Endometriosis pathogenesis: role played by MTHFR mutations


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

**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 (glutatione, 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).

**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).