Active Folate Versus Folic Acid: The Role of 5-MTHF (Methylfolate) in Human Health

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Folate is the generic term for vitamin B9, a water-soluble vitamin that includes chemically similar compounds essential in periods of rapid cell growth and division, in the maintenance of new cells, and in the making of DNA and RNA. While best recognized for pregnancy and fertility support, recognition is growing that it also benefits cardiovascular health, mood, and cognition.

Recent data suggest the need to distinguish between naturally occurring folates and folic acid (FA), terms often mistaken and used interchangeably, both by practitioners and consumers, causing considerable confusion.[1]

In particular, 5-Methyltetrahydrofolate [methylfolate, 5-MTHF, or (6S)-5-MTHF], has been evaluated as a better alternative to folic-acid supplementation.[2-5] In this article, I endeavor to clearly identify the difference between folic acid and folate, pointing out why Quatrefolic, the 5-MTHF glucosamine salt from Gnosis by Lesaffre, is the ideal choice, suitable for anyone but in particular for those expressing methylenetetrahydrofolatereductase (MTHFR) polymorphism, which is approximately 40% of the global population.[6-10]

FOLATE: SOURCES AND DEFICIENCY

People can't synthesize folate, and due to its water-soluble nature, the body stores it to a limited extent. Therefore, folate must be obtained from their diets. Although naturally occurring folates are found in various foods, such as green leafy vegetables, sprouts, fruits, brewer's yeast, and animal liver (Figure 1), it's exceedingly difficult for most people to get the daily recommended amount of folate through food alone. Furthermore, food folates are unstable, and can be oxidized by heat, light, and/or metal ions, so cooking can reduce bioavailability.

While implementing specific food-processing procedures can minimize folate degradation, the absorption of folate is much more effective with fortified foods and supplements, such as 5-MTHF/folate and folic acid. In fact, in the last decades, the main form of folate supplementation has been FA. Prescription of FA to women in the preconception period and during pregnancy is a consolidated practice.[11-14]

The recommended dietary allowances (RDAs) for folate are 400 µg/day for adults and 600 µg/day for women of childbearing age.[15] Furthermore, many countries have initiated mandatory food fortification with FA to compensate for the losses and maintain adequate dietary intakes.

Figure 1. Folate intakes are typically poor in many individuals' diets for several reasons. Natural folates: (1) are susceptible to oxidation, (2) can rapidly lose activity in foods, and (3) are largely destroyed by cooking, to 90%. Moreover, they have a low and incomplete bioavailability.

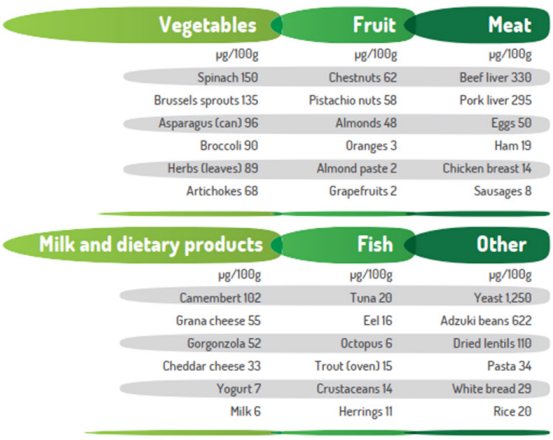


Fig 1: Typical folate intakes are poor in many individuals' diets for several reasons. Natural folates are susceptible to oxidation, they rapidly lose activity in foods, and are largely destroyed by cooking to 90%. Moreover, they have a low and incomplete bioavailability.

Still, folate deficiency is incredibly common and may occur when: (1) dietary intake is inadequate; (2) an increased need isn't matched by increased intake, as in physiological conditions such as pregnancy, lactation, and children's growth; (3) absorption or excretion is altered or losses occur; or (4) metabolism or drug use interfere with the body's ability to use folate.

Deficiency of folate may be asymptomatic or present with the symptoms of anemia, diarrhea, loss of appetite, and weight loss. Additional signs are weakness, sore tongue, headaches, heart palpitations, irritability, and behavioral disorders.[6,16]

Folate Forms and Metabolization

The bioavailability and metabolism of the different folate forms vary due to their respective chemical structures. All forms of folates, natural or synthetic, must be converted to the circulating form 5-MTHF to exert their biological activity. The structurally related compounds included in the folate group are FA, natural folates, and 5-MTHF.

FA. FA is the oxidized, monoglutamate precursor form of folate that was synthesized in pure crystalline form for the first time in the 1940s. Many dietary supplements include it as do fortified foods, such as cereal-based products, pasta, enriched bread, and fruit juice. FA doesn't occur in nature and has no biological functions. To be utilized, the human body must metabolize and reduce it to 5-MTHF using a multistep enzymatic conversion.

Natural folates. Natural folates occur in foods and also exist in many chemical forms of polyglutamate. Food folates are hydrolyzed to the monoglutamate form in the gut before absorption by active transport across the intestinal mucosa. Therefore, before entering the bloodstream, the monoglutamate form is reduced to tetrahydrofolate (THF) and converted into methyl forms (5-MTHF).

5-MTHF. The biologically active form 5-MTHF, the predominant physiological form of folate found in blood and in umbilical cord blood, is also available in small amounts in foods. It's widely available as a food ingredient and doesn't require metabolization.

Drawbacks of FA

FA is first reduced to dihydrofolate by the enzyme dihydrofolate reductase (DHFR) and then to tetrahydrofolate (THF). This is a rate-limiting step, leading to DHFR's weak activity in humans, with considerable interindividual variations. High doses of FA can lead to a rapid saturation or inhibition of the DHFR enzyme, resulting in an accumulation of unmetabolized FA (UMFA) and the UMFA syndrome.[13-17]

Additionally, some people have genetic variations that decrease the activity of DHFR. Levels of circulating UMFA in the population are persistent in countries where the FA fortification of grains and cereals has been implemented.[18] UMFA may compete with natural folate (5-MTHF) for the folate transporter and the folate receptor, thus depleting active folate for participation in the metabolic cycles.

A 2014 published study clearly showed that 86% of FA in the hepatic portal vein is unmetabolized, while almost all the natural folate was converted correctly.[19,20] Detectable levels of UMFA occur temporarily in plasma after the consumption of >200 μg FA, with concentrations increasing in parallel to that of total FA after supplementation. UMFA has been detected in cord and infant blood, a source of concern due to potential adverse effects on health, as I will further describe.[18,21]

While it's ideal that people obtain nutrients from food, the population can't universally assume that it can rely on the diet for food folates. THF is a critical player in folate metabolism as a folate-acceptor molecule. THF is first converted to 5,10-methylene-THF and then later is reduced to 5-MTHF by MTHFR.[22]

Genetic polymorphism may impair the MTHFR activity and the related metabolization of food folates and folic acid in 5-MTHF. MTHFR is highly polymorphic in the general population, with multiple MTHFR gene alterations having been identified. Today, 35 rare but deleterious mutations in MTHFR, polymorphisms, and nine common variants have been reported. The two most common are C677T and A1298C. The numbers refer to their location on the gene.

A polymorphic MTHFR enzyme may function with approximately 55% to 70% efficiency as compared to a normal MTHFR enzyme. The incidence of people presenting a form of polymorphism of MTHFR is about 40% worldwide. This polymorphism is associated with an increased thermolability and reduced specific activity of MTHFR in vivo, resulting in a residual enzyme activity of 65% for heterozygous carriers and only 30% for homozygous carriers.[23,24]

The limited conversion of FA may jeopardize folate availability and increase the risk of adverse health outcomes. Cutting-edge scientific research has shed light on how much the MTHFR polymorphism is implicated in chronic disease states and how folate nutrition may contribute to replacing methylation adequately and improving overall health.

Supplementation with active folate 5-MTHF bypasses the entire folate metabolization, which is potentially impaired by MTHFR polymorphism, and 5-MTHF is directly absorbed to exert the biological activity. Therefore, using 5-MTHF as a food supplement instead of FA is strongly recommended for external supplementation.[13]

Among the available ingredients, Quatrefolic, the glucosamine salt of 5-MTHF, patented by Gnosis by Lesaffre, offers a significant advantage over previous generations of folates (Figure 2). Thanks to its high solubility and bioavailability, the supplement delivers

Figure 2. Quatrefolic, the Glucosamine Salt of 5-MTHF With High Solubility and Bioavailability

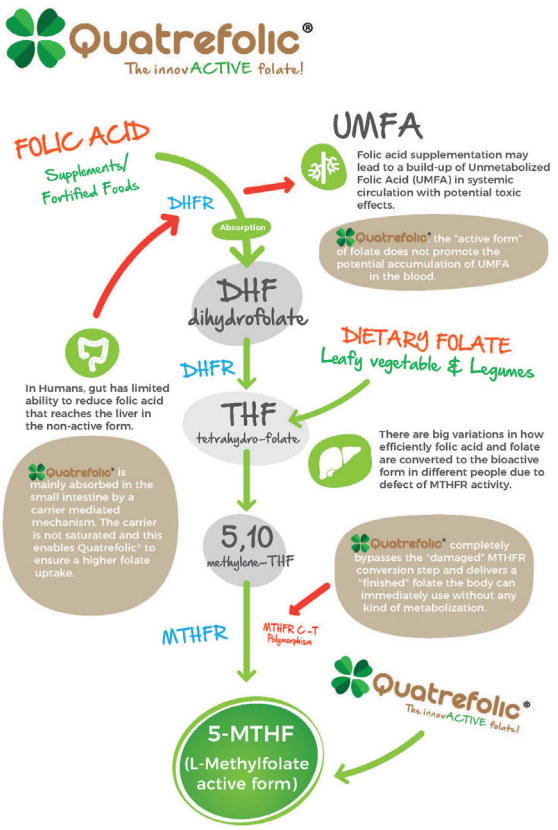
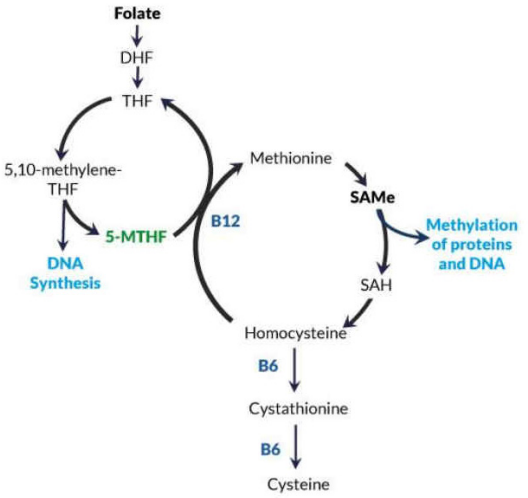


Figure 3. In the folate-dependent, one-carbon metabolism, the 5MTHF provides methyl groups to the S-adenosylmethionine (SAMe, SAM) cycle through homocysteine (Hcy) conversion to methionine. SAMe is the primary methyl donor to the methyl groups in the body and is required in the methylation of a diverse number of targets, including phospholipids, DNA, ribonucleic acid, neurotransmitters, and proteins. Hcy is a byproduct of the one-carbon cycle and is accumulated in the bloodstream when it can't be remethylated to methionine. Plasma Hcy levels are an indirect indicator of folate levels.[18]



Abbreviations: 5MTHF, 5-methyltetrahydrofolate; DHF, dihydrofolate; SAH, S adenosylhomocysteine; THF, tetrahydrofolate.

finished folate directly used by an organism without any specific form of metabolism, which makes it the ideal choice because it's suitable for everyone regardless of MTHFR polymorphism.

ACTIVE FOLATE AND HOMOCYSTEINE

Regardless of how the active form of folate 5-MTHF has been obtained, the methylfolate, in concert with vitamin B12, enters the one-carbon metabolism. This metabolism is a network of interrelated biochemical reactions that occurs in all of the body's cells, and it's vital for various functions, including detoxification, energy production, immune function, maintenance and regulation of genes, mood balancing, and control of inflammation. It's essential for sustaining life and for inhibiting or slowing the development of age-associated diseases.

Perturbations of one-carbon metabolism, owing to low levels of 5-MTHF, critically contribute to increasing the circulating homocysteine (Hcy) levels and to a toxic accumulation in the bloodstream (Figure 3).[22]

Prolonged exposure to high Hcy, hyperhomocysteinemia (HCys), can damage the blood vessels, contributing to blood clots, and can lead to the onset of cardiovascular disease, including atherosclerosis, stroke, and inflammatory syndromes as well as neuronal pathologies. Because healthy blood vessels and folate levels are essential for fertility and pregnancy, high Hcy can make it difficult to conceive and maintain a pregnancy.[25]

Mazza et al demonstrated the capacity of 400 µg of Quatrefolic, in conjunction with B6 and B12, to lower Hcy serum levels better than conventional vitamin supplementation with highly dosed folic acid (5 mg/day). Quatrefolic was tested on hypertensive people with a low cardiovascular risk—104 patients with HCys of ≥15 µmol/L.

Significant HCys reduction occurred as compared to baseline, from 21.5 µmol/L to 10.0 µmol/L. Moreover, the treatment was significantly effective. The ideal HCys level was reached in 55.8% of cases in the Quatrefolic group, and it was substantially higher than that of the control. Polymorphisms in folate pathway genes could be one reason for fertility complications in some women with unexplained infertility.[26]

ACTIVE FOLATE OVER FOLIC ACID

Averting Birth Defects

Pregnant women have a five-to-ten-fold higher requirement for folate than do women who aren't pregnant. Folate is needed in cell growth, cell division, cell synthesis,

and repair of DNA. During pregnancy, folate requirements increase not only to support embryonic and fetal development and maternal tissue growth but also to reduce the risk of low birth weight, preterm birth, elevated Hcy levels, and related adverse pregnancy outcomes.

The indication is to take folate for 3 months before conception and to continue taking it for at least the first 3 months of pregnancy to prevent having a baby with neural tube defects (NTDs), a malformation that develops in the first 28 days of pregnancy, before many women even know that they're pregnant.[22,23]

Due to an inability to properly process FA, pregnant women with MTHFR gene polymorphisms may have an increased risk of many deleterious defects. Moreover, elevated Hcy caused by folate deficiency is one of the independent risk factors for many pregnancy-related disorders.

Some studies have explored the effects of 5-MTHF supplementation for individuals with MTHFR polymorphisms—wild-type CC or homozygous TT. Prinz-Langenohl et al[27] demonstrated that 5-MTHF supplementation isn't affected by MTHFR gene polymorphism. In another chronic, bioavailability study, Litynski et al have shown a significant prolonged effect in reducing Hcy levels at six months after ceasing treatment with 5-MTHF in homozygous individuals (TT), at 12.1 ± 2.5 as compared to 16.9 ± 6.8 for folic acid ($P < .01$).[28]

Other studies suggest that folate insufficiency due to MTHFR deficiency is bypassed by 5-MTHF supplementation.[27-29] Hence, active 5-MTHF, such as Quatrefolic, appears to be a preferred option for folate supplementation in individuals with MTHFR polymorphism.

Many studies have reported that hyperhomocysteinemia was associated with numerous pregnancy complications, including recurrent pregnancy loss,[30] NTDs,[31] preeclampsia,[32] preterm delivery,[33] placental abruption,[34,35] fetal growth restriction,36 and gestational diabetes mellitus.[37] Cawley et al also observed that neonatal birth weight and maternal Hcy levels were negatively correlated.[38] While the beneficial effects of folate supplementation in reduction of the risks of NTDs have been clearly demonstrated,[39-41] more robust meta-analyses are needed to assess its efficacy in preventing other congenital disabilities.[42-44]

Interestingly, many studies have observed folate-and-Hcy metabolism anomalies in children affected by autism spectrum disorder (ASD).[45,46] More important, folate supplementation during pregnancy may reduce the risk of delivering newborns affected by ASD[22,47] and may improve children's language competency.[48]

But a clinically validated option exists. Supplementation for hypertensive individuals with 400 µg of Quatrefolic for two months was found to be more effective in reducing Hcy blood levels than folic acid.[26] Additionally, the supplementation of pregnant women with Quatrefolic until the twenty-fourth week of pregnancy was more efficient in increasing 5-MTHF blood levels than the same dose of folic acid.[49] The study also confirmed the importance of folate supplementation to avoid developing NTDs.

In a recent retrospective study of 269 individuals, Cirillo et al investigated the role of a vitamin B complex supplement—Quatrefolic, vitamin B12, and vitamin B6 (Inpha Duemila, Normocis)—compared to FA supplementation only, in relation to clinical pregnancy and live birth in infertile women undergoing homologous assisted reproductive technology (ART).

A higher percentage of women in the vitamin B complex group had a clinical pregnancy and live birth when compared to the percentage of the FA group. The researchers concluded that women supplemented with Quatrefolic and vitamin B12 have a higher chance of clinical pregnancy and live birth. Supplementation with vitamin B complex might be considered in clinical practice with women undergoing ART.[50]

Efficacy of 5-MTHF in Infertility

The level of folate and Hcy status is critical in the early stages of human reproduction. Investigation of the role of Hcy metabolism in patients with unexplained female sterility or secondary sterility due to recurrent pregnancy loss shows a positive association. Women and men with fertility problems may have low folate availability, which is often related to the MTHFR enzyme polymorphism. Preconceptional folate supplementation has been linked to beneficial reproductive outcomes in both natural pregnancies and those after ART treatment.

An increasing volume of publications related to folates and fertility problems have been published over the past few years, showing that 5-MTHF is a better option than folic acid to correct metabolic defects in gametes and embryos. In patients with repeated miscarriages and ART failures, Servy and Menezo observed a strong impact for the C677T MTHFR isoform.[51] Both partners could be responsible for the failure; it isn't restricted to women.

Based on these observations, couples with fertility problems, especially if at least one of the partners is a carrier of one of the two main MTHFR isoforms (C677T or A1298C) and if he or she has a folate-deficient diet, should be supplemented with 5-MTHF rather than folic acid to bypass the bottleneck created by the deficiency of MTHFR.[51-56]

Observational studies have been conducted with Quatrefolic in couples with fertility problems and have shown promising results.[22,57] In Servy et al's case series, seven couples with more than five miscarriages and a history of inefficient supplementation with high doses of FA (5 mg/day) to prevent pregnancy loss, were supplemented for four months with Quatrefolic.[57] Among seven couples, both partners in five carried the main MTHFR isoform (C677T). After the supplementation

with 400 µg/day of Quatrefolic, six couples achieved pregnancy. Three were spontaneous pregnancies and deliveries, two had pregnancies at 16 and 25 weeks, and one had just started a pregnancy.

Another larger case series included 33 couples with fertility problems that had lasted for at least four years, such as recurrent fetal loss, premature ovarian insufficiency, or abnormal sperm parameters. Two-thirds of them had failed ART attempts.[52] For all the couples, at least one of the partners was a carrier of one of the two main MTHFR isoforms (C677T or A1298C), and the women had been previously treated unsuccessfully with high doses of FA (5 mg/day).

In that study, before attempting conception or ART, all couples were supplemented with 800 µg/day of Quatrefolic, either Impryl or Tetrafolic, for 74 days, which corresponds to the entire cycle of spermatogenesis (Figure 4). This led to successful pregnancy spontaneously for 13 couples and with ART for 17 couples. The researchers concluded that a physiological dose of 800 µg/day of Quatrefolic bypasses the MTHFR block, and they suggest that it's an effective treatment for such couples.

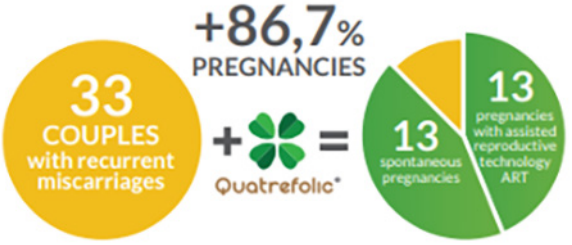
More recently, Clement et al showed that couples with at least 3 years of fertility problems, with one of the partners being homozygous for MTHFR isoforms, have higher circulating Hcy levels than the heterozygous or wild-type patients.[53] The supplementation of 89 couples with 600 µg/day Quatrefolic (either Impryl or Tetrafolic) for 3 months was effective in significantly decreasing plasma Hcy levels. The authors concluded that couples with a long history of infertility should be analyzed for MTHFR single-nucleotide polymorphisms and Hcy and should be treated with a physiological dose of 5-MTHF instead of high doses of FA.

No UMFA Risk

Several studies have reported an increase in serum UMFA levels after implementing FA fortification, with possible concerns about potential overdoses and adverse effects.[1,20] Variability in the presence or persistence of UMFA in the population that it may be accumulated in the blood due to different conditions, such as uncontrolled FA intake or impairment of the FA reduction pathway. High doses of FA can lead to UMFA syndrome, which is suspected of causing immune dysfunction and other adverse pathological effects, such as cancer, especially colorectal and prostate.[61-63] However, the causal effect between UMFA and those pathologies has yet to be demonstrated.[64]

A dose of about 100 to 200 µg of FA is known to be unlikely to cause the appearance of UMFA in the blood but FA can be detected after a supplementation period of 14 weeks at 400 µg and can lead to UMFA appearance in serum.[24] In contrast, daily supplementation with the reduced active form 5-MTHF, Quatrefolic, seems not to produce UMFA because it's directly used by cells, and

Figure 4. Quatrefolic Can Bypass the Methylenetetrahydrofolatereductase (MTHFR) Block



enters the one-carbon cycle required to synthesize DNA and red blood cells.[17,23,27,52,57] Bailey et al's study supported that finding, showing that 5-MTHF enables folate repletion more quickly and uniformly than FA and without exposure to UMFA.[17]

CONCLUSIONS

Testing every pregnant woman for the existence of a mutated MTHFR gene isn't a standard medical protocol, but women expressing MTHFR polymorphism may not experience the perceived advantage of FA supplementation and can be at potential risk because they are less able to transform FA. Because the association between the MTHFR polymorphism and a low folate concentration has been assessed, the direct supplementation of an active form, such as Quatrefolic (5-MTHF), through fertility supplements, prenatal vitamins, and dietary supplements, should be strongly considered as being universally beneficial.

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