active folate and human fertility

IMPACT OF ACTIVE FOLATE AND HOMOCYSTEINE

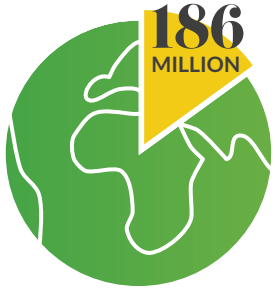
According to the World Health Organization, almost **15% of reproductive-aged couples worldwide** are affected by fertility problems.
Available data suggests that between 48 million couples and 186 million individuals have infertility globally.

Infertility is considered as a disease of the male or female reproductive system, defined by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse.

While female infertility alone represents 35% of all infertility cases, male's represent 20–50% of them.

As it exists a wide range of causes, a low level of folate could play a crucial role. Indeed, folate is not only a nutrient needed in pregnancy to help to prevent neural tube defects (NTD) and pregnancy outcomes but it is also a vitamin essential for reproductive health. **According to the NBJ report, in 2020, folate supplements (vitamin B) represented 26% of global supplements sales in this application.**

Infertile individuals globally



Aliakbari, F. et al. Reprod Biol Endocrinol. 2020; "World Health Organization https://www.who.int/health-topics/infertility; Tamura T., Picciano MF. Am J Clin Nutr. 2006; Nutrition Business Journal, 2020 Condition Specific Report.

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Fertility issues and Folate levels

WOMEN INFERTILITY

Female infertility comprises a wide range of causes affecting ovarian development, maturation of oocytes, and fertilization competence, as well as preimplantation development, implantation, and fetal growth.

MALE INFERTILITY

Male infertility is a disorder caused by numerous genetic and environmental factors that lead to defects in spermatogenesis.

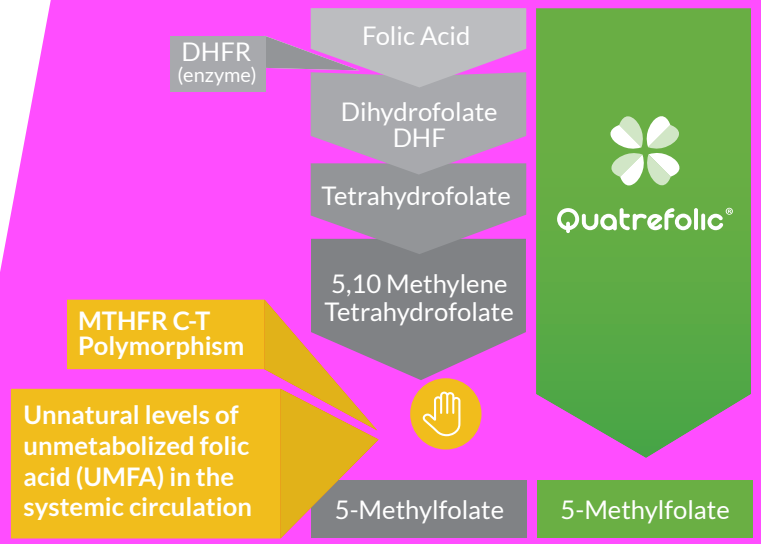
LOW Folate!

Level of folate and homocysteine status are critical factors in the early stages of human reproduction. Women and men experiencing fertility issues can present low folate availability, often linked to the presence of MTHFR enzyme polymorphism. Preconceptional folate supplementation has been linked to beneficial reproductive outcomes in both natural pregnancies and those after assisted reproductive technology (ART) treatment.

In women, folate is indispensable during the periods of rapid cell growth and proliferation, which occur during follicular and embryonic development. Insufficient folate status disrupts DNA methylation and integrity, increases blood homocysteine levels and oxidative stress one of the factors related to the pathogenesis of fertility disorders.

In men, studies support a positive correlation between serum folate concentrations, density, and normal morphology of sperm. Folate is essential in spermatogenesis and low levels in semen has been related to poor sperm DNA stability and damage. Studies have also pointed out that MTHFR gene can contribute to male infertility.

Quatrefolic® guarantees all the benefits of active folate for reproduction and fertility for both men and women.

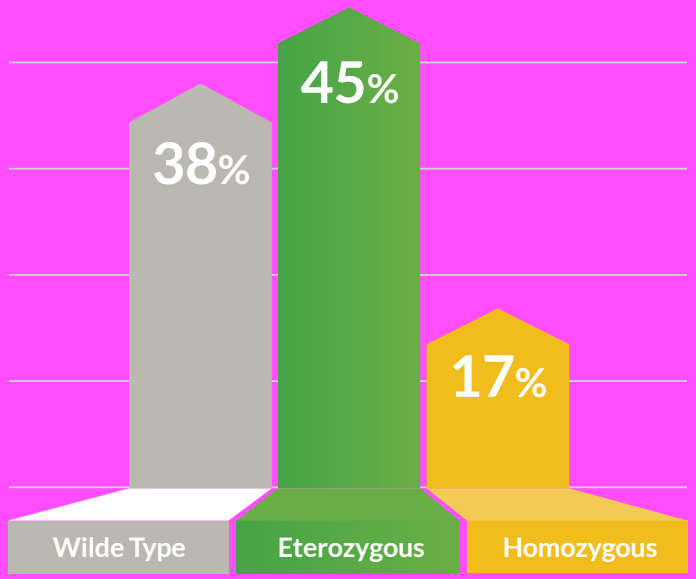


Quatrefolic® demonstrates to be effective in fertility both in women and men (with MTHFR polymorphism), because it is the active folate form immediately bioavailable without metabolization.

Yatsenko SA, Rajkovic A. Biol Reprod. 2019; Forges T. et al. Hum Reprod Update 2007; Bykowska-Derda A. et al. Appl Sci 2020; Rotondo JC, et al. Front Cell Dev Biol. 2021

A case series study (Servy et al. 2018) has evaluated the effect of Quatrefolic® in couples with recurrent miscarriages, lasting for at least 4 years; at least one of the partners was a carrier of one of the two main MTHFR isoforms.
The selected population showed a strong link between an impaired folate cycle, due to the presence of MTHFR, and consequently the capacity to achieve conception and carry a pregnancy to term.

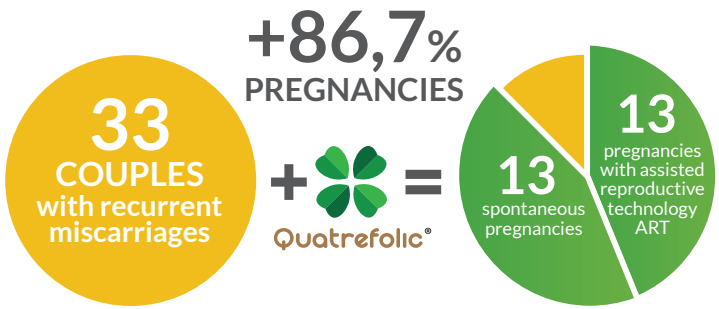
Women distribution of MTHFR polymorphism



The C677T polymorphism distribution of the women population in the clinical trial is very close to what is generally observed in Europe

Quatrefolic® has been supplemented in men and women (with B vitamin complex and zinc) at the dosage of 800 µg/day, according to the 5-MTHF glucosamine salt requirements in healthy women. Most of the women had been previously treated unsuccessfully with high doses of folic acid (5 mg/day).

The couples had long history of infertility with repeated fetal loss, premature ovarian failure or abnormal sperm parameters.
Of 33 couples, 13 spontaneous pregnancies were observed at the end of the treatment and other 13 pregnancies were obtained after assisted reproductive technology (ART), with the overall ongoing pregnancy rate of 86.7%.



The study highlights that the conventional use of large doses of folic acid (5 mg/day) has become obsolete.

A physiological dose of Quatrefolic® (800 µg) bypasses the MTHFR polymorphism and is suggested to be an effective treatment for couple fertility problems.

Laanpere M. et al. Nutrition reviews 2010; Scaglione F. et al. Xenobiotica 2014; Servy E.J. et al. J Assist Reprod Genet. 2018

Homocysteine and human fertility

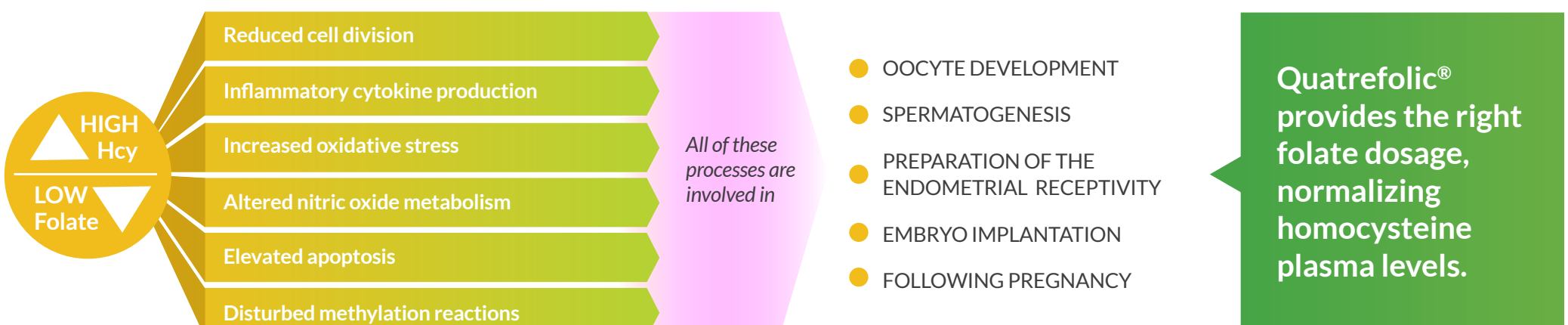
High levels of homocysteine and low folate can make more difficult to get pregnant for women and increase the risk of early miscarriage. Investigation of the role of homocysteine metabolism in patients with unexplained female sterility or secondary sterility due to recurrent pregnancy loss shows positive association. In men, folate deficiency results in homocysteine overproduction with subsequent excessive oxidative stress, chaotic methylation reactions, protein synthesis, and spermatogenesis deficiency.

Homocysteine is an inhibitor of the methylation process and a powerful pro-oxidant. It has a negative effect on spermatogenesis, and its concentration in the ejaculate is inversely correlated with fertility outcome.

Also, the polymorphisms of the MTHFR enzyme have been related to higher plasma homocysteine levels. Study has found that the polymorphisms would result in fetal non-viability rates of 4–7%, thus playing a significant role in human fertility.

The choice of right folate, such as Quatrefolic®, is recommended for right level of folate in healthy pregnancy.

Quatrefolic® provides the right folate dosage, it does not require metabolism of MTHFR enzyme, it is ready to enter human metabolism and, if necessary, normalizes homocysteine plasma levels.



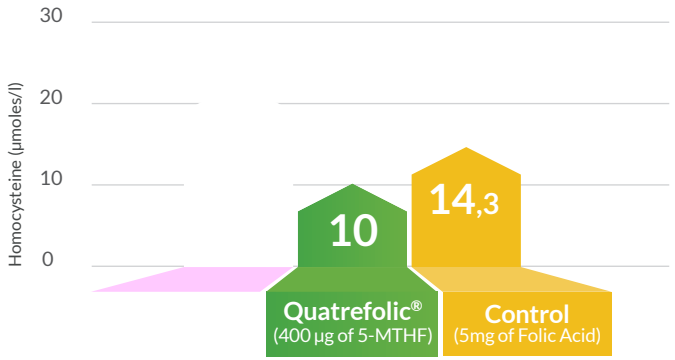
Jacquesson-Fournols L. et al. J Gynecol Women's Health 2017; Goyco Ortiz LE. et al. J Assist Reprod Genet 2019; Menezo, Y.J.R et al. Reprod Biomed Online 2016; Forges T. et al. Hum Reprod Update 2007; D'Elia P.Q. et al. Reprod Biomed Online. 2014; Altmäe S. et al. Fertil Steril. 2010; D'Uva M. et al. Thromb J. 2007; Reyes-Engel A. et al. Mol Hum Reprod. 2002

Quatrefolic® normalizes homocysteine

Published results (Mazza et al. 2016) demonstrate the capacity of Quatrefolic® (400 µg plus B6 and B12) to lower homocysteine serum level better than conventional vitamin supplementation with highly dosed folic acid (5 mg/day).

Quatrefolic® was tested on hypertensive subjects at low cardiovascular risk (104 patients with HCys ≥15 µmol/L). The result shows significant HCys reduction in comparison with baseline from 21.5 µmol/L to 10.0 µmol/L.

Moreover, 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 the control one.
Polymorphisms in folate pathway genes could be one reason for fertility complications in some women with unexplained infertility.

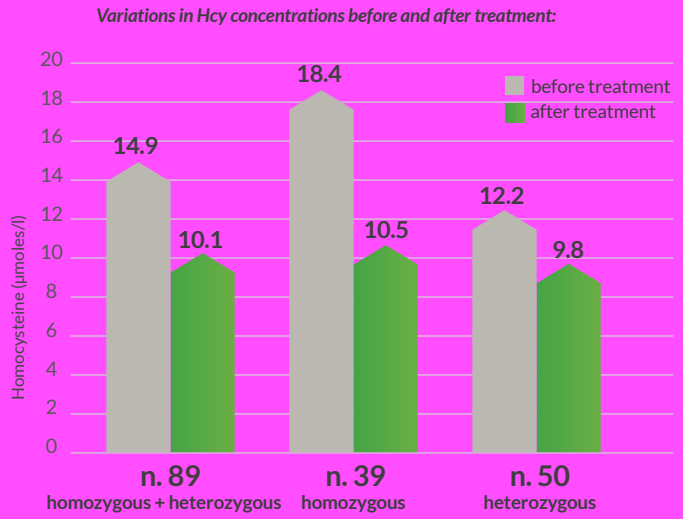


More recently, Clement et al. has recommended to analyze couples with a long history of infertility for MTHFR polymorphism and homocysteine, before starting Assisted Reproductive Technology (ART) attempts.

Volunteers with a history of repeated miscarriages (>3) or were facing infertility for >3 years and had at least 3 ART failures, were tested for MTHFR polymorphism (C677 T) and treated for at least 3 months with Quatrefolic® (600 µg per day complemented with B components and zinc).

In the 89 couples included, Quatrefolic® reduced rapidly the Hcy level of 42.7% in homozygous and 20.1% in heterozygous subjects, with no significant difference (p = 0.12) between the normalized homocysteine level of homozygous and heterozygous (10.5 µmol/L vs. 9.8 µmol/L).

Quatrefolic® bypasses folate metabolism disturbances and may improve male and female fertility.



Mazza A. et al. Biol Regul Homeost Agents 2016; Clément A. et al. J Gynecol Obstet Hum Reprod. 2020;

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