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Analysis of vitamin D receptor gene polymorphisms in women with and without endometriosis

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ABSTRACT

An aberrant immunologic mechanism has been suggested to be involved in the pathogenesis of endometriosis. Genetic alterations in the vitamin D receptor gene (*VDR*) may lead to important defects in gene activation that principally affect immune function. We have hypothesized a possible relationship between endometriosis and/or infertility and the *VDR* polymorphisms (*ApaI, TaqI, FokI,* and *BmsI*). The study was a case–control study including 132 women with endometriosis-related infertility, 62 women with idiopathic infertility, and 133 controls. *VDR* polymorphisms were studied by restriction fragment length polymorphism. We found relatively similar *VDR* polymorphism genotype frequencies in cases and controls. When patients with minimal/mild and moderate/severe endometriosis were studied separately, no difference was found. When we compared infertile groups with and without endometriosis there was no statistically significant difference. The data suggest that *VDR* polymorphisms did not play an important role in the pathogenesis of endometriosis and/or infertility in the Brazilian women studied.

1. Introduction

Endometriosis is a common estrogen-dependent gynecologic disease, defined as the growth of endometrial tissue outside the uterine cavity, that often results in a vast array of gynecologic problems, including dyspareunia, dysmenorrhea, pelvic pain, and infertility [1]. Susceptibility to endometriosis depends on a complex interaction of immunologic, genetic, and hormonal factors [2,3].

Numerous hypotheses have been put forward to explain the presence of ectopic endometrial tissue and stroma. Levander [4] attempted to link 2 previous theories: metaplasia proposed by Meyer [5] and retrograde tubal endometrial reflux proposed by Sampson [6]. The presence of this abnormal menstrual reflux would irritate the peritoneum. In defending itself, the peritoneum would secrete activating and growth factors, which facilitate implantation and growth and could thus induce metaplasia [4]. This unifying theory is supported by modern immunologic concepts. The immune system participates in the homeostasis of the peritoneal cavity. Modifications in the peritoneal cavity functioning have been advanced to explain endometriosis and its consequences [7,8].

Some authors have suggested that endometriosis may have an autoimmune component because it is often associated with the presence of antinuclear, antiphospholipid, and antiendometrial autoantibodies as well as an abrogated cell-mediated immunity reaction manifested, for example, by decreased activity of natural killer cells and cytotoxic T lymphocytes [7–9]. Genetic factors play a role in the pathogenesis of endometriosis [3,10] and autoimmunity genes are therefore reasonable candidate genes for endometriosis [11].

Vitamin D is a hormone that has essential roles in endocrine functions, regulating cell replication, and other metabolic pathways, such as those involved in immune response. Vitamin D suppresses lymphocyte proliferation and immunoglobulin synthesis and inhibits the action of proinflammatory transcription factors and the production of different cytokines, such as interleukin 2 and interleukin 12, among others [12]. Most of the biologic activities of vitamin D are mediated by a high-affinity receptor that acts as a transcription factor activated by the ligand receptor gene of vitamin D [*VDR*; OMIM 601769). *VDR*, located on chromosome 12 (12q13.11), is a member of the family of steroid receptors that mediates the effects of vitamin D in regulating the transcription of multiple genes [13] The *VDR* gene is expressed in most cells of the immune system, including $CD4^+$ and $CD8^+$, as well as antigen-presenting cells, macrophages, and dendritic cells; these cells also possess the first hydroxylase, which catalyzes the synthesis of active vitamin D [14].

Genetic alterations in the *VDR* gene may lead to important defects in gene activation principally affecting calcium metabolism, cell proliferation, and immune function. The function of the *VDR* gene is influenced by several genetic polymorphisms associated with susceptibility to a range of diseases, such as osteoar-

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