EDITORIAL

Familial Endometriosis

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Despite extensive basic and clinical research efforts, there are many unanswered questions regarding pathogenesis and pathophysiology of endometriosis. Previous studies have identified numerous factors associated with an increased risk of developing endometriosis, including a family history of endometriosis.[1] There are few studies, however, that have assessed endometriosis in families from different geographic locations and attempted to identify specific biologic markers that might be involved in the pathogenesis of the disease.

The article by Matalliotakis and colleagues in the February issue of the *Journal of the Society for Gynecologic Investigation* identifies a Greek family with endometriosis with low levels of serum-soluble class-I and class-II human leukocyte antigen (HLA) levels compared with healthy subjects. Serum vascular endothelial growth factor (VEGF) levels were significantly higher than in controls, and three of the seven family members expressed epidermal growth factor receptor. Whereas others have failed to observe an association between surface HLA type and endometriosis,[2,3] the current study suggests an association with soluble HLA and familial endometriosis.

The potential role of soluble HLA molecules has been studied in a variety of disease states.[4] The concentration of soluble HLA molecules in individuals is partially dependent on genotype and varies with immunologic activity. It is usually higher in infections and inflammatory disease states and decreases in cancer patients as the disease progresses.[4] Soluble class-I HLA concentrations are elevated in patients with rheumatoid arthritis and systemic lupus erythematosis, in which they increase with disease activity.[4,5] Less is known about soluble class-II concentrations in inflammatory disease states. It is interesting that while endometriosis is considered an inflammatory disease state,[6] soluble HLA levels in this Greek family were actually lower than in controls, and levels appeared to be lowest in advanced stages of disease. This observation is similar to that observed in cancer patients with advanced disease. Further research on the relationship among HLA levels, disease stage, and treatment-related changes may provide insight into the potential immunoregulatory role of soluble HLA in patients with endometriosis.

The observation of increased VEGF levels in the reported case of familial endometriosis is consistent with other studies. Women with endometriosis have increased peritoneal fluid concentrations of VEGF,[7] and the expression of VEGF is higher in cycle phase–matched ectopic endometrium from women with endometriosis than in controls.[8] In addition to VEGF production by endometriotic implants, activated peritoneal macrophages also secrete VEGF. Factors known to upregulate VEGF are relevant to the peritoneal fluid environment, including prostaglandins and the inflammatory cytokines interleukin-1β and transforming growth factor-β.[9,10] Important work is under way in this area to potentially identify safe and clinically effective agents that disrupt VEGF activity. This case of familial endometriosis with increased serum VEGF levels emphasizes the importance of developing new anti-angiogenic therapies for endometriosis.

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1071-5576/03/$30.00
doi:10.1016/S1071-5576(03)00026-1