C-reactive protein is a marker for the diagnosis of adnexitis*

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Abstract

The study reports the C-reactive protein (CRP) plasma concentrations in 115 women with a presumed diagnosis of acute adnexitis. In addition to CRP, blood sedimentation rate, white blood cell count and the body temperature were evaluated and compared with the clinical findings. Diagnosis was confirmed or excluded by laparoscopy (n = 69) or laparotomy (n = 9). Clinical examinations and conventional laboratory examinations were of limited value in the diagnosis of acute adnexitis. In contrast, CRP was a highly sensitive indicator of inflammatory pelvic disease. Furthermore, the CRP determination was superior in assessing the efficacy of an antibiotic treatment.

Keywords: Adnexitis; C-reactive protein; White blood cell count; Blood sedimentation rate; Body temperature; Laparoscopy; Antibiotic treatment.

Introduction

The diagnosis of acute inflammatory

pelvic disease commonly is based on a number of clinical criteria [4,12,13,15,17]. Unfortunately, compared with laparoscopic observations, classical symptoms and conventional laboratory parameters (sedimentation rate (SR), white blood cell count (WBC) and body temperature (BT)) are either inaccurate or highly unsatisfactory [4,13,15,17,18]. Although laparoscopy is routinely used to verify acute pelvic inflammation [4,12—14,17], this method is not innocuous [5,23,26], and noninvasive diagnostic procedures would be considered advantageous.

In this regard, increases in the concentration of a functionally heterogeneous group of plasma proteins that react to acute infections are a response to the "acute phase reaction" [16,21]. Clinical experience with the measurement of C-reactive protein, orosomucoid and haptoglobine has been obtained in pediatrics [22,24,25,27] and in other fields of medicine [9,28,31]. In obstetrics, the C-reactive protein has had a role in ascertaining the presence of amniotic infection after premature rupture of membranes [3,19]. Some investigations have also shown the possible clinical value of acute phase proteins in the diagnosis and follow-up of bacterial genital infections [1,8,14].

The development of monospecific antisera against acute phase reactants and the intro-

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duction of laser nephelometry recently simplified the analysis of these proteins [6,30]. Using nephelometric technique, quantitative acute phase protein determination can be performed with a high degree of accuracy [6,30]. Preliminary data with nephelometric measurement confirm the clinical value of the acute phase proteins in the diagnosis of pelvic inflammatory disease [20]. The present study was designed to investigate the validity of CRP compared with conventional laboratory parameters and the classical clinical symptoms of acute pelvic inflammatory disease.

Material and methods

One hundred fifteen premenopausal patients admitted to our department with acute pelvic pain and a suspected diagnosis of adnexitis were studied. Major confounding pelvic disorders, i.e., appendicitis, urinary tract infections, abnormal early intrauterine and ectopic pregnancy, and genital malignancies were already roughly excluded by a combination of intensive abdominal examination by a surgeon, urinalysis, beta-hCG determination and ultrasound examination of the lower abdomen. During the further course of the preliminary investigation, the findings of gynecologic bimanual examination [10,11,15], SR, BT, and WBC were used to confirm the provisional diagnosis. Blood samples for the measurement of the CRP were obtained from each patient on admission and retrospectively correlated with the final diagnosis.

The leading symptom mentioned by all patients was lower abdominal pain and abnormal vaginal discharge. This was accompanied by adnexal tenderness or palpable adnexal mass on bimanual examination. These findings were not analyzed in detail, but only summarized as positive or negative clinical symptomatology. In 78 patients, the definite diagnosis of adnexitis was verified or excluded by use of laparoscopy ($n = 69$) or laparotomy ($n = 9$) using the criteria specified below. Laparotomy was performed only if it became necessary to combine the need for surgical treatment with diagnosis. After the termination of all diagnostic procedures (without knowledge of the CRP concentration at the time of diagnosis), the patients were divided into two groups, based upon an established diagnosis of acute inflammatory pelvic disease (adnexitis positive) or the exclusion of this condition (adnexitis negative).

Definition of "adnexitis positive" patients
— positive clinical symptomatology [10, 11,15] and
— combined elevation of at least two of the conventional laboratory parameters (SR, WBC, BT) ($n = 27$)

In all other cases with either abnormal clinical findings or only pathological laboratory criteria, diagnosis was confirmed by laparoscopy ($n = 20$) or laparotomy ($n = 9$)

Definition of "adnexitis negative" patients
— uncertain acute genital problem with no palpable findings and rapid disappearance of complaints after admission; and normal laboratory values (BT, SR and WBS) ($n = 10$)

In all other cases with uncertain acute genital problem with or without palpable findings and elevation of only one of the conventional laboratory parameters, the true intrapelvic conditions were verified by laparoscopy ($n = 49$)

Axillary BT was preferred and considered abnormal if above 37 °C. SR determinations were made by the method of Westergren [32] and were considered an additional suspicious sign of inflammation if accelerated by more than 20 mm/120 min. The upper limit of WBC was 10,000 mm³ [31,33]. CRP plasma levels were performed using the immunonephelometric method (Behring laser nephelometric modular system) [29,30]. The
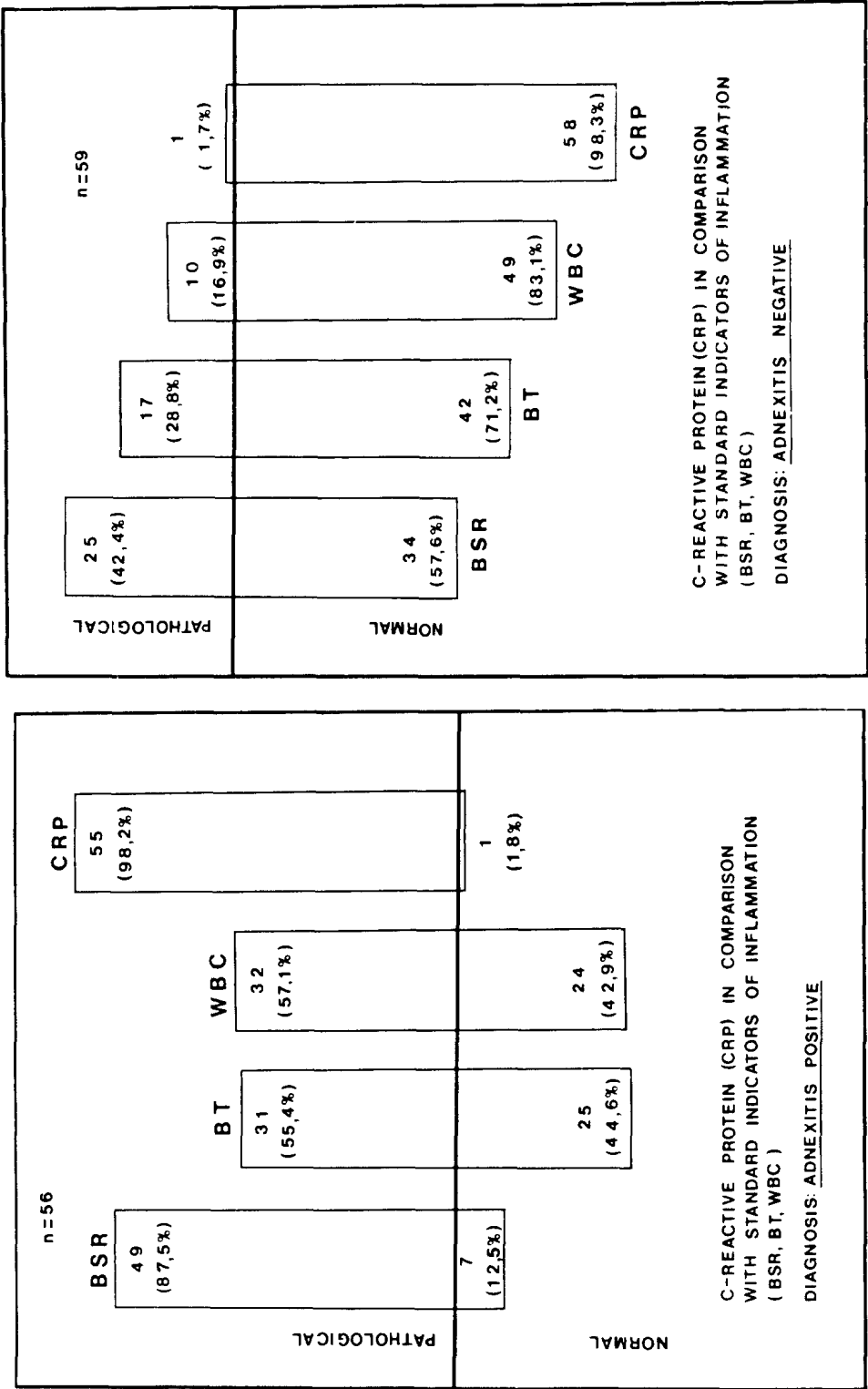
n=59

PATHOLOGICAL | NORMAL

BSR 25 (42,4%) / 34 (57,6%)

BT 17 (28,8%) / 42 (71,2%)

WBC 10 (16,9%) / 49 (83,1%)

CRP 1 (1,7%) / 58 (98,3%)

C-REACTIVE PROTEIN (CRP) IN COMPARISON
WITH STANDARD INDICATORS OF INFLAMMATION
(BSR, BT, WBC)

DIAGNOSIS: ADNEXITIS NEGATIVE

n=56

PATHOLOGICAL | NORMAL

BSR 49 (87,5%) / 7 (12,5%)

BT 31 (55,4%) / 25 (44,6%)

WBC 32 (57,1%) / 24 (42,9%)

CRP 55 (98,2%) / 1 (1,8%)

C-REACTIVE PROTEIN (CRP) IN COMPARISON
WITH STANDARD INDICATORS OF INFLAMMATION
(BSR, BT, WBC)

DIAGNOSIS: ADNEXITIS POSITIVE

Fig. 1. Comparison of BSR, BT, WBC and CRP values in patients with adnexitis. BSR compared with CRP, $P < 0.05$; BT, WBC compared with CRP, $P < 0.001$.

Fig. 2. Comparison of BSR, BT, WBC and CRP values in patients without adnexitis. WBC compared with CRP, $P < 0.01$; BSR, BT compared with CRP, $P < 0.001$.

Table I.   Median values and ranges of BSR, BT, WBC and CRP in patients with adnexitis and without adnexitis.

	Cut-off	Adnexitis positive (n = 56)		Adnexitis negative (n = 59)	
		Median	Range	Median	Range
BSR (mm/2 h)	20	60	3—100	45	3—84
BT (ax. °C)	37.0	37.2	36.4—39.3	36.9	36.4—38.4
WBC ($\times 10^3 \mu$l)	10	10.6	5.3—21.6	8.9	5.0—17.3
CRP (mg/dl)	0.6	4.7	0.5—21.6	0.4	0.2—0.9

quantitative determination became possible using monospecific antisera against CRP and appropriate reference standards (Behring Corporation, Marburg, Germany) [19,30]. Plasma titers of more than 0.6 mg/dl were considered to be abnormal.

The Chi-square test was used to perform statistical qualitative analysis. The Kruskal-Wallis and the Mann-Whitney U tests were used for quantitative statistical evaluations. The positive and negative predictive value of each laboratory parameter was calculated.

Results

Of the 115 patients, 56 were "adnexitis positive" and 59 were "adnexitis negative". Among the "adnexitis positive" patients, 87.5% (49/56) demonstrated an elevated SR, whereas only 55.4% had an increased BT. The frequency of abnormal WBC was equally unsatisfactory as a predictive test; only 57.1% (32/56) of the patients had abnormal values (Fig. 1).

The CRP values analyzed retrospectively demonstrated the best sensitivity of all laboratory parameters in "adnexitis positive" patients. This test had a significantly higher percentage of abnormal results compared with the BSR ($P < 0.05$), and the BT and WBC ($P < 0.001$) (Fig. 1).

The validity of CRP measurement was also characterized by the highest specificity of all methods, showing truly negative CRP plasma values (< 0.6 mg/dl) in 98.3% (58/59) of "adnexitis negative" patients. In only one patient were false positive CRP titers found (Fig. 2).

The incidence of false positive results of the other laboratory parameters was significantly higher than that of the CRP. An abnormal SR was obtained in 42.4% (25/59) ($P < 0.001$), and 16.9% (10/59) ($P < 0.01$) had an abnormal WBC (Fig. 2). Slightly more than 1/4 of patients (28.8% or 17/59) ($P < 0.001$), demonstrated an increased BT.
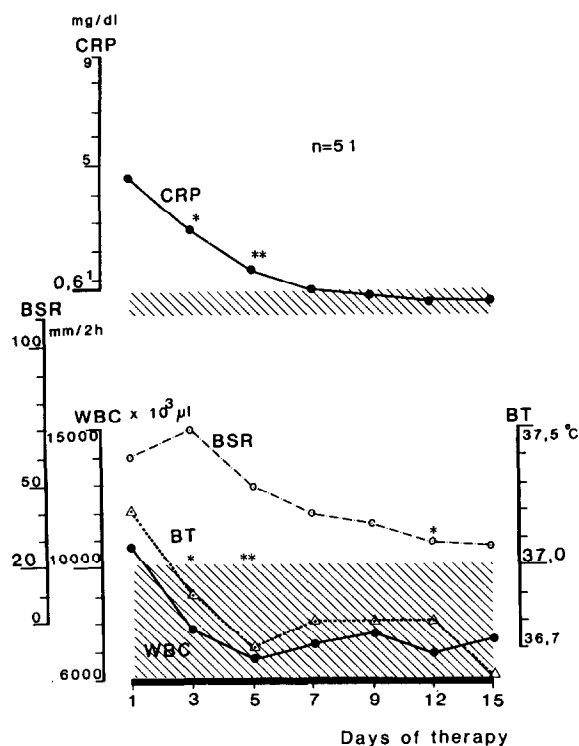

Fig. 3.   Changes of median values of CRP, BSR, BT and WBC in patients with adnexitis, responding to antibiotic treatment (n = 51). *$P < 0.01$, **$P < 0.001$, compared to the plasma concentration before therapy.

Table II. CRP, BSR, BT and WBC values of four patients (A, B, C, D) at the time of the diagnosis (Diag.) of the adnexitis and at the time of the detection of the Douglas⁴ or tubo-ovarian abscess (Absc.), respectively.

Patient	A*		B*		C		D	
	Diag.	Absc.	Diag.	Absc.	Diag.	Absc.	Diag.	Absc.
CRP (mg/dl)	17	15	8.6	8	4.1	3.1	2.5	2.7
BSR (mm/2 h)	98	160	87	110	77	101	62	86
BT (ax. °C)	37.6	38.5	37.8	37.9	36.6	36.9	36.7	36.6
WBC (× 10^3 μl)	12.6	24	10.9	22.4	11.2	9.9	8.5	8.7

The superiority of the CRP as a discriminator between healthy and infected patients was also documented by the median values and ranges of the laboratory parameters (Table I). In cases of PID, the CRP plasma concentration increased to higher levels, compared with other values and the absolute values showed close correlation to the extent of the inflammation.

In the "adnexitis negative" patient population ($n = 59$), verification by laparoscopy was conducted in 49 patients. Sixteen of these 49 women had no pathologic changes and 33 had other intrapelvic disorders: sactosalpinx or adhesions ($n = 15$), postoperative adhesions ($n = 5$), ovarian cysts ($n = 3$), Allen-Masters Syndrome ($n = 4$), endometriosis ($n = 3$), uterus myomatosus ($n = 2$) and ovarian cancer, Stage I (FIGO) ($n = 1$).

The CRP protein was useful not only in detecting adnexitis but also in monitoring the effect of antimicrobial therapy. Figure 3 shows the CRP plasma concentrations, SR values, BT and WBC of 51 of the 56 "adnexitis positive" patients who responded to antibiotic treatment. Treatment response was indicated by a decreased CRP along with improvement of symptoms. A decline of at least 30% was observed on the third day and by nearly 70% on the fifth day of therapy (Fig. 3). In all cases, normal values were reached 12 days after initiation of effective antibiotic treatment (Fig. 3). BT and WBC, if increased, became normal in 96% of women within 3 days after start of therapy. SR declined more slowly and remained slightly elevated even after 2 weeks of drug therapy (Fig. 3).

In four patients neither single agent treatment nor combined therapy influenced the disease course. The data of these 4 patients are presented in Table II. Treatment failure and the development of an abscess was accompanied by stable CRP plasma concentrations. The evaluation of the other parameters was variable (Table II). (One patient came out of our control after diagnosis of PID.

Discussion

The present study reports data from 115 patients with a preliminary diagnosis of acute adnexitis. Confirmation of the initial impression occurred only in 48.7% of cases. This figure is not different from that of other authors who report agreement in 35—65% of cases [2,4,15,17].

In our hands, BT showed false negative results in 44.6% of the patients with confirmed adnexitis, whereas 28.8% of the women without adnexitis demonstrated elevated temperature, i.e., false positive values. Similar observations have been published by other authors [4,14].

The analysis of the SR is somewhat better, but not really efficient. Abnormal values were found in 87.5% of patients with verified adnexitis. On the other hand, 42.2% of the SR determinations were false positive. Studies published by other investigators [4,14,18] reported a comparable inaccuracy for the SR. The WBC also had a limited

diagnostic accuracy. That agrees with other reports [4,10,18]. Use of the WBC in our series led to false positive results in 16.9% and false negative results in 42.9%.

In contrast, measurement of the CRP appears to be a real improvement. Investigations by Hajj et al. [8] described a 98% accuracy in diagnosing an infectious genital process. They failed, however, to compare these data to the commonly used diagnostic procedures as clinical symptoms, palpable findings, body temperature, BSR, and WBC. Our results in following the CRP as a marker for effect of antibiotics are similar to those of Angermann et al. [1], who monitored 16 patients with adnexal inflammation.

In summary, C-reactive protein is superior to the conventional laboratory tests for diagnosis as well as follow-up of antibiotic treatment in patients with PID. The unacceptably high degree of differential diagnostic errors of the noninvasive methods can be markedly reduced by additional use of CRP.

As CRP is only specific for inflammation, problems of interpretation may exist if inflammation of the lower abdomen is present in organs not belonging to the genital tract. Such patients need further investigation, including laparoscopy. Misleading results are also possible in patients with infections outside the pelvic region. Nevertheless, the routine determination of CRP plasma concentration should become a constant part of gynecologic workup and follow-up for PID.

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