# Endometriosis pathogenesis : role played by MTHFR mutations

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*Can endometriosis in infertile patients be linked to the oxidative stress due to MTHFR mutations?*

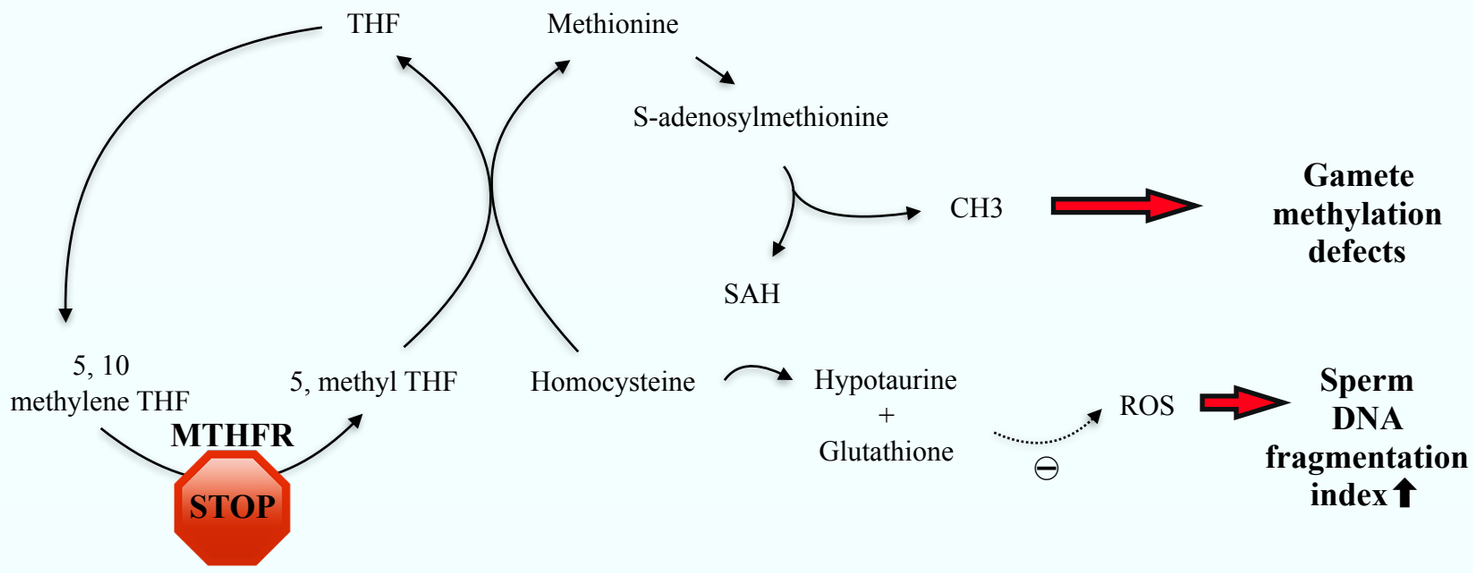
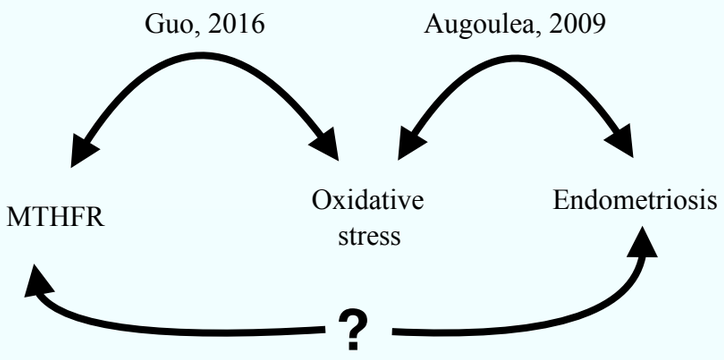



Fig 1 : MTHFR, oxidative stress and consequences on gametes.

## Background




- Oxidative stress is implicated in the physiology of endometriosis by causing a general inflammatory response in the peritoneal cavity (Augoulea, 2009).
- MTHFR is involved in the genesis of major antioxidant molecules(gluthatione, hypotaurine) (fig1). Oxidative stress can be induced by polymorphisms of MTHFR through the increased homocysteine level (Guo, 2016).
- To our knowledge, no study in the literature analyzed the role played by MTHFR in the endometriosis genesis of infertile patients.

## What is known already : impact of MTHFR mutations

- **Sperm DNA defects** : increased in homozygous (p=0.0006) and in the heterozygous patients (p=0.029), compared with the control (wild type) population (Cornet et al., 2017).
- **Successful implantation** : fourfold higher for wild type than for c. 677T homozygotes (55 vs 12.5%) p<0.05 (Enciso et al, 2016).
- **Embryo that failed to implant** : higher incidence of c.677T homozygotes (p<0.05) (Enciso et al, 2016).
- **Infertile population** : higher incidence of c.1298C homozygotes (p<0.05) : women +++ (Enciso et al, 2016).

## Methods

- Patients diagnosed with endometriosis according to the ESHRE 2013 guidelines with recurrent ART failures (2 to 7).
- MTHFR c.677T was determined from a venous blood sample, using real time PCR with the RealFast™ assay (ViennaLab Diagnostic GMBH, Vienna, Austria).
- Patients carrying MTHFR mutations were treated with 5MTHF (5 Methylene Tetrahydrofolate), a treatment by-passing the problems linked to MTHFR impaired activity.

## Study design

- January 2016 to 2018 : 30 infertile patients suffering from endometriosis and having had at least 1 ART (Assisted Reproductive Technologies) cycle failure.
- At first, we compared the MTHFR mutations distribution in our population.
- Patients carrying a MTHFR mutation were afterwards treated and we compared the pregnancy rates obtained before and after treatment.

## Results

- 60% of our patients were carrying the MTHFR mutation (46.7% in a heterozygous state, 13.3% in a homozygous state).
- This proportion is significantly more important (p<0.05) than the proportion of patients carrying MTHFR mutations in the general population : 50.5% (Zappacosta, 2009) (fig2).
- After we treated infertile couples with endometriosis and recurrent ART failures (2-7) carrying MTHFR mutations, we significantly improved their ART outcomes (average ongoing pregnancy rate per cycle : 23.4% before vs 29.6% after treatment, p<0.05).

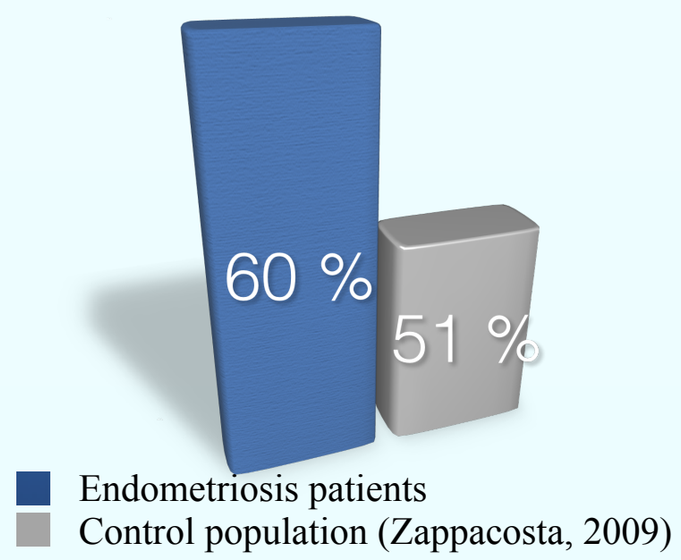



Fig 2 : Proportion of patients carrying MTHFR mutations.

## Conclusions

- Endometriosis can be explained by MTHFR mutations. The resulting oxidative stress impairs the fertility of the female patients.
- Therefore, by improving the methylation and decreasing the oxidative stress, treating MTHFR mutation carriers improves the quality of the gametes and their ART outcomes.

**It is essential to screen infertile couples for MTHFR mutations (both c.677T and c.1298C).**