Effect of oestrogen treatment on clinical and laboratory manifestations of rheumatoid arthritis

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SUMMARY The effect of administration of 12.5 µg ethinyloestradiol to 10 female patients with active rheumatoid arthritis was investigated in a prospective double blind crossover study. Some improvement during oestrogen treatment was found in 30 m walking time, haemoglobin concentration, and thrombocytosis. Erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) deteriorated in both periods, but less in the oestrogen period. Grip strength improved during both periods. The number of swollen joints decreased, whereas the joint tenderness score increased during the oestrogen period.

Key words: ethinyloestradiol.

Sex hormones are one of the influences on the course of rheumatoid arthritis. It is well known that rheumatoid arthritis has a higher incidence in women. The epidemiological evidence that contraceptive and non-contraceptive female sex hormones decrease the incidence of rheumatoid arthritis in women seems contradictory to this.^{1 2} In several models of experimental arthropathy in animals both oestrogenic and androgenic hormones modulate the severity of the arthritis.^{3 4} The effect of exogenous sex hormones on the activity of rheumatoid arthritis was studied 20 years ago. The results were conflicting,^{5 6} and this line of investigation was not explored further.

We have studied the effect of low doses of oestrogens on rheumatoid arthritis in a 24 week prospective double blind crossover study. Some improvement during oestrogen therapy was noted.

Patients and methods

Ten female patients with adult onset, seropositive, classical (American Rheumatism Association (ARA) criteria) rheumatoid arthritis were admitted to the study. They had active disease shown by at least three of the following characteristics: (a) tenderness of more than six joints; (b) swelling of more than three joints; (c) Ritchie articular index

greater than 20; (d) ESR greater than 35 mm/1st h; (e) CRP greater than 30 mg/l; (f) early morning stiffness of more than 30 minutes. All patients were taking non-steroidal anti-inflammatory drugs, and three patients were taking a slow acting anti-rheumatic drug (two hydroxychloroquine and one D-penicillamine). No major changes in treatment were made in the three months before the start of the study. No patient was using prednisone; no contraindication for oestrogen treatment was found in any of the patients.

Seven women were postmenopausal (last menstrual cycle more than one year previously) and three premenopausal. The latter were using non-hormonal contraceptive devices. The age range was 27-68 years with a mean of 55.9 years; the disease duration ranged from one to 35 years with a mean of 16.3 years. All patients were ARA functional class 2. The study design was approved by the Ethical Committee, and the patients gave their informed consent.

Patients were randomly allocated to one of two treatment groups; 12.5 µg ethinyloestradiol or placebo was given in three cycles of four weeks (three weeks treatment followed by one 'withdrawal' week), total 12 weeks. This was followed by 12 weeks on the alternative treatment. The three premenopausal women started their treatment on the fifth day of their menses. Afterwards it was known that six women had started with placebo and four with oestrogens.

Assessment included clinical evaluation and blood

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tests at baseline, 12, and 24 weeks. Clinical evaluation was performed by the same investigator (JWJB) at the same time of day, and both investigator and patient were unaware of the assigned treatment. Clinical evaluation included joint tenderness score and swollen joints score, as described by Ritchie⁷; grip strength measured with the same sphygmomanometer cuff inflated to 30 mmHg, wrapped in a standard sleeve (average of three recordings for each hand); and 30 m walking time.

Blood tests included ESR (Westergren), CRP (nephelometric), haemoglobin concentration, and number of thrombocytes (both by the Coulter counter).

Compliance was measured by the concentration of sex hormone binding globulins (by ammonium sulphate precipitation⁸), which increases significantly during oestrogen treatment.

To assess a possible influence of oestrogen treatment the data obtained were analysed based on the percentage changes during 12 weeks treatment (oestrogens *v* placebo). Statistical differences were calculated by a signed rank test.

Results

Nine patients completed the study; one woman stopped after 22 weeks because of abdominal discomfort due to ovarian cysts. Afterwards it was found that she was first treated with oestrogens and in the second period with placebo. Her data are included in the final assessment.

Two treatment periods were compared: the 'placebo' period (six women the first 12 weeks plus four women the second 12 weeks) and the 'oestrogen' period (four women the first 12 weeks plus six women the second 12 weeks).

In Table 1 the mean values and standard errors of the mean of the relevant parameters are given separately at the start of the placebo and of the oestrogen treatment period. Disease activity, as

Table 2. Mean values (and standard errors of the mean) of changes in clinical and laboratory measurements before and after both treatment periods, given as percentage changes

	Oestrogen treatment	Placebo treatment	p Value
Joint tenderness score	+26.9 (13.2)	+0.6 (5.8)	0.10
Swollen joints score	-1.5 (7.8)	+11.2 (9.9)	>0.50
Grip strength	+15.0 (5.7)	+19.9 (10.5)	0.11
30 m walking time	-9.7 (4.2)	+3.4 (2.5)	0.03*
ESR	+20.6 (6.7)	+39.5 (21.2)	>0.50
CRP	+35.5 (17.3)	+58.2 (26.8)	0.08
Haemoglobin	+1.9 (1.0)	-4.4 (1.6)	0.04*
Thrombocytes	-0.7 (3.5)	+6.5 (3.7)	0.03*

*p Values <0.05; signed rank test.

measured by clinical and laboratory data, was similar at the start of both treatment periods.

As there was a wide variety of disease activity in the individual patients the changes found are given as percentage changes during both treatment periods. These changes are shown in Table 2. Some differences between the placebo and the oestrogen treatment periods were then found. Joint tenderness score increased in the oestrogen period but not during the placebo period. The swollen joints score increased during placebo treatment but not during oestrogen treatment. During both periods grip strength increased. During oestrogen treatment the walking time improved, but worsened during placebo.

The laboratory parameters ESR and CRP increased during both periods, but more during the placebo period. The haemoglobin concentration and thrombocytosis improved during oestrogen treatment and worsened during placebo. The improvements in walking time, haemoglobin concentration and thrombocytosis were statistically significant and point to a beneficial effect of oestrogen treatment. All women showed an increase in sex hormone binding globulins during oestrogen treatment, reflecting treatment compliance.

Some side effects were noted. During oestrogen treatment nearly all the postmenopausal women experienced some subjective signs due to hormonal treatment; in three women this led to vaginal spotting. During follow up for at least six months no further blood loss was observed. One premenopausal woman stopped two weeks prematurely because of abdominal pain due to ovarian cysts, as described above.

Discussion

The influence of sex hormones on the various rheumatic diseases is intriguing. Most rheumatic

Table 1. Mean values (and standard errors of the mean) of clinical and laboratory measurements before both treatment periods

	Oestrogen treatment	Placebo treatment
Joint tenderness score	14.1 (1.7)	14.7 (1.3)
Swollen joints score	6.5 (0.5)	6.8 (0.6)
Grip strength (mmHg)	52 (7)	52 (7)
30 m walking time (s)	14.4 (1.4)	13.7 (1.3)
ESR (mm/1st h)	28.1 (4.0)	29.2 (4.2)
CRP (mg/l)	34 (6)	34 (6)
Haemoglobin (g/l)	94 (2.0)	97 (2.0)
Thrombocytes $\times 10^{-9}/l$	353 (18)	365 (27)

diseases have a higher incidence in women. It is thought that women are immunologically more reactive than men and are, therefore, more susceptible to immunologically mediated disorders such as systemic lupus erythematosus (SLE) and rheumatoid arthritis. This is explained by the ability of sex hormones to modulate immune reactivity, with androgens suppressing and oestrogens augmenting this reactivity.⁹ In the clinical situation this seems to hold for SLE, where oestrogens can worsen and androgens can ameliorate disease activity.^{10, 11}

In contrast with SLE, in rheumatoid arthritis oestrogens seem to have a preventive effect on the incidence of the disease, as shown by epidemiological studies. In addition, there are suggestions that oestrogens can ameliorate disease activity; the disease improves during pregnancy,¹² in premenopausal women disease activity fluctuates with the menstrual cycle,¹³ and the present study also suggests an ameliorating effect of oestrogens.

In this study we used a low dosage of oestrogens as there are possible risks during long term oestrogen treatment. In four women mild side effects were noted; it thus can be concluded that this low dosage of ethinyloestradiol was biologically active. As progesterone has also been implicated in immunomodulation¹⁴ we preferred not to use a combination preparation, to prevent confusion in interpretation. In fact four patient groups should be discerned: (a) the patients who were treated with placebo during the first 12 weeks or (b) during the second 12 weeks and (c) the patients who were treated with oestrogens during the first period or (d) during the second period. Unfortunately the number of patients was too small to assess these groups separately. This could bias the results by abating the possible differences.

The duration of the treatment periods was relatively short: 12 weeks. Usually disease modifying antirheumatic drugs have a delayed response, with a possible beneficial effect after more than three months. In our study some improvement had already been noted within three months. Of the eight parameters, five seemed to improve during oestrogen treatment and only one during the placebo period. In addition, two of the three parameters that did not improve during oestrogen treatment deteriorated more during the placebo period. This study in only 10 patients and during a short period suggests that further research in this direction might be fruitful.

At present we can only speculate about the mechanisms involved. A direct interaction between hormones and lymphocytes is likely in view of the presence of oestrogen receptors on human blood mononuclear cells and thymocytes.¹⁵ The present

state of research, however, seems to point to an increase in immune reactivity due to oestrogens. Perhaps this is not true in rheumatoid arthritis, where oestrogens ameliorate disease activity. There are several possibilities that can be considered: (a) the effect of oestrogens is restricted to subsets of lymphocytes, e.g., they affect T suppressor cells but not T helper cells; (b) the balance between oestrogens and androgens is different in rheumatoid arthritis compared with SLE, for example; exogenous oestrogens can exert a different influence upon this balance; (c) non-immunological mechanisms, such as the influence of oestrogens on chondrocytes,¹⁶ have a pivotal role. Clearly more studies in this area are needed.

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