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Chapter

The Role of Estrogens in Rheumatoid Arthritis Physiopathology

Maria Fernanda Romo-García, Martín Zapata-Zuñiga, José Antonio Enciso-Moreno and Julio Enrique Castañeda-Delgado

Abstract

Rheumatoid arthritis (RA) is a chronic, inflammatory joint disease that can lead to irreversible disability. It affects women in a higher proportion than men (3:1 cases). Several reports suggest a link between female sexual hormones (estrogens) and RA features. It's been described that biological processes where basal estrogen levels are altered like in menstruation, pregnancy, and menopause modifies RA onset, flare, disease severity, and inflammation. Estrogens have a direct action upon the immune system though ERα and ERβ receptors, which have distinct affinity to estrogen concentrations and modifications and have effects upon RA in a dose and receptor dependent manner. The studies focused on dose dependent response at experimental settings reveal a wide (from 25 pg/L to several μg/L) and even contradictory spectrum of effects in patients and cells. This chapter summarizes the contributions and effects of estrogens in RA physiopathology, clinical features, and discusses the possible contributions of estrogen administration and concentration of hormone replacement therapy (HRT) to improve the quality of life and reduce the symptoms of RA patients based on the knowledge of the biology of these hormones.

Keywords: rheumatoid arthritis, physiopathology, immune function, estrogen

1. The RA-gender-hormones link

Rheumatoid arthritis (RA) is defined as a chronic, inflammatory joint disease that without effective and timely treatment can lead to irreversible disability by cumulative joint damage. This autoimmune disease is characterized in most cases by autoantibodies against immunoglobulin G (RF) and citrullinated proteins (ACPAs) [1–3]. The alterations in the immune response is only one face of the disease since it has been described as a heterogeneous disease [4, 5]. This is supported by the wide variation in responsiveness to different rheumatic treatments [6]. Research suggests this might be due to variations in the distribution/expression of estrogen receptors (ERs) in immune cells; ERs often bind to promoter regions in the DNA associated with transcription factors (e.g., NF-κB, SP1, AP-1, C/EBPβ) that are important for immune cell function [7].
could possibly be related to “premenstrual tension syndrome” and alteration in pain perception [44], but in a study where only objective measures of disease activity were measured, a significant cyclical change in finger joint size (FJS) was seen in 4 of 7 patients with RA, with all peaks occurring within 6 days of the start of menstruation [45] while on contrary, the morning stiffness was reduced during the post-ovulatory phase where estrogen and progesterone are high [46], indicating that this worsening of symptoms might be related to variations in hormone levels [47]. Based on this evidence, a relation between low levels of estrogen (at luteal phase) can correspond to enhancement of RA symptoms. Contrary to what occurs on pregnancy, where high estrogen levels seem to have a protective effect. Until now there is no follow up study available to display the effect of cyclical variations in estrogen levels and symptoms severity in RA patients.

3.2 Arthritis and pregnancy

As stated previously, the relationship of RA onset and sex hormones has been widely studied. This phenomena was described first 80 years ago [8] and was noticed that pregnant patients with RA usually go into remission [48] in a 20–40% by the third trimester and 50% had low disease activity [49]. Prospective studies have shown that only 48–66% of women with RA experience improvement in pregnancy, with 20% becoming quiescent by the third trimester and 16% in complete remission (no joints with active disease without therapy) [32, 50].

It has been hypothesized that estradiol might be the principal regulator of immune response during pregnancy, nevertheless other estrogens might be implicated in this immune regulation, as an example we can cite estriol (E3) which is mainly produced during pregnancy [51, 52], and estetrol (E4) is synthesized exclusively by the fetal liver during pregnancy being able to reach the maternal circulation through the placenta [53]; thus, these two estrogens, specifically E4 could have an important role in the immune regulation during pregnancy; nevertheless, there is scarce information about its possible function during pregnancy.

A shift from a Th1/Th17 pro-inflammatory response to a Th2/Treg response has been observed in pregnancy [54, 55]. This could explain the decrease of IL-2 during pregnancy, while soluble TNF receptor, p55 and p75, increases [56]. The role of the immune system in pregnancy is very important. It has been observed that a depletion of immune cells can cause the termination of the pregnancy. Nevertheless, it is not very clear how such changes in T helper cell function could impact the implantation process. It has been suggested that the response could be induced by trophoblastic cells that can secrete IL-6, IL-8, MCP-1, and GRO-α, early in pregnancy [43].

During the first trimester, NK cells, dendritic cells, macrophages, and regulatory T cells (Treg) infiltrate the decidua and accumulate around the trophoblastic cells [57–59]. This regulation of the immune response could be the cause beneath the clinical improvement observed in RA during pregnancy.

3.3 Menopause and arthritis

RA onset is common in the peri-menopausal age, which is not the case with SLE [60] and while hormone replace therapy (HRT) is proposed as therapy for women with RA, OCP and postmenopausal hormones significantly increased the risk of SLE [61]. Also, there is an inverse trend for RA incidence when women reach menopause after 51 years compared to those who reach menopause before 45 years of age. This is consistent with a decline in the production of sex hormones and suggesting that changes in immune regulation due to the availability of estrogen receptors in
diethylstilbestrol, bisphenol-A, p-nonylphenol, and di-2-ethylhexylphthalate), the concentrations needed for this effect were higher, from 10 to 6 to 10–5 M [69].

5. Estrogens and their possible ameliorative effect upon arthritis: therapeutic approach

Given the previously displayed effects of estrogens on the immune system and in RA, it is natural to suppose that a hormone therapy could have certain effects upon the disease but, the studies exploring this possibility are scarce. Three major considerations have been identified as roadblock for such research to be conducted: (1) cut-off point in estrogen levels determining the effects of this molecule on the immune system, (2) the various effects of the same molecule at different concentrations lead to different effects depending ER$\alpha$ or ER$\beta$ receptor, and (3) effects dependent of the chemical modification (hydroxylation) of estrogens.

The hypothesis that hormonal therapy could ameliorate RA arises from the evidence of reported improvement in multiple pregnancies and contraceptive use [109], but this evidence became more solid when the estrogen at physiological levels administration in models of type II collagen-induced arthritis model (CIA) ameliorated arthritis and suppressed T-cell-dependent autoimmune reactions [52, 90]. In this experiment, female mice were implanted with E2 release devices, which induced a chronic estrous phase, the high doses of E2 caused a 35-day delay of the onset of RA disease but without affecting frequency and severity; this delay was reduced to 10 days with lower E2 concentrations of 25 days with physiological E3 proved to be as efficient as the high dose E2 causing a 25 day delay [90]. E3 seems to have more pronounced effects than E2; this estrogen E3 is mainly produced in pregnancy [51, 52]. In EAE models, it seems that the estrogen-mediated protection is dependent upon ER$\alpha$. For example in EAE homozygous ER$\alpha$KO treated with estriol, no protective effect was registered, while WT mice presented a significant decrease in disease severity and significant reductions in pro inflammatory cytokines TNF, IFN$\gamma$, IL-2, and an increase in levels of the Th2 cytokine IL-5 [110]. The effect of estrogens at interact with ER$\alpha$ receptor is not only limited to the immune response; in murine ovariectomized mice with estrogen treatment by pellet implantation, a dramatic increase in bone mass was observed. This was mediated by ER$\alpha$-mediated apoptosis of osteoclasts through activating FasL/Fas signaling [111]. This could be an indicator that similar protective effects of estrogens may be present in immune cells due to the expression of ER$\alpha$ in CD4 + T lymphocytes.

Estrogens have been demonstrated to have anti-inflammatory activity. In CIA models, estrogen supplementation reduced paw inflammation efficiently and decreased paw volume by 48% ($P < 0.01$) [91], but we need to be aware that the activity of several estrogens (E1, E2, E3, and E4) is different and it depends not only on the hormone itself but also by the specific disease or even the specific clinical profile of the patient that is taking them. 2-methoxyestradiol on CIA model (20 days after the injection of type II collagen) produce a significant decrease in the arthritis index compared with that in the control mice ($P < 0.05$) despite it was not as efficient as estradiol [112]. Despite this is the most tested estrogen among studies for its effect in RA, Estradiol E2, in clinical applications, shows several side effects such as: hypertension, increased coagulation, and cancer incidence but a feature that both share is that they are protective in experimental autoimmune encephalomyelitis (EAE) and CIA [113].

The clinical data available is scarce and most of the available trials only evaluate the protective effect of OCP (oral contraceptive pill) and hormone replacement
therapy (HRP) for RA. In a study of association between postmenopausal hormone therapy (PMH) use and the risk of rheumatoid arthritis (RA) in a subset of the Epidemiological Investigation of RA (EIRA) study, the users of PMH had a decreased risk of ACPA-positive RA compared with never users, mainly with a combined therapy (estrogen plus progestagens), they propose that PMH use might reduce the risk of ACPA-positive RA in post-menopausal women over 50 years of age, but not of ACPA-negative RA [114].

Regarding the role of OCP use in RA, there is a theory which explains that recent decrease in incidence of RA in women in the past 50 years may be in part due to increased use of the OCP, even when may be confounded by OC use being related to pregnancy avoidance and high social class [115]. During a 14 month period, 23,000 women who were using oral contraceptives were recruited, and a similar number of those who had never used OCP as controls and evaluated every 6 month intervals. Patients were classified as “current user,” “former user,” and “never user.” The cases were categorized according to the woman’s contraceptive status at the time of RA diagnosis (event). The trend for former users was $\chi^2 = 5.7$, ($p < 0.02$) and for the never users $\chi^2 = 15.0$, ($p < 0.01$) but the current users $\chi^2 = 0–85$, ($p > 0.05$) and for those who were aged 40–44 years at diagnosis had a significantly lower risk of rheumatoid arthritis than similarly aged never users (relative risk 0.29). At the end of the follow-up, women who were using the pill at the time of diagnosis had a statistically non-significant 20% reduction in their risk of rheumatoid arthritis but early in the study current users had a significant 50% risk reduction [116]. The same cohort was classified in groups of “takers” and “never takers” and was analyzed too for the incidence of RA. The standardized rate for takers was 49% of the control rate ($p < 0.01$) and resulted interesting an observed tendency for an increased incidence of RA forward 35 years; this tendency was conserved only in the group of “never takers” and suppressed in the takers [117].

In the Swedish EIRA study (population-based case-control) including 2641 cases and 4251 controls participants were questioned about OCP (oral contraceptive pill) full term need to be mentioned consumption, and potential confounders in order to calculate the ORs adjusted for age, residential area, smoking, and alcohol consumption. Compared with never users, the OCP users had a decreased risk of ACPA-positive RA (OR = 0.84) (95% CI 0.74–0.96) compared to the never users. Also the consumption for more than 7 years decreased the risk of both ACPA-positive ($p = 0.0037$) and ACPA-negative RA ($p = 0.0356$) compared to never users of OCP [118].

Most of the studies agree that the current or ever use of the OCP has a protective effect against RA, probably more delaying the onset rather than a preventing RA. But until now there is not a final conclusion because even the meta-analysis results are contradictory. In the meta-analysis of six case-control and three longitudinal studies, the overall pooled odds ratio of the studies was 0.73 for the adjusted results (95% CI 0.61–0.85) with the conclusion that OCP consumption prevents the progression to severe disease by modifying the disease process [119]. On the contrary in a meta-analysis performed by Qi et al. in 2014, the authors identified 1116 publications in PubMed and EMBASE databases. The meta-analysis of 12 case-control and 5 cohort studies were analyzed. Potential publication bias was evaluated using Begg’s funnel plots and quantified by the Egger’s test, as a sensitivity analysis was performed to investigate the influence of potential confounding factors like age, smoking, parity/pregnancy, body mass index, and social class on risk of develop RA. Here, no statistically significant association was observed between oral contraceptives and RA risk (RR = 0.88, 95% CI = 0.75–1.03) concluding that OCP consumption was not significantly associated with RA risk [120].

HRT (hormone replacement therapy) has been studied in regard to RA new-onset. On a study in a prospective cohort of 31,336 Iowa women (from 55 to
69 years) followed up during 11 years, 158 incident cases of RA were registered. Of the factors that showed an inverse association with RA, the authors identified pregnancy (P trend = 0.01) and age at menopause (P trend = 0.03), whereas polycystic ovary syndrome (relative risk [RR], 2.58; 95% confidence interval [CI], 1.06–6.30), endometriosis (RR, 1.72; 95% CI, 0.93–3.18), and hormone replacement therapy (RR, 1.47; 95% CI, 1.04–2.06) were positively associated with RA. If HRT is administered before RA is associated with a higher risk of developing the disease, studies suggest that when HRT is administered during RA, they have a favorable effect. In 88 postmenopausal women with RA who received HRT, vitamin D3, and calcium supplementation or vitamin D3 and calcium supplementation alone for 2 years, HRT use had a significant effect upon active RA, ameliorating effects on inflammation (ESR p = 0.025) DAS28 (p = 0.036) and was associated with slower progression of radiological joint destruction (p = 0.026) [121]. The continuous hormonal therapy given to suppress menstruation for regulation of menstrual bleeding, pelvic pain, and dysmenorrhea seems to have demonstrated improvement in RA [122].

6. Novel hormone analogs in RA

Recently, novel hormone analogs have been developed. ERβ-041 is a selective ERβ agonist and has showed interesting effects in several inflammatory rodent models, including endometriosis, rheumatoid arthritis, inflammatory bowel, and sepsis [123, 124] where a strong effect on reduction of inflammation was observed. This selective effect was the antecedent for the development of other ERβ agonists like MF101 [125] that could be useful to modulate the inflammation and cytokine production in RA. No clinical trial data on these molecules have been published so far.

7. Conclusions

Given the higher prevalence of RA cases that occur in women, it is natural to suspect that such differences are due to sexual hormones, specifically estrogens, which have been explored as part of pathophysiology, development, and progression of RA disease. Antecedents point to estrogens as strong modulators of immune response and function associated to RA. The role that sex hormones play in the development, cell activation, and alterations in immune function in autoimmune diseases is still a matter of intense research. The administration of estrogens may have a protective effect on RA development or in the onset of disease, delaying it. Also, experimental evidence suggests that estrogens demonstrated anti-inflammatory activity in animal models of RA. Such effects are mediated by modifications in antibody production and in post-translational modification of antibodies like sialylation (addition of syalic acid), involved on increased risk of RA in conditions with low estrogen levels such as menopause. Estrogens administration to RA patients could be a strategy to improve the quality of life through hormone replacement therapy (HRT). This, in resource limited settings were biological therapy cannot be afforded and in patients that are refractory to standard MTX therapy or that have failed to respond to such therapies.

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Conflict of interest

No conflict of interest is declared.

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