Impact of MTHFR isoform C667T on fertility through sperm DNA fragmentation index (DFI) and sperm nucleus decondensation (SDI)

Arthur Clement, Dominique Cornet, Marc Cohen, Laetitia Jacquesson, Edouard Amar, Paul Neveux, Patrice Clement, Yves Menezo.

Laboratoire CLEMENT, Paris
American Hospital of Paris
Clinique de la Muette, Paris
London Fertility Associates, London

In couples with sperm DNA damages, can subfertility and ART failures be explained by MTHFR isoforms ?

Background

The study of sperm DNA structure is essential in the evaluation of the causes of infertility. DFI is involved in ART failures (Spano, 2000; Saleh, 2003). SDI anomalies lead to developmental arrest at early stages and to recurrent ART failures (Junca, 2012). According to a recent meta-analysis, MTHFR polymorphism increases the male infertility risks (Gong, 2015).

MTHFR is a step in the 1-Carbon Cycle (1-CC): it allows the synthesis of major anti-oxidant molecules and correct DNA methylation process, part of epigenetics and imprinting (fig 1).

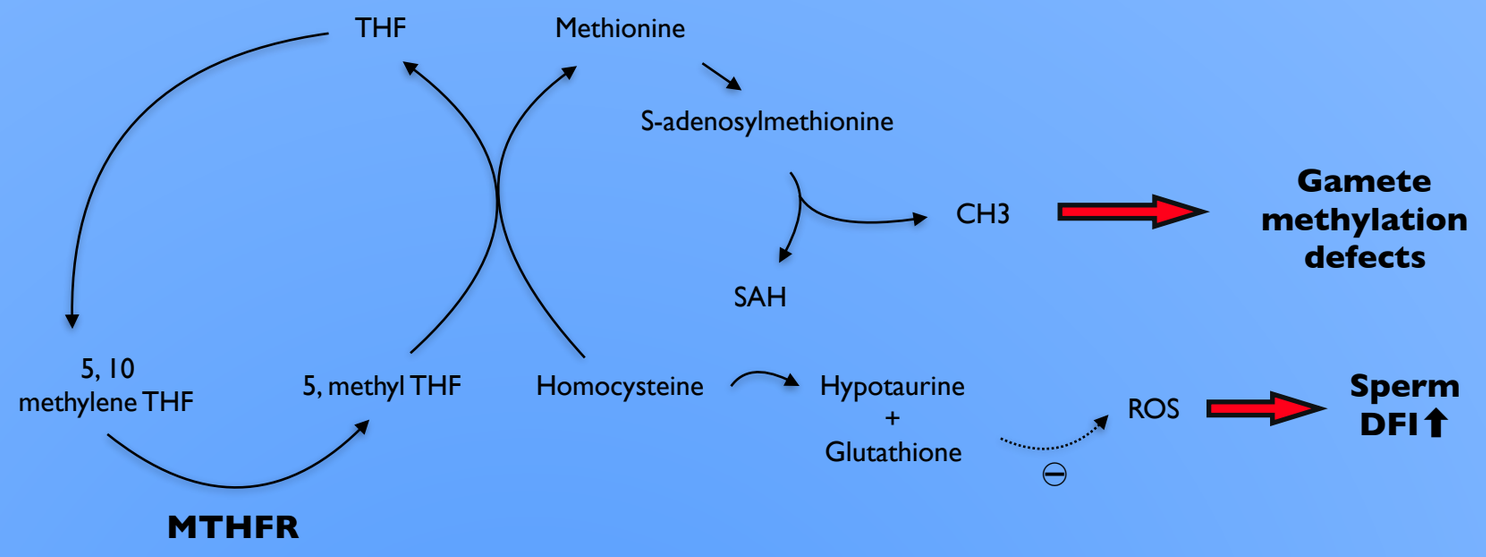

Fig 1 : MTHFR, oxydative stress and consequences on male gametes.

Study design

This is a retrospective study involving subfertile couples controlled for C677T isoforms in several french ART centers. Men who were either heterozygous or homozygous for MTHFR C677T were compared to a general population of subfertile male patients. Male partners were tested for DFI and SDI.

Methods

Determination of C677T isoform was performed with Real Time Polymerase Chain Reaction.

DFI and SDI are measured using protocols similar to SCSA® (Sperm Chromatin Structure Assay) and HDS (High DNA Stainibility) respectively.

Results

77 and 18 patients were respectively heterozygous and homozygous carriers for the MTHFR C677T isoform. These patients faced 3 to 9 consecutive IVF/ICSI failures and/or miscarriages. Their DFI and SDI were compared to our control group involving more than 1400 patients.

DNA damages measured as SDI are increased in both populations: homozygous ($p=0.0006$) and heterozygous ($p= 0.029$) patients when compared with the control population (fig 2). Homozygous and heterozygous carriers of MTHFR C677T showed no increase in DFI (fig 3).

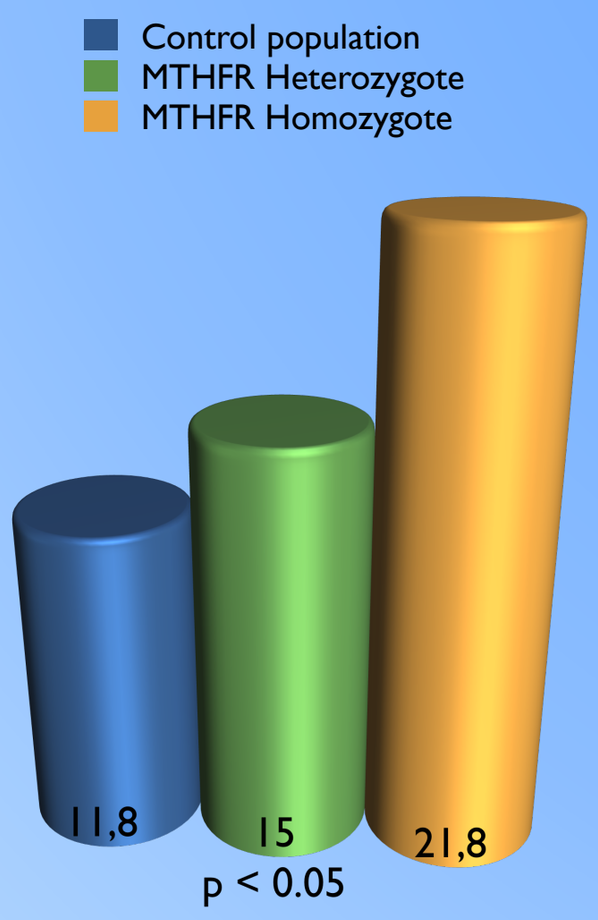

Fig 2: SDI according to MTHFR isoforms.

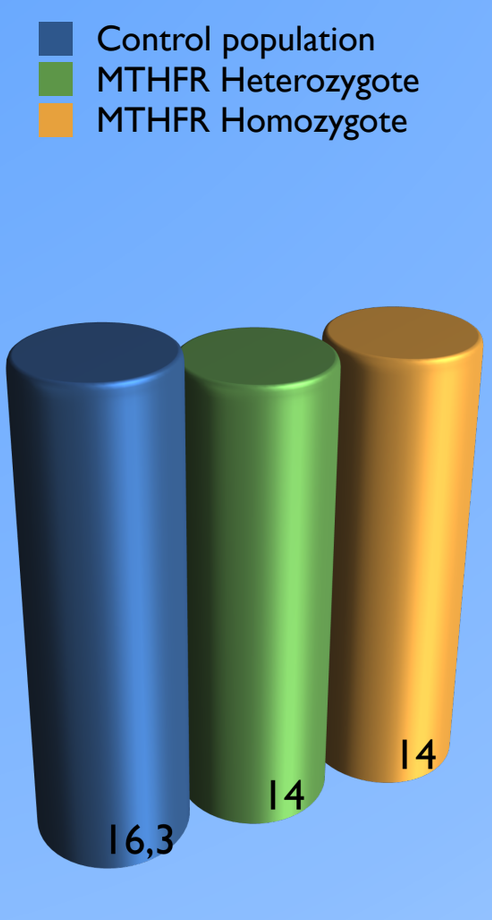

Fig 3: DFI according to MTHFR isoforms.

Conclusions

In order to prevent ART failures and improve ART outcomes, patients with high DFI or SDI could be tested for MTHFR isoforms and be treated with compound of the 1-CC that downstream the MTHFR, such as 5 Methyl tetrahydrofolic acid.