# C-reactive protein of serum and peritoneal fluid in endometriosis

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#### ABSTRACT

**Background:** Endometriosis is defined as the existence of endometrial-like tissue outside the uterus. Diagnosis of endometriosis is a challenging theme. Despite the broad search for innovative laboratory tests and advances in imaging technologies, there are still no easy, non-invasive diagnostic tests available. Due to inflammatory process of endometriosis, still C-reactive protein (CRP) level may be the target of initial screening. The aim of this study was to investigate CRP levels as a marker of inflammatory process in serum and peritoneal fluid of patients with endometriosis. **Materials and Methods:** In a case control study, 179 patients with endometriosis (N = 90) and without endometriosis (N = 89) were evaluated. The venous blood samples were obtained from all patients before laparoscopy and the peritoneal fluid samples were collected from pelvis before any manipulation. Student's t-test was applied to compare the parameters between two groups.

**Findings:** There was no significant difference between the CRP serum level in patients with endometriosis and infertile women without endometriosis. There was a significant difference in peritoneal level of CRP between case and control groups (p < 0.05).

**Conclusions:** The findings suggested that measurement of this marker in patients' serum or plasma cannot be used to diagnose endometriosis. It is further recommended that a combination of different markers might be helpful in this regard that could be studied in future.

Key words: Endometriosis, inflammation, C-reactive protein, serum, peritoneal fluid, infertility

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## INTRODUCTION

Indometriosis is defined as the existence of endometrial-like tissue outside the uterus which is associated with pelvic pain and infertility and is seen as much as 10% in women in reproductive age<sup>[1]</sup> and 50% in women with chronic pelvic pain or infertility.<sup>[2-5]</sup> The most common clinical symptoms of endometriosis include infertility, pelvic mass, dysmenorrhea, pelvic pain,<sup>[6]</sup> deep dyspareunia, and urinary and cyclic bowel alterations.<sup>[4,7,8]</sup>

Pathogenesis of this disease is complex and multi factorial;<sup>[5]</sup> despite extensive studies its etiology has remained ambiguous.<sup>[9,10]</sup> A combination of various published theories, which strived to explain endometriosis impaired immunologic response, genetic predispositions and inflammatory components as possible causes of this disease.<sup>[11-20]</sup>

CA125 is the cell surface antigen and it is expressed by derivatives of coelomic and mullerianepithelia<sup>[6]</sup> it is the most common indicator for diagnosis of endometriosis.<sup>[13,21-24]</sup> Due to its limitation, it usually increases in advanced stage of endometriosis and yet because of the low sensitivity of this assay its utilization is

restricted in detection of minimal or mild endometriosis,<sup>[25]</sup> therefore it is not suitable for routine screening.<sup>[6]</sup> Kitawaki et al. showed that the accuracy of CA125 testing is still limited suggesting transvaginal ultrasonography for initial screening of endometriosis.<sup>[26]</sup> Aromatase<sup>[27]</sup> and leukocyte subsets<sup>[28]</sup> are other recommended secondary tests for this screening.

It is broadly accepted that endometriosis is a pelvic inflammatory process that is related to distort functioning of immune cells in the peritoneal area.<sup>[29]</sup> C-reactive protein (CRP) level rises radically during inflammation and therefore it is a member of the acute phase reactant.<sup>[30]</sup> In the clinical practice this protein is supplemented as a marker of on-going inflammation<sup>[13,31,32]</sup> and as for monitoring infectious process.<sup>[13]</sup>

There are three studies that have measured levels of CRP. The first of these showed that CRP in stage III and IV in women with endometriosis more likely in those with more advanced disease.<sup>[13]</sup> The study of Xavier et al. that was conducted more recently did not find significant difference in serum level of CRP between patients with endometriosis and healthy controls.<sup>[33]</sup> Furthermore, in a study conducted by Matarese et al. the result of CRP was below the sensitivity threshold of the test.<sup>[31]</sup>

Diagnosis of endometriosis is a challenging theme; and despite the broad search for innovative laboratory tests and advances in imaging technologies there are still no easy, non-invasive diagnostic tests available<sup>[6]</sup> but due to inflammatory process of endometriosis, still CRP level may be target of initial screening. The inflammatory process in endometriosis also exist widely in peritoneal compartment. Therefore, the difference between peritoneal level of CRP in women with endometriosis and healthy cases is hypothesized.

## **MATERIALS AND METHODS**

#### I – Patients

This case-control study included patients with and without endometriosis. 392 women who were subject to laparoscopy for the evaluation of infertility or pelvic pain at the Isfahan Fertility and Infertility Centre were considered. The patients with hypertension, coronary arterial diseases, diabetes, renal diseases, active pelvic inflammatory disease or polycystic ovarian syndrome were excluded. After laparoscopy the patients were allocated into two groups; women with (group I, n = 90) and without (group II, n = 89) endometriosis. The official informs consent was obtained for all subjects.

This study was approved by ethical committee of Isfahan University of Medical Sciences

#### 2- Collection of serum and peritoneal fluid

The venous blood samples were obtained from all patients before laparoscopy. The samples were centrifuged and the serums were stored at  $-20^{\circ}$  C until measurement. The peritoneal fluid samples were collected from pelvis before any manipulation. The bloody fluids and insufficient samples were excluded. The peritoneal fluid samples were also centrifuged and the supernatant were stored at  $-20^{\circ}$  C until measurement.

#### 3- Measurement

The serum and peritoneal levels of CRP were measured using enzyme immunoassay kit (Monobind Inc., CA, USA). Briefly, samples were added to a streptavidin coated wells, and then biotinylated monoclonal and enzyme labelled antibodies were added. Reaction between the CRP antibodies and native CRP formed a complex that bind with streptavidin. After incubation and washing, the enzyme CRP antibody bound conjugate is separated from unbound one. Finally the enzyme present on the wells is reacted with substrate to produce colour. The absorbance was read at 450 nm using micro-plate reader.

## 4- Statistical analyses

Data are expressed as mean  $\pm$  SEM. Unpaired t-tests was applied to compare the parameters between the groups. Value of p < 0.05 was considered as statistically significant.

## **FINDINGS**

## Patient's demographic data

There was no statistically significant difference between patients suffering endometriosis and control group in age, respectively: [28.9 (range: 19-44) versus, 30.2 (range: 24-42)].

## Response of CRP level to endometriosis

The data for CRP levels in serum and peritoneal from the patients with endometriosis (case) and nonendometriosis (control) is demonstrated in figure I. The results indicated that the serum and peritoneal levels of CRP were significantly different between case and control groups (p < 0.05). No significant difference in serum level of CRP between patients with endometriosis and healthy controls was detected; however there was significant difference in peritoneal level of CRP between case and control groups (p < 0.05).

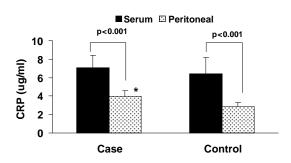


Figure 1. CRP levels in serum and peritoneal from the patients with endometriosis (case) and non-endometriosis (control) The star (\*) indicates significant difference from control group (p < 0.05).

# DISCUSSION

The serum and peritoneal levels of CRP between women with endometriosis and infertile women without endometriosis was compared in the present study.

No significant difference between the serum level of CRP between the two groups was found, which also complies with the findings of Matarese et al.<sup>[31]</sup> and Xavier et al.<sup>[33]</sup>According to the findings, it seems that no on-going systemic inflammatory process occurs in endometriosis.

Compared to the control group, the CRP level of the peritoneal fluid were higher in patients with endometriosis (p<0.05). Pelvic endometriosis is a chronic inflammatory disease that is in association with a general inflammatory response in the peritoneal cavity.<sup>[34,35]</sup> This disease is known to have an immunological background.<sup>[36]</sup> Macrophage constitutes 82- 99% of the all the cell population of peritoneal fluid.<sup>[37-39]</sup> Literature has repeatedly reported an increase of total peritoneal fluid cell numbers, cell concentration and macrophages in endometriosis patients in compare to the control.<sup>[40-43]</sup> The study of Dunselman et al. also confirmed that there is an increase in the number and concentration of peritoneal cells in patients with endometriosis as compared to the control group.<sup>[38]</sup>

The rise in the number of peritoneal macrophages in women with endometriosis may signify that the endometrial tissue in the peritoneal cavity is recognized as a foreign entity that should be eliminated, thus cells such as retrograde endometrial tissues are killed by peritoneal macrophages and their presence concludes into inflammatory process.<sup>[37]</sup>

Previous studies also reported that the peritoneal fluid mononuclear cells in women with endometriosis are more

than in controls and that most of these cells have a more differentiated phenotype.<sup>[38,44,45]</sup> Monocytes of the blood storm are attracted and changed to differentiated macrophages. This leads to an elevated concentration of peritoneal cells. A severe inflammatory process will conclude into considerable change of the number of peritoneal cells.<sup>[38]</sup>

In vitro studies indicated that CRP can be produced by vascular and organ-specific cells in response to inflammatory stimulus.<sup>[46-50]</sup> Furthermore, the study of Haider et al. demonstrated that the peripheral blood mononuclear cells (PBMC) also contribute to the CRP production.<sup>[51]</sup> The concentration of complement factors, acute-phase proteins and immunoglobulins in the abdominal cavity may be increased after vascular permeability has changed in patients with endometriosis. Moreover, in an advanced stage of differentiation, macrophages secret some of the acute phase proteins and complement factors.<sup>[52]</sup>

It is likely that the increase of CRP in peritoneal fluid of endometriosis patients is resulted from peritoneal macrophages producing them in response to the local inflammation in peritoneal cavity. Many studies maintain this notion, proposing that various local products such as cytokines are secreted by the activated macrophages in the peritoneal fluid of women with endometriosis.<sup>[37,53,56]</sup> The peritoneal macrophages are strong producers of inflammatory cytokine.<sup>[57,60]</sup> In the peritoneal fluid of women with endometriosis there is an increased number of cytokines and pro inflammatory cells.<sup>[45,61]</sup>

Tsudo et al. assumes that cytokines can be produced by immune competent cells as well as by endometrial implant.<sup>[62]</sup> Moreover, they can also be produced by ectopic endometrial tissue.<sup>[62-64]</sup>

Macrophages are the major source of cytokines. Cytokines that are originated in bone marrow circulate as monocytes and move to different body cavities,<sup>[65]</sup> and cytokines that are released abundantly during inflammatory process can also stimulate CRP activation in peripheral blood mononuclear cells.<sup>[51]</sup>

CRP is a member of the class if acute phase reactants and it rise dramatically during inflammatory processes occurring in the body.<sup>[30]</sup> It seems that the other cause of this increment in CRP level is due to a rise in the peritoneal concentration of some cytokines, which is produced by macrophages that induced CRP production.

## CONCLUSION

The fact that endometriosis involves local inflammation is known for sure.<sup>[66]</sup> Our findings suggested higher peritoneal fluid CRP level in endometriosis patients in comparison to non-endometriosis patients, but no differences in serum level. However, it is further recommended that a combination of different markers might be helpful in this regard and other studies can investigate to find such useful markers.

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