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LETTER TO THE EDITOR

Unbalanced Pro-Inflammatory and Anti-Inflammatory Cytokines Ratio and Endometriosis: A Contributive Pathogenic Role?

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To The Editor

We recently read the original research entitled "Serum and Peritoneal Fluid Cytokine Profiles in Infertile Women with Endometriosis" by Tarokh *et al.* published in your journal. In this paper, the authors evaluated the concentration of interferon (IFN)-γ and other cytokines within serum and peritoneal fluid (PF) of infertile patients affected by endometriosis (1). Notably, they found a significantly reduced serum IFN-γ ($p=0.001$) and increased transforming growth factor (TGF)-β1 ($p=0.030$), in PF of 30 patients, compared with the 30 healthy women. Moreover, the ratio between pro-inflammatory and anti-inflammatory cytokines (specifically, interleukin (IL)-17 and IL-23 in serum samples, tumor necrosis factor (TNF)-α and IL-10, IL-17 and IL-10 ratios in PF samples) increased the values in patients with endometriosis. The rationale of this study is the aberrant activity of inflammatory pathways (among which, NF-kB) in the development and establishment of this benign chronic disease. It is a known fact that there is a strong relationship between estrogen production (which occurs within endometriotic nodules due to aberrant aromatase expression and activity (2)) and pro-inflammatory cytokines production (3). Moreover, current first-line approaches to treating symptoms (in primis dysmenorrhea) further consist of the administration of anti-inflammatory non-steroidal drugs (NSAIDs), aiming to reduce the prostaglandin production by inhibiting cyclooxygenase enzymes (4). Overall, a methodological concern of this study was that the authors did not precisely report, in the "materials and methods" section, which phenotype of endometriosis the patients had; in fact, it is likely that ovarian endometriosis, deep endometriosis and superficial (peritoneal) endometriosis have different pathogenesis, along with distinguished histological and molecular characteristics (5,6). For this reason, Tarokh *et al.* should report whether or not only patients with a specific phenotype of endometriosis or a combination of them were considered eligible.

With regards to this topic, a more elevated amount of pro-inflammatory reactions, as well as a higher vascularization and neurogenesis have been reported for deep implants of endometriosis, tending to have a more aggressive biological behavior in comparison with other endometriotic phenotypes (7-9).

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However, the authors should be congratulated on their consistent findings (1). Overall, inflammation and, in particular, immune cell regulators may have a critical role in the genesis and establishment of endometriosis (10); accordingly, a great variety of new drugs targeting inflammatory-related pathways are being investigated to treat this hormone-dependent disease, although none has reached late clinical trials, except for studies *in vitro* and on animals (with the exception of infliximab, an anti TNF-α monoclonal antibody, which obtained disappointing results in a phase II exploratory proof of concept trial) (11). In the coming years, the growing knowledge on the pathogenesis of endometriosis will give more detailed conclusion on this topic.

Keywords: Cytokines, Endometriosis, Inflammation

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Authors' Response

Majid Tarokh, Tahereh Poordast, Behrouz Gharesi-Fard

The Authors' Reply: We wish to appreciate you for your professional letter. As it is stated in the "materials and methods" section, we obtained peritoneal fluid from endometriosis patients in stage III and IV (Late endometriosis) of the disease (1). According to the revised American Society for Reproductive Medicine (rASRM) for classification of endometriosis, the disease is classified into one of four stages (I-minimal, II-mild, III-moderate, and IV-severe) depending on location, extent, and depth of endometriosis implants; presence and severity of adhesions; and presence and size of ovarian endometrioma (2). When the score is 15-40, the stage is 3, and when the score is more than 40, the stage is IV (3). Almost always, moderate and severe endometriosis is characterized by chocolate cysts and more severe adhesions and deep infiltrative endometriosis (DIE) (3). While in the late endometriosis endometrioma, OMA and DIE may exist at the same time, the superficial peritoneal implants also exist in certain affected locations. Our cases were in stage 3 or 4, and all had a combination of superficial, OMA and DIE. However, it is to be noted that there exist controversies as to the scoring system of endometriosis (3,4,5).

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