Interleukin-19 and interleukin-22 serum levels are decreased in patients with ovarian endometrioma

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Objective: To determine the serum levels of interleukin (IL)-10 family ILs in women with ovarian endometriosis and investigate the correlation of these levels with disease activity.
Design: A case-control laboratory study.
Setting: Tertiary-care university hospital.
Patient(s): Two hundred nineteen women, with (n = 112) and without (n = 107) endometriosis.
Intervention(s): Complete surgical excision with pathological analysis.
Main Outcome Measure(s): Blood samples were obtained during surgical procedures. IL-10, -19, -20, and -22 were assayed by ELISA in sera, and the concentrations correlated with the extent and the severity of the disease.
Result(s): IL-19 was detectable in 18.3% and IL-22 in 47.9% of sera samples from all 219 women studied. Serum IL-19 was lower in women with endometriosis (median, 292.7 pg/mL; range, 32.2–1,339.3) than in endometriosis-free women (median, 1,035.8 pg/mL; range, 32.2–2,000.0). In addition, serum IL-22 levels were decreased in women affected by endometriosis (median, 352.0 pg/mL; range, 31.2–1,392.2) as compared with endometriosis-free women (median, 709.2 pg/mL; range, 73.3–2,012.0). We found significant correlations between serum IL-22 concentrations and intensity of deep dyspareunia ($r = -0.303$) and noncyclic chronic pelvic pain ($r = -0.212$). IL-19 was correlated with the intensity of deep dyspareunia ($r = -0.749$).
Conclusion(s): Serum IL-19 and IL-22 are decreased in women with ovarian endometrioma. IL-10 family ILs may be involved in the pathogenesis of endometriosis. (Fertil Steril® 2013;99: 219–26. ©2013 by American Society for Reproductive Medicine.)
Key Words: IL-19, IL-22, endometrioma, cytokines, inflammation, pathogenesis

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Endometriosis is a chronic gynecologic disease characterized by the presence of endometrial tissue outside of the uterus (1). This enigmatic disease represents a public health issue affecting 10%–15% of women of reproductive age and causing pain and infertility (2). The implantation and proliferation of endometrial tissue commonly affects peritoneum, ovary, and pelvic organs and occasionally bowel, ureter, bladder, or lungs (3).

It is now accepted that there are three different types of endometriosis: peritoneal superficial endometriosis, ovarian endometrioma (OMA), and deeply infiltrating endometriosis (DIE). Some investigators consider these types of endometriosis to have different pathogeneses (4). However, disease establishment and progression is believed to occur through a complex series of events involving the attachment of endometrial tissue to the peritoneal surface (5), invasion and progressive estrogen-dependent proliferation (6), vasculogenesis, angiogenesis (7), and chronic inflammation (8, 9). The immune system is considered to play a crucial role in these different steps by the generation of a suboptimal immune response that may not adequately clear the ectopic implant,

Received April 26, 2012; revised August 25, 2012; accepted August 27, 2012; published online September 29, 2012.
P.S. has nothing to disclose. B.B. has nothing to disclose. S.C. has nothing to disclose. I.S. has nothing to disclose. D.B. has nothing to disclose. D.d.Z. has nothing to disclose. B.W. has nothing to disclose. C.C. has nothing to disclose. F.B. has nothing to disclose.
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Fertility and Sterility® Vol. 99, No. 1, January 2013 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2012.08.055

leading to progression of the disease and to inflammation (10). In particular, a large bulk of evidence indicates that the development of endometriosis is under the control of inflammatory mediators and immunocompetent cells, in particular through the production of interleukins (IL) (11).

IL-10 family ILs (IL-10, IL-19, IL-20, IL-22) exert anti-inflammatory activity in many autoimmune and inflammatory diseases and malignancies, especially in psoriasis, inflammatory bowel diseases, systemic lupus erythematosus, liver inflammation, and melanoma (12). Despite their structural homology and the use of similar or partially identical receptor complexes, members of the IL-10 family possess distinct physiological roles (12).

IL-10 suppresses the release of proinflammatory cytokines and limits tissue disruption caused by inflammation (12). IL-19, IL-20, and IL-22 regulate the functions of immune cells, essentially in the skin, lungs, and reproductive organs as well as various glands (13). These cytokines are expressed in epithelial layers and protect epithelial cells from invasion by extracellular pathogens (12). Moreover, IL-19, IL-20, and IL-22 cytokines enhance tissue remodeling and healing (12). In addition, previous studies have shown deregulated IL-19, IL-20, and IL-22 expression in human inflamed tissues, supporting the role of these cytokines in inflammatory diseases (13, 14).

Many authors have tried to identify abnormal levels of a wide range of cytokines in endometriosis, partly to provide insights into the pathogenesis of disease and partly to assess their use as putative biomarkers (11). Among IL-10 family ILs, only IL-10 has been studied in endometriosis. No difference in serum IL-10 levels has been found between women with and women without endometriosis (15, 16). In peripheral blood one study showed increased IL-10 mRNA and protein (17), whereas unchanged IL-10 levels were observed in another report (18).

IL-10 family ILs were selected because they could play a role in the pathogenesis of endometriosis by their anti-inflammatory and tissue repair properties (12).

In the present study, we assayed IL-10, IL-19, IL-20, and IL-22 in sera banking on a large series of women with OMA and controls. The goal of this study was to investigate the relationship between endometrioma and the serum level of IL-10 family ILs.

MATERIALS AND METHODS

Patients

The study protocol was approved by the ethics committee of our institution. From January 2005 to December 2010, a continuous series of 219 patients has been recruited into this study after providing informed written consent, as described elsewhere (19). Briefly, all the patients of this study had a benign ovarian cyst and were <41 years old. Women were allocated to two groups according to the surgical findings (20): the endometriosis group consisted of subjects with histologically proven endometrioma (OMA) (n = 112), and the control group consisted of women with histologically proven nonendometriotic benign ovarian cysts, without any macroscopic endometriotic lesion as checked during a thorough examination of the abdominopelvic cavity (n = 107). During surgery, endometriosis was staged and scored (total, implant, and adhesion scores) according to the revised American Fertility Society (rAFS) classification (21), and the presence of partial or complete posterior cul-de-sac obliteration was documented. In addition, to circumvent the wide anatomical heterogeneity of the disease, we performed a specific surgical workup to correctly phenotype the patients studied (22), focusing on women with isolated OMA. According to the previously described classification, women with isolated OMA corresponded to women with OMA and sometimes associated peritoneal endometriosis with adhesions, exclusive of deeply infiltrative endometriosis (23, 24). In addition women with infectious diseases such as hepatitis C virus, hepatitis B virus, or human immunodeficiency virus and women with malignancies or with autoimmune or inflammatory diseases were not included in this study. None of the included women were pregnant.

The study analysis used a prospectively managed database (23). For each patient, personal history data were obtained during face-to-face interviews conducted by the surgeon during the month before surgery. We used a highly structured previously published questionnaire (19). The following data were recorded: age, parity, gravidity, height, weight, body mass index (BMI), history of hormone and/or surgical treatment for endometriosis, existence of gynecologic pain symptoms (dysmenorrhea, deep dyspareunia, non-cyclic chronic pelvic pain [NCCPP]), gastrointestinal (GI) (25), and lower urinary (LU) tract (26) symptoms.

According to a previous publication, NCCPP is defined as intermittent or permanent pelvic pain not related to the menstrual cycle (26).

Pain intensity was evaluated preoperatively using a 10-cm visual analog scale (VAS) (27). Biological features of inflammation such as C-reactive protein (mg/L), white blood cell count (U/mL), and erythrocyte sedimentation rate (ESR; mm/hour) were also collected for each patient. Serum tumor markers were recorded for each patient: CA125 (UI/mL) and CA19-9 (UI/mL).

Collection of Serum

Samples were collected in the operating room from all study participants. Briefly, after the insertion of the peripheral venous catheter (PVC), 5–10 mL of venous blood samples were collected, using the PVC to draw blood.

The blood samples were centrifuged at 2,000 rpm for 12 minutes at 4°C, and serum supernatants were collected. Aliquots of those samples were stored at 70°C until needed for analysis (22).

Measurement of Cytokine Concentration

In all patients, IL-10, IL-19, IL-20, and IL-22 were assayed in sera by ELISA (R&D Systems, Inc.), according to the manufacturer's recommendations. The range of determination was 31.2–2,000 pg/mL (22). IL serum levels below 31.2 pg/mL were undetectable and were considered as 0 pg/mL for statistical analysis. Each sample was tested in duplicate and reflected the mean of the two measurements. The intra-assay