Article

Effect of ovarian involvement on peritoneal fluid cytokine concentrations in endometriosis patients

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Abstract

Peritoneal fluid cytokines are important for initiation and progression of endometriosis. The objective of this study was to compare a group of five cytokines (interleukins IL-1β, IL-6, IL-8, IL-13 and tumour necrosis factor α; TNFα) in peritoneal fluid of endometriosis patients with ovarian involvement (Group I, $n = 17$) to those in patients without ovarian involvement (Group II, $n = 33$) and to a reference group without endometriosis (Group III, $n = 25$). All three groups were comparable regarding age, parity and body mass index. IL-8 concentrations were significantly higher in groups I and II compared with the reference group ($P = 0.01$ and 0.02, respectively). Similarly, TNFα concentrations were significantly higher in groups I and II compared with the reference group ($P < 0.0001$ and 0.0004, respectively). All other cytokines were comparable in the three groups. No significant differences were found between groups I and II with respect to the cytokines measured. In conclusion, peritoneal fluid IL-8 and TNFα concentrations are significantly higher in endometriosis. Ovarian involvement does not alter the pattern of cytokines. It appears that the inflammatory mediators of endometriosis are similar with and without ovarian involvement.

Keywords: *cytokines, endometrioma, pathogenesis, peritoneal fluid*

Introduction

Endometriosis is one of the most common benign gynaecological disorders and is present in >10% of women of reproductive age in the USA. In spite of extensive basic and clinical research to unveil the aetiology of this disease, little is known. The current consensus is that endometriosis is associated with a local pelvic inflammatory process with altered function of the local and systemic immune responses (Bedaiwy and Falcone, 2004). Increased production of pro-inflammatory cytokines, such as the interleukins IL-1, IL-8, tumour necrosis factor α (TNFα) (Arici *et al.*, 1997) and vascular endothelial growth factor have been consistently demonstrated in the peritoneal fluid (PF) of endometriosis patients (Bedaiwy *et al.*, 2002; Bedaiwy and Falcone, 2004). In addition, previous studies have shown that cytokines in PF and the endometrium affect fertilization, implantation and future pregnancy outcome (Bulletti *et al.*, 2005; Esfandiari *et al.*, 2005; Norwitz, 2006).

Since retrograde menstruation is observed in almost all cycling women, endometriosis is postulated to develop as a result of the coexistence of a defect in clearance of endometrial cells in the menstrual efflux from pelvic peritoneal surfaces. One popular hypothesis is that women who are liable to get endometriosis have a defective or abnormal immune system that prevents timely clearance of deposited endometrial cells (Lamb and Nichols,

1986; Lebovic *et al.*, 2001). However, several investigators have demonstrated that the immunological perturbations in nonhuman primates with induced pelvic endometriosis are secondary to the presence of the ectopic endometrium, rather than being a possible aetiopathogenic factor. It is likely that molecular changes such as immunological alterations are secondary to the presence of ectopic endometrium (Gashaw *et al.*, 2006).

While ovarian endometriosis is a common site of pelvic endometriosis, the ovary, under physiological conditions, is a site for inflammatory reactions mediated by numerous cytokines, particularly around the time of ovulation, and so the ovary is the single most important source for PF (Maathuis *et al.*, 1978; Syrop and Halme, 1987). It is unclear if the presence of ovarian endometriosis contributes in a unique way to the inflammatory environment of the peritoneum.

The specific aims of this study were: (i) to compare a group of cytokines in the PF of endometriosis patients with ovarian involvement to those in endometriosis patients without ovarian involvement; and (ii) to compare the concentrations of different cytokines in both cohorts to a reference group without endometriosis.

Materials and methods

The Institutional Review Board of the Cleveland Clinic Foundation approved this study. The study included a cohort of 75 consecutive women who underwent laparoscopy from January 1998 to December 2003 at the Minimally Invasive Surgery unit in the Cleveland Clinic Foundation. The indications for laparoscopy included chronic pelvic pain, infertility, tubal ligation, or sterilization reversal. All patients included in this study had no significant co-morbidities except for the primary indication of surgery. After obtaining their informed consent, intraoperative peritoneal samples were collected. From 121 women who underwent laparoscopy in the period of study, 46 were excluded because of blood-contaminated PF and no patients were excluded for frozen pelvis (**Figure 1**). All patients included in the study had general anaesthesia using the same approach. In the patients with endometriosis, the involvement of the ovary was reported and the severity of the disease was graded according to the revised four-stage American Fertility Society scoring system (American Society for Reproductive Medicine, 1997). After surgery and pathological examination, the included cohort was subdivided into three subgroups which

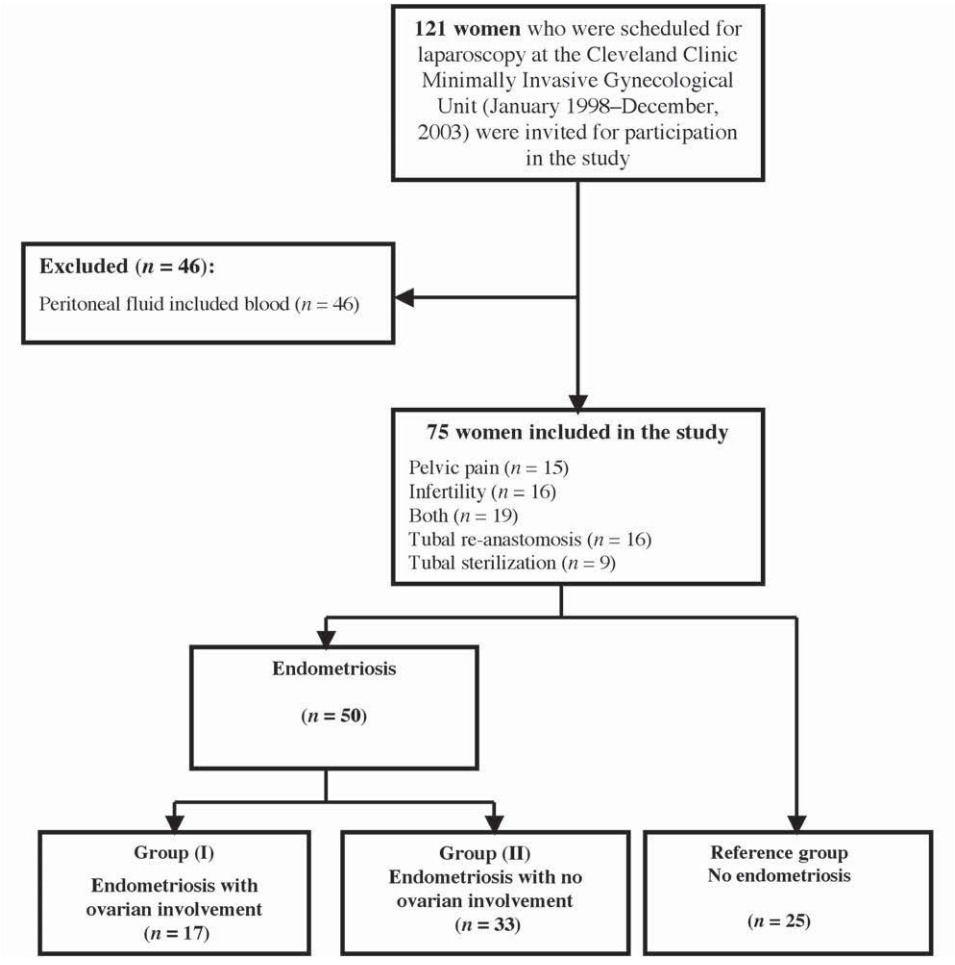

Figure 1. Flow chart showing the composition of the three study groups.