Chapter

The Role of Estrogens in Rheumatoid Arthritis Physiopathology

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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/EBPb) that are important for immune cell function [7].

Phase	Sub phase	Estrogen concentration [E2] pg/ml
Ovulation	Early follicular	30–100 pg/ml
	Late follicular	100–400 pg/ml
	Luteal Phase	60–150 pg/ml
Pregnancy	1 semester	188–2497 pg/ml
	2 semester	1278–7197 pg/ml
	3 Semester	6137–3460 pg/ml
Postpartum	Lactation	35.9–54.4 pg/ml
	No lactation	97.10 pg/ml
Weaning		81.6 pg/ml

Table 1.
Average levels of estrogens on distinct phases of the reproductive cycle.

The relation of immune response and estrogens in RA began with the observation of S. Hench in 1938, where he found pregnancy ameliorated RA, this was the basis for the formulation of his hypothesis sustaining that hormone deficiency could lead to the development of RA, but at that moment, he hypothesized adrenal insufficiency as the responsible of RA pathogenesis [8]. Furthermore, administration of corticosteroids was prescribed for RA patients and the results of the therapy were considered "a miracle cure for RA," but in the case of women, the regulation of adrenal glands seems to be only a part of the therapy. Other studies demonstrate that sexual hormones seem to have a very important role in RA pathogenesis. For example, in vitro studies demonstrated that the achieved concentrations of cortisol do not affect inflammatory cell function, as did the serum of pregnant women, which is rich in sexual hormones. Also the corticosteroid levels return to normality 3 days after delivery, which does not coincide with the pattern of rheumatoid arthritis relapse, common after the third month of delivery [9]. This antecedent opened a new field of study focused on hormones and RA. When concentrations of hormones were analyzed in synovial fluid, a correlation was found in this tissue including, dehydroepiandrosterone (DHEA) which levels are inversely correlated with disease severity and associated with autoimmunity [10, 11] and corticotrophin-releasing hormone (CRH) which levels remain constant in synovial fluids and tissues from RA patients despite the steroid treatment [12]. The dysregulated production of estrogen levels in RA is not exclusive of women; higher estradiol (E2) concentrations and decreased androgen levels have been found in women and men synovia [13]. These concentrations are correlated with those measured in serum in 66% of the patients (14 of 21 patients). The estradiol mean concentrations was 38.25–9.74 pg/ml in serum and 18.83–5.70 pg/ml in synovia; these concentrations showed a positive correlation ($R = 0.79$, $P < 0.0003$) [13–15].

Fluctuations in estrogen levels appear to remarkably impact immunologic profile. Estrogen concentration during lactation is slightly low compared to normal levels (35.9–54.4 pg/ml vs. 63.3–216 pg/ml) upon the normal higher levels (100–400 pg/ml in the late follicular stage) (**Table 1**); together, prolactin and estrogen levels could lead to a change in immune response [16, 17].

2. Prevalence, incidence, and severity of RA in women

Autoimmune diseases affect approximately 8% of the population, out of this percentage 78% are women [18, 19] and for the specific case of RA, the proportion

is 3 to 1 compared to men [20, 21]. Also, RA is much more severe in women compared to men (**Table 2**). For example, in a multiple logistic regression analysis for all point and period remissions, male gender seemed to be a strong predictor of remission; for women, the frequency of remission at 18, 24, and 60 months was 30.4, 32.1, and 30.8%, respectively; meanwhile for men, the remission rate was 41.7, 48.0, and 52.4% [22]. Additionally, in another study from a total of 1709 RA patients, (77% female) women had a longer disease duration ($P < 0.001$) despite the fact that at baseline, women had a lower frequency of anti-CCP positivity ($P = 0.03$) and lower CRP ($P < 0.001$), and at 12 months, men achieved remission more frequently (18% vs. 12%, $P = 0.045$) compared to women [23].

The estrogen dysregulation has been associated with disease severity and acceleration of lumbar facet joint damage in arthritis [25, 26]. Added to this, some disorders of the reproductive system seem to increase the risk to develop RA, for example, physician-diagnosed polycystic ovary syndrome (RR 2.58; 95% CI, 1.06–6.30) and endometriosis (RR 1.72; 95% CI, 0.93–3.18) [27, 28]. Suggesting an important role of sex hormones and menstrual cycle regulation as risk factors associated with autoimmune diseases.

These differences could be attributed to the fact that women respond after immunization with a more exacerbated antibody production and an increase in cell-mediated responses. Thus, female patients show higher CD4+ T-cell counts, higher levels of IgM, and T-helper 1 (Th1) cytokine production [29]. This suggests that differences in immune response could be mediated by the hormonal ratios observed during pregnancy and postpartum in women with RA.

There is an increased risk of RA worsening or new onset of disease especially after the first trimester postpartum (**Table 3**), where several immune and hormonal changes are detected like: elevation of monocyte-related transcripts [30], decrease in corticosteroids, estrogen, progesterone, IL-4, IL-10, and humoral immunity, and increase of TNF-α and IFN-γ [31]. These postpartum flares occur within the first 4 months in most patients with chronic RA [32, 33], even a 62% had more affected joints at postpartum; these results were similar when the analysis was restricted to tender joints only [32]. Aggravation of disease activity (in 6 of 9 patients with RA)

Reference	Year	Features men	Features women	Main findings
BARFOT [22]	2007	DAS28 = 5.09 CRP 27	DAS28 5.37 CRP 18	Women had a much lower remission rate than men, although their disease activity before treatment seemed similar
AIR [23]	2014	DAS28 = 5.6 CRP 32 ERS 34 CCP positives 80.7%	DAS28 5.6 CRP 28 ERS 33 CCP positives 74.7%	At 12 months, men achieved remission more frequently (18% vs. 12%, P = 0.045). In anti-TNF failure, remission rates were higher in men than in women
QUEST RA n = 6400 [24]	2009	DAS28 = 3.8 ESR 23 HAQ = 0.8	DAS28 4.3 ESR 30 HAQ = 1.1	30% of men and 17% of women in QUEST-RA were in DAS28 remission
AIR n = 1709 [23]	2014		Lower frequency of anti-CCP (P = 0.03) Lower CRP (P < 0.001)	Female had longer disease duration At 12 months, men achieved remission more frequently (18% vs. 12%, P = 0.045)

Table 2.
Baseline and remission characteristics of RA in men vs. women: comparison of different clinical characteristics of female RA patients compared to male RA patients and the difference in remission rates documented on various studies.

Reference	Period evaluated after delivery (months)	Percentage/fold increase of RA onset
Oka [35]	<6	9.7%
	6–12	2.7%
Del Junco et al. [36]	N.E.	5 fold
Nelson et al. [37]	<6	9.7%
Iijima et al. [33]	12	0.08%
Silman et al. [38]	3	5 fold onset
Ostensen et al. [34]	3–6	66.6%

Table 3.
Percentage of healthy subjects who presented RA onset after delivery or post-partum.

was detected at 6 and 12 weeks postpartum as a progressive decrease in leucocyte counts and increased CPR, whose levels where normal during pregnancy [34]. In the "Pregnancy induced Amelioration of Rheumatoid Arthritis" (PARA) study, 118 patients were followed up until 26 weeks postpartum and levels of autoantibodies anti-CCP, IgM-RF, IgG-RF, and IgA-RF were measured. The median levels of autoantibodies during pregnancy were stable and declined postpartum. When hemodilution was taken into account, an increase in the levels of antibodies explains the symptom onset as well as the start of symptoms due to inflammatory processes directly related to immunoglobulin actions [8].

These dramatic postpartum changes can explain why there is a three to fivefold increased risk of onset during the first 3 months postpartum, with the highest risk being after a first pregnancy [38], in the cohort of Iijima composed by 2547 patients, and the same results were obtained [33]. The available studies on pregnancies in women with RA suggest that outcomes are worse than in the general population [39].

Such RA onset coincides with hormonal changes in the postpartum period, and only the changes during postpartum contribute to RA. During breastfeeding prolactin [40] by itself increases the antibody production and pro-inflammatory cytokines [41] and after the first pregnancy the risk of RA increases several times [42]. An additional link between sex-hormones and increased risk of RA come from data showing that the administration of drugs for lactation suppression which mainly are high-dose estrogens, increased risk of RA development [26]. Given that several cytokines are regulated by estrogens, so a decrease in this hormone could be responsible for flare and disease onset as it contributes to the activation of the immune system necessary for the delivery [43].

Estrogen seems to orchestrate several key features of the immune response and may be a critical factor in the incidence and severity of the disease in women. Small variations in estrogen concentration can have a very wide range of effects, even some of them could be opposite even when they are provoked by the same molecule.

3. Influence of reproductive cycle hormones and their role in RA immune response

3.1 Arthritis and menstruation

Since 1980, it was noted that young women with rheumatoid arthritis (RA) report an exacerbation of symptoms just before or at the time of menstruation, it

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

immune cells and circulating estrogens might also have an effect on RA onset on these late menopausal women [26].

4. Molecular aspects of estrogen effects in immune response

4.1 Regulation by estrogen receptors

ERα (NR3A1) and ERβ (NR3A2) that are encoded by ESR-1 and ESR-2 genes expressed on human chromosomes 6 and 14, respectively [62]. It is estimated that both receptors regulate 40% of the genes in cell line U2OS [63], but despite both are estrogen receptors (ERs), ERα and ERβ microarray analysis had demonstrated that they regulate different genes [7, 64, 65]. The activation of one or other of these ERs has specific effects in distinct, non-overlapping or even antagonist effects determined by factors like distribution, expression, dimerization, splice variant ER isoforms, signaling pathways triggered, physiological stage, and interaction with specific co-activators/−repressors [62]. One example of the distribution of these receptors is given in T lymphocytes, CD4+ cells which have higher ERα levels, B cells have higher ERβ expression than ERα and CD8+ cells have lower expression of both receptors [66], murine splenic DCs express ERα but has negligible ERβ expression and bone marrow-derived and peritoneal macrophages also express ERα and few if any ERβ [67, 68], so given the expression, lower or higher concentrations of estrogens will be needed to activate the receptors with the lowest expression [69].

In general terms, the effect of ERα on the immune system is more prominent than ERβ due to regulating multiple NF-kB pathway members to control cytokine responses. This, given that ERs are ligand-dependent transcription factors that mediate long-range chromatin interactions and form complexes at gene regulatory elements, thus promoting epigenetic changes and transcription [70]. Also, its promotion of strong antigen-specific Th1 cell responses was demonstrated in ERα-deficient mice where E2 effects on Th1 responses were not observed [71], apart from but this receptor is not only delimited to the cells at periphery, its expression seems to have effects in the thymus and spleen since deletion of ERα led to hypoplasia of both organs and contribute to the increased frequency of immature CD4 + CD8+ thymocytes and decreased CD4 + CD8− cells [72].

4.2 Estrogen dose and receptor dependent effects

As mentioned previously, estrogen receptors (ER) are expressed in the immune cells; TaqMan RT-PCR analyses indicate that in CD4 + T-helper cells express higher concentrations of ERα, B cells ERβ, and CD8+ T cells; monocytes express both ERs at lower concentrations [66]; this proportion is important because despite both receptors are present in all PBMCs, the functions elicited by their activation vary depending on the proportion of each receptor on such cells. A wider description of such differential effects is made for several cell types:

T cells: CD4+ T responds to E2 administration at low physiological levels (of 60–100 pg/ml in castrated female mice) increasing antigen specific responses, production of IFNγ and IL2 as well as inducing FoxP3 positive Treg cell differentiation [71, 73–75]. During the reproductive cycle CD4+, T cells increase on preovulatory (late follicular) [76], decrease in the luteal phase (60–150 pg/ml) compared to the early follicular phase (30–100 pg/mL) [77] and increased in the first trimester of pregnancy (8.9%, vs. 4.4% of controls) and 6–8 weeks following delivery [78]. Regarding CD8+ T cells, there is not much evidence, in models of collagen-II induce

RA, CD8+, lymphocytes were significantly diminished in the spleen of the estradiol-treated animals and were suppressed in the thymus [79].

Fibroblast-like synoviocytes: on FLS (**Figure 1**), estrogens induce an increase of MMP invasion of cartilage when these cells were transfected with ERα, thus estrogen levels can influence joint erosion degradation of extracellular matrix [80]. Regarding this antecedent, an increase in hormonal levels at synovia could influence cytokine levels but it is not clear if the effects of estrogen upon certain cytokines like TNF-α, IL-10, and IL-6 are unidirectional or could be an initial trigger of aromatase activity. For example, TNF-α, IL-1, and IL-6 stimulate fibroblast aromatase activity in a dose-dependent manner; the aromatase enzyme complex is involved in the peripheral conversion of androgens (testosterone and androstenedione) to estrogens (estrone and estradiol, respectively) [81].

B cells: concentrations of E2 ranging 75 pg/ml or above activate ERs, leading to an upregulation of CD22, SHP-1, BCL-2, and V-CAM-1. This can alter the survival of immature B cells that would normally be deleted [82]. Also a decrease in transitional B cells and increased marginal zone B cells [83] has been observed. In the presence of estrogen, BAFF increased its expression by 5-fold, but this characteristic was more pronounced in cells isolated from women than in those from man [84]. An overexpression of BAFF in transgenic mice leads to manifestations of autoimmune disease [85], and similar BAFF increase has been reported in the serum of patients with RA, [86] even at early stages of RA and correlates with the titers of IgM rheumatoid factor and anti-cyclic citrullinated peptide autoantibody (R = 0.76 and R = 0.49) [87]. It has been hypothesized that high levels of estrogens during pregnancy could prevent B cell apoptosis and therefore enhance survival of autoreactive cells [88]. Implications of estrogen signaling on auto reactive B cell expansion and autoantibodies production have not been evaluated in the clinical setting.

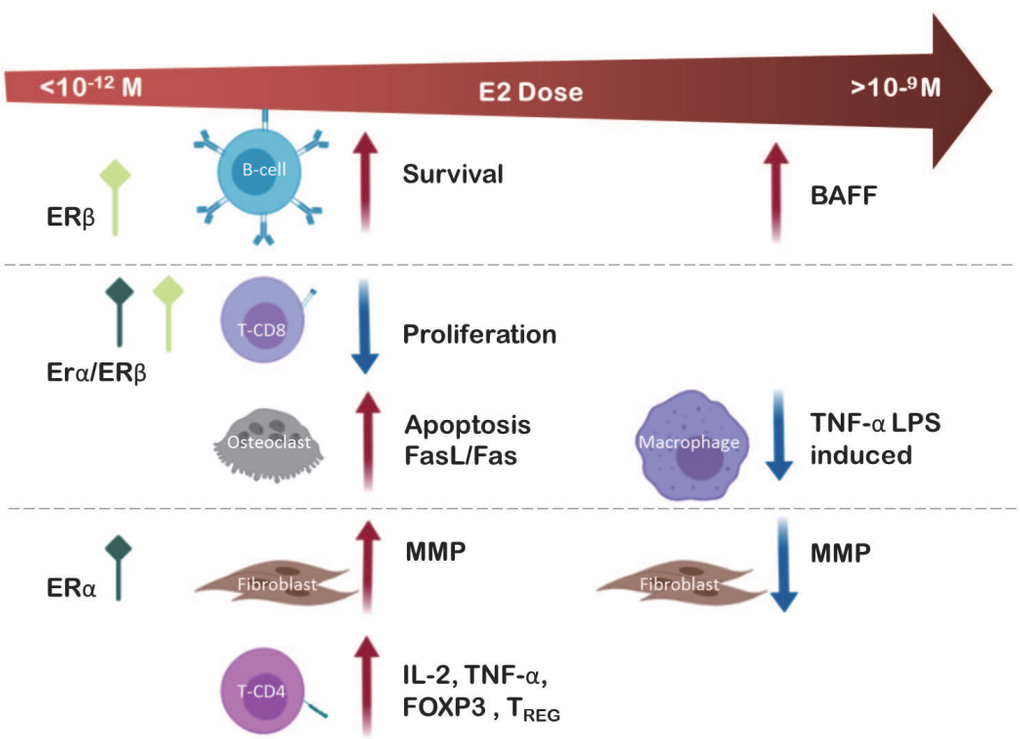

Figure 1.
E2 cell receptors in different cell populations: different effects of estrogen concentrations upon estrogen receptors ER-α and ER-β present on each cell. Left: receptors and cells were they are present. Horizontal red arrow: gradient of estrogen concentrations. Blue arrows: decrease of an effect by estrogen concentration. Red arrows: increase of an effect by estrogen concentrations. This is an original image made explicitly for this publication and not subject to copyright.

Another field with scarce exploration and understudied outcome of the estrogen therapy on RA is the modification and decrease of autoantibodies by estrogen action. This novel mechanism is not clearly elucidated and a lot of investigation in this topic is needed, but the little existing evidence demonstrate that estrogens can influence antibodies production and activity by modification of glycosylation of antibodies like galactosylation of human IgG in healthy individuals [89]. The changes in immunogenesis of antibodies by estrogens was demonstrated in an experiment were the induction of anti-C11 autoantibodies was measured, lower anti-C11 levels were observed in the estrogen treated group as compared with their controls [90]. The same behavior was observed by Nielsen et al. [91] and further investigations demonstrated than on CIA models sustained levels of 0.36 mg of estradiol (comparable to estrus phase) had similar quantities of IgG anti-CII antibodies than controls but have not developed RA, this was due to the different Ig subclasses. Estradiol-treated mice produced more IgG1, and mice from the placebo group produced significantly higher levels of IgG3 [92]. Other changes that estrogens induce in autoantibodies are an increase in sialylation, which has been observed during pregnancy and within 3 months post-delivery (when RA risk is presumably higher) [93]. Antibodies sialylation affects inflammation; in the case of RA, the transition from preclinical asymptomatic autoimmunity to clinical phases is associated with a change in the sialylation of antibodies [94–96]. Changes in sialylation by estrogens have been explored already in RA patients. E2 treatment increases sialylation on postmenopausal RA women [97], so taken together if E2 induces anti-inflammatory IgG by inducing St6Gal1 expression in antibody-producing cells [98].

4.3 Estrogen effects: dependency on concentration and chemical modifications

Estrogen concentration: it seems to exist a cut-off point in the concentration of estrogens that determine different effects, because sensitivity of receptors even at sub physiological concentrations of estrogens. For example, in a model of collagen-induced arthritis (CIA) in female mice, after type II collagen (CII) immunization those treated with the ER antagonist ICI 182,780 (which binds to both ERα and ERβ but not to the surface receptor) doses that insufficient to block estrus cycle, were sufficient for block the E3-mediated suppression of CIA [99, 100]. On the range of higher concentrations, estradiol (E2) can inhibit the production of pro-inflammatory cytokines, like TNF-α, (IL)-1 β, and IL-6 and induce anti-inflammatory cytokines such as IL-4, IL-10, and TGF-β (Th2 phenotype). On the contrary, low concentration of E2 stimulates TNF, INF-γ, and IL-1 β production and exerts an inhibitor effect on NK cells [101, 102]. In brain tissue, it was demonstrated that 2-OH-estradiol protects neurons from oxidative stress at nanomolar concentrations (10 nmol/L) but 17-β-estradiol showed oxidative effects only at micromolar concentrations (1–10 μmoI/L); these concentrations were in the order of magnitude expected to activate their receptors (10–1000 nmol/L) demonstrating that physiological levels of estradiol may protect through receptor-dependent mechanisms from mitochondrial ROS, whereas higher concentrations may act through independent ER mechanisms [103]. This wide range of dose dependent effects could suggest us that a difference exists in the actions of estrogens between reproductive organs and its effects in the immune system. With respect to pro inflammatory cytokines such as TNF-αβ IL-1 and IL-6, estrogen effects seem to be bimodal where pharmacological concentrations (**Table 3**) of 50,000–100,000 pg/ml (equivalent to 100 μg/L or 10^{-6} M) decrease or inhibit the cytokine production and physiological concentrations of 5000 pg/ml increase cytokine production [104, 105]; this agree with other results where macrophages treated with doses of 0.001–100 nM

(10^{-9} M) equivalent to therapeutic concentrations of estradiol for 24 reduced LPS-induced TNF-α production [106]. Despite all evidence there is no clear explanation about how estrogens (estradiol or estriol) interfere in the clinical outcomes and immune response in RA depending on ERα/ERβ or evidence of the effects associated to a certain dose range. This could be useful for the development of more selective ERα or ERβ agonists and antagonists.

Estrogen chemical modifications: as mentioned before, a correlation exists between estrogen concentration in synovial fluid and serum estrogens ($R = 0.79$, $P < 0.0003$), and concentration of free estrogens (E2) is higher in RA as compared to controls [13–15]. Therefore, measured estrogen concentration in synovia could reflect a general overview of estrogen body concentrations. There is a significantly higher level of androstenedione (a precursor of estrone and estradiol) in synovial fluid of RA patients as estrone (E1), suggesting that these higher levels are the result of an elevated activity of aromatase [14]. Available steroid pre-hormones are rapidly converted to estrogens, which seems to have pro-inflammatory activity in the synovial tissue. When analyzed more in detail, it was found that increased estrogen concentrations in RA synovial fluid (in women as in men) were 16α-hydroxyestrone and 4-hydroxyestradiol (hydroxylated forms), while the estrone levels were detected increased on RA patients, the 2-hydroxyestrone showed no differences comparing RA vs. healthy controls [14], and depending on its modifications, estrogens can trigger very different effect in the body. For example, the hydroxylated forms of estradiol, 16OH-E2 and 2OH-E2 enhance the proliferation of THP-1 (**Figure 2**) monocytes at high concentrations (10^{-9} M). Meanwhile, the hydroxylated estrones 4OH-E1 and 2OH-E1 enhance cell proliferation at low concentration (10^{-10} M), [107], which are inhibited by antiestrogen drugs [108], except for 2OH-E1, which still induced proliferative effect (10^{-10} M) [107]. In some cases, estrogens produce the same affect but have different target cells in a dose dependent manner because of the proportion of expression of ERs; E2 and endocrine disrupting chemicals (EDCs) affect cell mutagenesis through ERα. At 10–8 M is observed an inhibition on the mitogenesis of B cells and at 10–6 M in T cells. For the EDCs

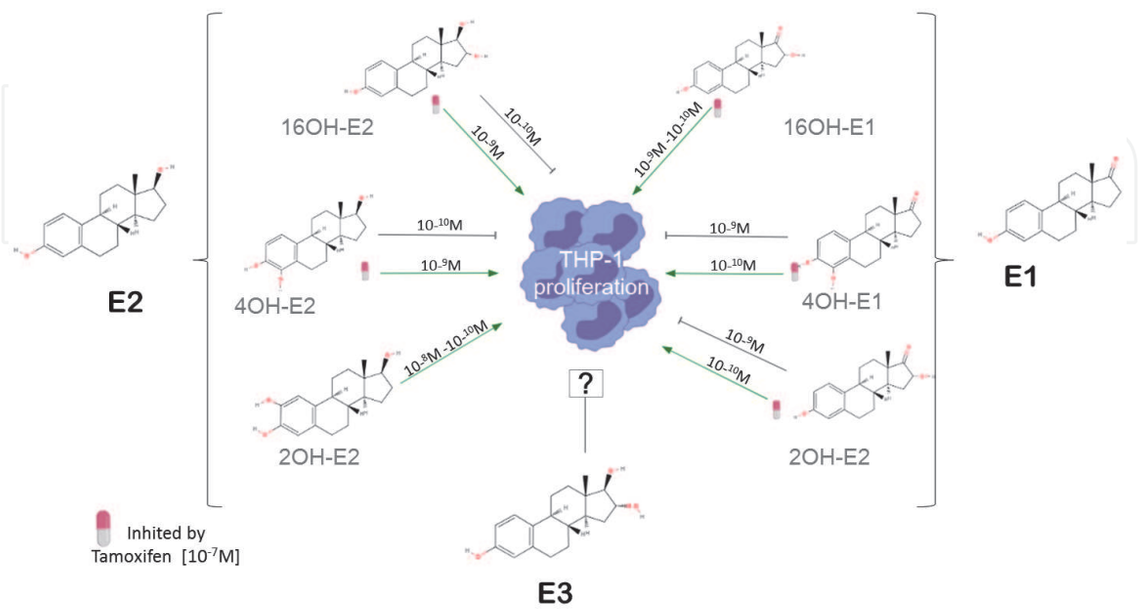

Figure 2.
Estrogen modifications and concentrations: image showing the differences between the effects depending of the estrogen modifications. Activity of different estrogen modifications upon proliferation of THP-1 cells and concentrations needed for achieve the effect. Green lines: increase in proliferation. Red lines: decrease in proliferation. This is an original image made explicitly for this publication and not subject to copyright.

(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 ERα or ERβ 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 ERα. For example in EAE homozygous ERαKO 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, IFNγ, IL-2, and an increase in levels of the Th2 cytokine IL-5 [110]. The effect of estrogens at interact with ERα 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 ERα-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 ERα 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% ($P < 0{\cdot}01$) [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 $\chi 2 = l5.0$, ($p < 0.01$) but the current users $\chi 2 = 0–85$, ($p > 005$) 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].

wIn 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. ERB-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, 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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