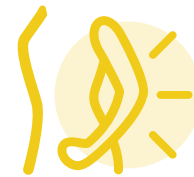




active folate and pregnancy



THE GENETIC POLYMORPHISM FACTS

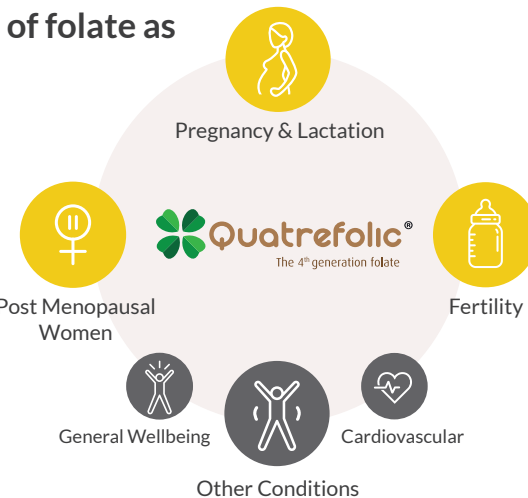
The folate market, the exponential increase of the biologically active form of folate as Quatrefolic®

As the demand of dietary supplements is increasing, the use of folate has known a breakthrough during the past years. Slowly the market showed a bigger interest in the vitamin B9 as it has proved benefits in a wide range of applications.

Historically the market share was dominated by the non biologically active form of folate, the folic acid. **However, today, we can assist to an inversion of the balance. The advance of scientific studies supports that not everyone can benefit of folic acid supplementation in the same way.**

Therefore, the natural form is preferred and represents more than half of the shares. The trend of switching from folic acid into reduced folate is worldwide, from USA to EMEA, and is also starting in some emerging countries.

In this context, Quatrefolic® represents a real opportunity to offer innovative solutions to answer this market need.



Quatrefolic® and Pregnancy Outcome VS Folic Acid

Adequate folate intake is particularly important for pregnant women, with a requirement of 5–10-fold higher compared to non-pregnant ones. Folate is needed in cell growth, cell division, cell synthesis and repair of DNA.

During pregnancy folate requirements increase to support embryonic and fetal development and maternal tissue growth but also to reduce risk of low birth weight, preterm birth, elevated homocysteine levels and related adverse pregnancy outcomes.

For these reasons, and because humans cannot synthesize folate, its supplementation is required before and during pregnancy, with a daily dose established worldwide by relative Health Authorities (i.e. FDA, EFSA)

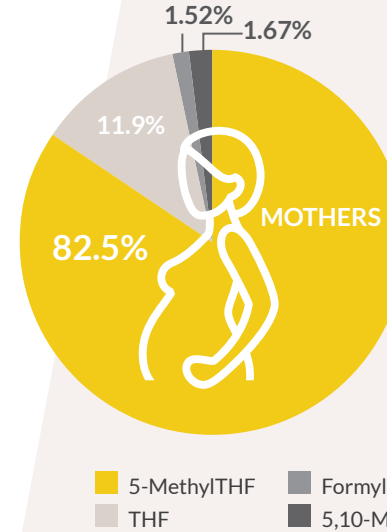
One important difference among prenatal vitamins is the source of folate. Folate (vitamin B9) is a generic definition of a group of correlated compounds. It includes the folic acid, the synthetic form of folate that is not biologically active and the 5-methyltetrahydrofolate (5-MTHF), the naturally occurring active folate in human plasma that constitutes 95–98% of folate in serum or red blood cells (RBCs).

In vivo, the body converts dietary folic acid to 5-MTHF (also named L-methylfolate) through a multi-steps process where the enzyme methylenetetrahydrofolate reductase (MTHFR) owns a key role. Some individuals, due to their unique genetic patterns and expression, have polymorphic forms of this enzyme and do not produce adequate or effective MTHFR, with a reduction of active 5-MTHF availability.

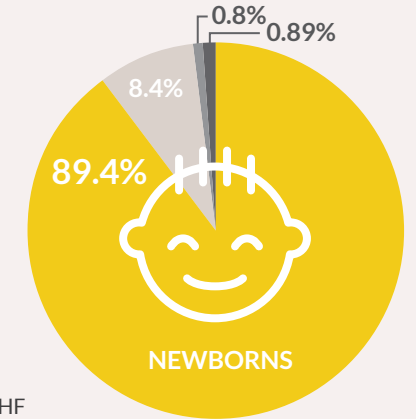
Since the association between MTHFR polymorphism and low folate concentration has been assessed 5-MTHF the direct supplementation of the active form 5-MTHF through prenatal vitamins should be strongly considered as universally beneficial.

Quatrefolic® as a source of 5-MTHF might be particularly useful to provide the nutritionally active form of folate during preconception, pregnancy and lactation.

Quatrefolic® provides naturally active folate (5-MTHF) to protect all women and babies and maximize the benefit of folate intake.

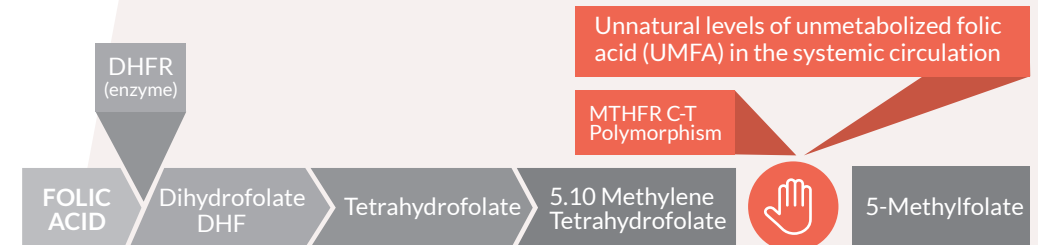


Relative percentage of the main folate forms and their percentage of total folate in maternal serum and umbilical cord serum from neonates



Obeid R. et al. J Perinat Med 2013

Polymorphic MTHFR enzyme may function with approximately 55% to 70% efficiency compared to a normal MTHFR enzyme. Nowadays a total of 9 common variants (polymorphisms) has been reported. The two most common ones are C677T and A1298C. The numbers refer to their location on the gene.



Safi J. et al. Pregnancy. 2012; Pitkin R.M. Am J Clin Nutr 2007; Castaño E. et al. PLOS ONE 2017; Nauman et al. Asia Pac J Clin Nutr. 2018; Kubo et al. Nutrients 2020; Van Mil N.H. et al. Reproduction. 2014; Sullivan M. et al. J Pharm Pharmacol 2015; Greenberg J.A. et al. Rev Obstet Gynecol 2011; Smith D.A. et al. Am J Clin Nutr 2008; Patanwala I. Am J Clin Nutr 2014; Van der Put N.M.J. et al. Am J Hum Genet 1998.



5-Methylfolate

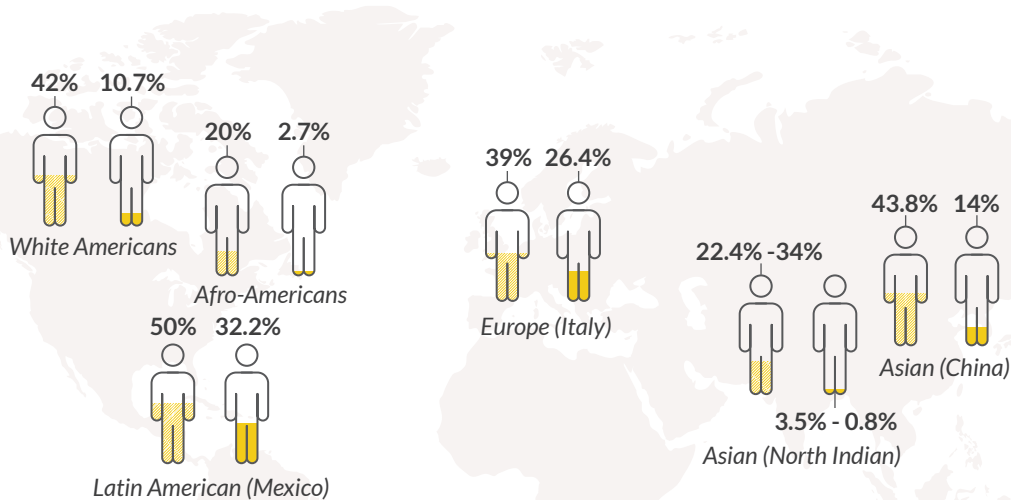
Quatrefolic®, MTHFR Polymorphism and Pregnancy care

Testing every pregnant woman for the existence of a mutated MTHFR gene is not a medical standard protocol. The MTHFR mutation test is prescribed by doctors to people with elevated homocysteine levels and to women with cases of spina bifida or malformations in previous pregnancies.

Choosing the right prenatal vitamins, with the active form of folate like Quatrefolic®, could represent a great advantage for women that could trust in the effective bioavailability of the 5-MTHF, independently by the presence or not of MTHFR polymorphism.

Frequency of MTHFR Polymorphism and Populations screening:

■ 677CT Heterozygous ■ 677TT Homozygous



Ulrich C.M., Potter J.D. Cancer Epidemiol Biomarkers Prev 2006; Wilcken B. et al. J Med Genet. 2003; Seremak-Mrozikiewicz A et al. Neuro Endocrinol Lett 2010; Botto L.D., Yang Q. Am J Epidemiol 2000; Plumptre et al. Am J Clin Nutr 2015; Greenberg J.A. et al. Rev Obstet Gynecol 2011; Obeid R. et al. J Perinat Med 2013; Patanwala I. Am J Clin Nutr 2014; Wang W. et al. Meta Gene 1 2013.



Pregnancy and Preeclampsia

Preeclampsia is a pregnancy complication characterized by high blood pressure and signs of damage to another organ system, most often the liver and kidneys, that occur in women after the 20th week of pregnancy. While rare, preeclampsia also may occur in a woman after delivering her baby, most often within 48 hours. This is called postpartum preeclampsia. It is a multifactorial and complex disorder where the involvement of MTHFR polymorphism is under evaluation: positive correlation has been found by Wang in 2013 in overall Caucasian, and East Asia populations.

Quatrefolic®, as it is the active folate, can better provide adequate levels of folate in pregnant women, independently of their genetic patterns.



Fertility

MTHFR polymorphism plays a significant role in human fertility. It is a recognized risk factor for male infertility and is associated with impair female fecundity.

Quatrefolic® bypasses folate metabolism disturbances and may improve male and female fertility, alleviate infertility, and increase success rates in infertility treatment, as shown in a case series study and described in a review published article.



Mood in Pregnancy and Postpartum

In a cohort study was showed that the prevalence of PPD (Post-Partum Depression) was significantly higher among pregnant women taking folic acid (FA) for a duration of 6 months or less than those who reported taking FA for a duration of more than 6 months during pregnancy ($P < 0.05$).

Quatrefolic® might offer protection against mood impairment during pregnancy and postpartum through the normalization of the level of folate in all women, providing the direct bioavailable form of folate.

Quatrefolic® and Hyperhomocysteinemia in Pregnancy

Homocysteine (Hcy) is a common amino acid found in the bloodstream and produced in the one carbon cycle. Elevated homocysteine level is considered an independent causal factor for pregnancy complications and adverse neonatal outcome.

Folate is an important regulator of Hcy metabolism and helps to maintain its normal plasma concentrations. Polymorphism of the enzyme MTHFR is commonly associated with defects in folate-dependent homocysteine metabolism. Disturbance of maternal and fetal homocysteine metabolism (and low level of active folate) has been associated with fetal neural tube defects, with various conditions characterized by placental vasculopathy, such as pre-eclampsia and abruption, and with recurrent pregnancy loss.

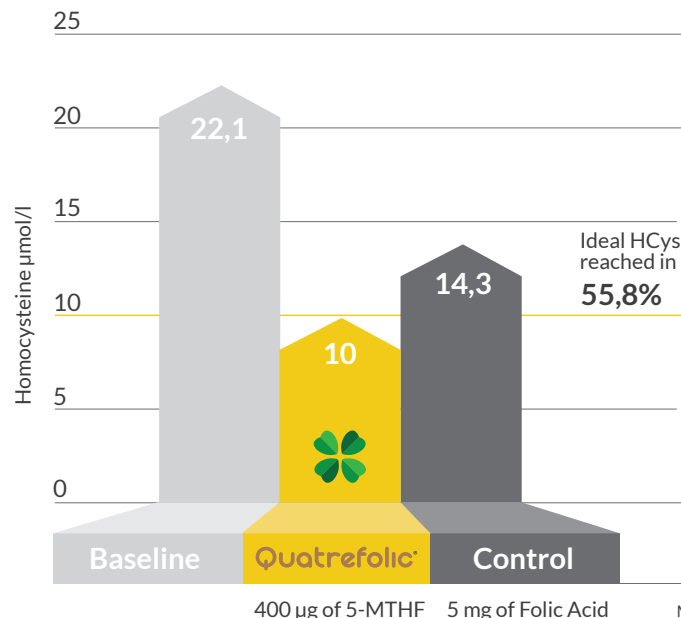
Quatrefolic® clinical data on Homocysteine reduction

The efficacy of Quatrefolic® (400 µg of Quatrefolic® plus B6, and B12) in lowering homocysteine serum levels (HCys) versus a conventional vitamin supplementation with highly dosed folic acid (5 mg/day) has been demonstrated in hypertensive subjects at low cardiovascular risk (104 patients with HCys 15 µmol/l).

Isotalo P.A. et al Am. J. Hum. Genet. 2000; Moustafa A.A. et al. Front Behav Neurosci 2014; Ambrosino P. et al Nutr Res 2015; Kedar R., Chandel D. Egypt J Med Hum Genet 2019; Gong M. et al. PLoS One. 2015; Laanpere M. et al. Nutr Rev 2010; Kelly C.B. et al. J Psychopharmacol 2004; Servy E.J. et al. J Assist Reprod Genet 2018; Clement A. et al. J Gynecol Obstet Hum Reprod. 2020.

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Quatrefolic® is effective in lowering Homocysteine.



Quatrefolic® offers a homocysteine-lowering and -normalizing effect clinically proven.

The result shows significant HCys reduction in comparison with baseline from 21.5 µmol/l to 10.0 µmol/l with the product containing Quatrefolic®. The treatment was significantly effective, and the ideal HCys level was reached in 55.8% of cases in the Quatrefolic® group, and it was significantly higher than in controls.



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