Analysis of *FOXP3* polymorphisms in infertile women with and without endometriosis

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Objective: To evaluate *FOXP3* polymorphisms (rs3761549, rs3761548, rs2232368, rs2232366, and rs2280883) in a group of infertile women with and without endometriosis and controls.
Design: Case control study.
Setting: Human Reproduction Outpatient Clinic of Faculdade de Medicina do ABC.
Patient(s): The study groups were 177 infertile women with endometriosis, 71 women with idiopathic infertility, and 171 fertile women as controls.
Intervention(s): The *FOXP3* polymorphisms were identified by *TaqMan* polymerase chain reaction (PCR). The results were analyzed statistically.
Main Outcome Measure(s): Genotype distribution, allele frequency, and haplotype analysis of the *FOXP3* polymorphisms.
Result(s): : Single-marker analysis revealed that *FOXP3* rs3761549 was significantly associated with endometriosis. In the infertile group without endometriosis, single-marker analysis revealed statistical difference for rs2280883 and rs2232368 *FOXP3* polymorphisms. No associations were found with rs3761548 and rs2232366 either for endometriosis-related infertility group or idiopathic infertility group. Haplotype analysis of five *FOXP3* polymorphisms identified a haplotype CTTGA associated with endometriosis and ACTAG associated with idiopathic infertility.
Conclusion(s): : This is the first study to report an association between *FOXP3* polymorphisms and endometriosis and/or infertility. These findings require replication in other populations but suggest that the *FOXP3* polymorphisms can be associated with risk of idiopathic infertility (rs2280883 and rs2232368) and endometriosis (rs3761549) in Brazilian women. (Fertil Steril® 2011;■:■–■. ©2011 by American Society for Reproductive Medicine.)

Key Words: Autoimmunity, endometriosis, infertility, *FOXP3* gene, polymorphism

Endometriosis is a common gynecological disease, defined as the growth of endometrial tissue outside the uterine cavity that often results in dyspaurenia, dysmenorrhea, pelvic pain, and infertility (1). Several studies have revealed many genetic markers related to the immune, neuroendocrine, and reproductive function among patients with endometriosis indicating associations between the development of endometriosis and genetic polymorphisms (2, 3).

Immunologic theories suggest that changes in the immune system could prevent the ability to eliminate the endometrium of the pelvic cavity (4). In women with endometriosis is possible that changes in immunity mediated by T cells facilitate the implantation of endometrial fragments or cells in ectopic locations (5). The immune cells that are likely to play roles in this destruction, including macrophages, natural killer (NK), and cytotoxic T cells, must be tightly regulated to ensure that the immune response is specific to sloughed endometrial fragments and not the intact uterine tissue. The cells that are almost certainly the key regulators of this response are a distinct population of T cells known as regulatory T cells called Tregs (6).

Besides the polymorphisms in genes as *PTPN22* (3), *VDR* (7), *CTLA4* (8), and *FCRL3* (unpublished data), already studied by this research group, recent studies have also associated the *FOXP3* gene (gene ID: 50943, Xp11.23) with homeostasis of the immune system and the development of autoimmune diseases (9, 10). The *FOXP3* gene is primarily expressed in $CD4^+$ $CD25^+$ Tregs in normal physiological conditions. It encodes FOXP3 protein, which regulates the activation of T cell, and functions as a transcriptional repressor and down-regulates cytokine production in T cells (11, 12). Polymorphisms of the *FOXP3* gene may change FOXP3 functionally or quantitatively, therefore leading to the lack of functional $CD4^+$ $CD25^+$ Tregs, resulting in autoimmune diseases (13).

In the present study we hypothesized that *FOXP3* polymorphisms might be involved in the pathogenesis of endometriosis and/or infertility. We examined five single nucleotide polymorphisms (SNPs) in the *FOXP3* gene (rs3761549, rs3761548, rs2232368, rs2232366, and rs2280883) with endometriosis-related infertility patients and idiopathic infertile patients and assessed the association of genotype and allele frequencies between them.

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