adults, pregnant women, and those with poor dietary habits or limited access to folate-fortified foods. Public health interventions, particularly the mandatory fortification of grains with folic acid, have markedly reduced deficiency rates in many developed nations, including the United States, Canada, and Australia. However, deficiency remains a concern in countries that have not implemented fortification policies, underscoring the need for continued nutritional education and targeted supplementation strategies. In special clinical contexts such as methotrexate toxicity, folinic acid (leucovorin) serves as rescue therapy to replenish reduced folate pools without interfering with chemotherapeutic efficacy. Understanding these key issues allows clinicians to approach folate deficiency comprehensively—recognizing at-risk populations, ensuring accurate diagnosis through combined hematologic and biochemical evaluation, and implementing both therapeutic and preventive measures to mitigate individual and population-level consequences [39].

Enhancing Healthcare Team Outcomes

Folic acid deficiency represents a largely preventable and effectively treatable nutritional disorder, yet it continues to impose significant health consequences when undetected or inadequately managed. Optimal outcomes require a collaborative, interprofessional healthcare model that integrates preventive education, early identification, and comprehensive management tailored to individual risk factors. Primary care physicians, internists, obstetricians, and nurse practitioners are positioned at the forefront of detection. Their responsibilities include identifying high-risk populations such as women of childbearing age, individuals with chronic alcohol dependence, patients undergoing hemodialysis, or those receiving folate-antagonist medications including methotrexate and phenytoin. Early screening and risk assessment during routine visits provide the foundation for timely intervention. Nurses and dietitians serve as key facilitators of patient education, ensuring consistent reinforcement of dietary recommendations and adherence to supplementation regimens. They guide patients in selecting folate-rich foods, promote the use of fortified products, and tailor nutritional plans to cultural preferences and socioeconomic conditions. For patients with limited health literacy, these professionals translate complex medical instructions into practical dietary strategies that can be sustained in everyday life. Pharmacists complement these efforts by reviewing prescribed medications to identify potential drug-nutrient interactions and advising patients on proper supplement use. Their expertise is crucial in preventing excessive folic acid intake that might obscure the clinical detection of concurrent vitamin B12 deficiency or contribute to unwanted metabolic effects in vulnerable populations [40].

Social workers and case managers address the broader determinants of health that often underlie nutritional deficiencies. By coordinating access to community food programs, financial assistance, and prenatal care services, they mitigate barriers that can perpetuate folate deficiency, particularly in underserved populations. Their role extends beyond logistical support, fostering patient engagement and adherence through consistent communication and advocacy. The effectiveness of these interventions depends on seamless interprofessional coordination. Shared electronic medical records, structured referral systems, and regular multidisciplinary meetings ensure that diagnostic findings, treatment updates, and patient concerns are consistently communicated. This collaboration minimizes duplication of efforts, prevents oversights, and strengthens continuity of care across clinical settings. Clinicians also bear a critical ethical and preventive duty to educate women of reproductive age about the role of folic acid in neural tube defect prevention. Failure to provide such counseling compromises fetal health outcomes and may expose practitioners to medicolegal accountability. Therefore, patient education must be integrated into reproductive health counseling, family planning, and primary prevention strategies. Through proactive teamwork, evidence-based guidelines, and ongoing follow-up, healthcare professionals can reduce the global burden of folic acid deficiency. This interprofessional collaboration not only improves hematologic and developmental outcomes but also strengthens public health systems by promoting equity, informed decision-making, and sustainable preventive care practices [40].

Conclusion:

In conclusion, folic acid deficiency is a preventable and treatable condition with far-reaching implications for individual and public health. Its role in nucleotide synthesis and methylation makes it critical for rapidly dividing cells, explaining its profound impact on hematopoiesis and fetal development. While therapeutic oral supplementation is highly effective in correcting deficiency and reversing hematological abnormalities, the primary focus must remain on prevention. This is especially crucial for women of reproductive age, where adequate periconceptional folic acid intake is paramount for preventing devastating neural tube defects in newborns. Successfully addressing this nutritional challenge requires a cohesive, interprofessional effort. Physicians, nurses, dietitians, and pharmacists must collaborate to identify at-risk individuals, provide targeted patient education on dietary sources and supplementation, and ensure long-term management for those with chronic predisposing conditions. Furthermore, sustained public health initiatives, including food fortification and community education programs, are vital for reducing the population-wide burden of deficiency. Through this integrated approach, healthcare teams can effectively mitigate

the complications of folic acid deficiency and improve outcomes across the lifespan.

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