

Estrogen and Autoimmune Disease

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Abstract Estrogenic hormones possess both immunostimulating and immunosuppressive properties. In systemic lupus erythematosus (SLE), pregnancy is associated with disease flares. In some situations, exogenous estrogen predisposes to development of new SLE, flares of preexisting SLE, and thromboses in susceptible individuals. In contrast, treatment with exogenous estrogen protects postmenopausal rheumatoid arthritis (RA) patients from active RA and osteoporosis. The search for estrogen-like compounds with anti-inflammatory properties may expand treatment options in RA.

Keywords Autoimmunity · Estrogen · Systemic lupus erythematosus · Rheumatoid arthritis · Sjogren's syndrome · Multiple sclerosis

Hormones and the immune system interact through a number of pathways, and understanding the interdependence of these systems is important in order to appreciate the pathogenesis of autoimmune disease. It is currently recognized that estrogen is an important immunomodulator with significant effects on cell proliferation, cytokine production, and differentiation of hematopoietic cells [1–5]. Estrogen is a transcriptional regulator that activates estrogen receptors which then translocate to the nucleus and bind to estrogen response elements in gene promoters [6]. Estrogen's effects on the immune system appear to be regulated differently through the two types of estrogen receptors,

alpha and beta. Lack of the alpha receptor in C57BL/6J/129 mice resulted in anti-dsDNA antibodies and mild glomerulonephritis [7], whereas disruption of the alpha receptor gene in autoimmune NZB/NZW mice resulted in attenuation of anti-dsDNA antibodies in females and increased longevity in males [8].

This review will discuss the influence of estrogens on systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). These autoimmune illnesses are of special interest because they are affected differently by estrogenic hormones. Identifying the stimulating and suppressive properties of estrogen affords the opportunity to design effective and relatively nontoxic treatments for these incurable diseases.

Box 1. Estrogen and systemic lupus erythematosus

Estrogen effects are mediated by the alpha receptor
Serum estrogen is below the norm in 25%
Abnormal estrogen metabolism in SLE
Reproduction in SLE:
 Normal fertility
 Conventional oral contraceptives safe
 New SLE, flares associated with reproductive events
 Ovulation induction promotes SLE onset, flares
Postmenopausal hormone replacement
 No increased flares
 Danger of thrombosis
Raloxifene prevents osteoporosis without stimulating flares

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Systemic lupus erythematosus

Human SLE has a predilection for females of child-bearing age [9] and may appear or exacerbate when serum

concentrations of reproductive hormones are elevated and when hormones are undergoing rapid change. Disease flares were increased in the 2-week period before onset of the menstrual period [10], and flares were decreased in number following natural menopause [11] or ovarian failure induced by cyclophosphamide therapy [12]. Costenbader et al. [13] reviewed the Nurse's Health Study and concluded that reproductive factors associated with increased risk for SLE were early age at menarche, use of oral contraceptives, and early menopause, surgical menopause, and postmenopausal hormone replacement.

In patients with preexisting SLE, lupus flares increased during pregnancy [14], but numbers of pregnancies and live births during a woman's lifetime did not predict an increased probability of developing lupus *de novo* [15]. A shift away from Th1 responses and towards Th2 responses occurs during normal pregnancy and is important in maintaining the intact fetal-maternal unit. Estrogen in high concentrations, or estrogen acting in concert with other reproductive hormones, is believed to stimulate increased Th2 cytokines during gestation. This response would be desirable in a normal pregnancy. In the SLE patient, excessive Th2 responses could lead to increased production of autoantibodies and activated disease [16]. This theory has been brought into question [17] based upon a study in which estrogen concentrations did not increase during the second and third trimesters of lupus pregnancies. The abnormal response was thought to result from damage to the placenta or abnormal steroid metabolism in the placenta.

Autoantibodies and rheumatic symptoms have been reported in previously healthy women taking combination oral contraceptives with a high content of synthetic estrogen, but other studies showed no new evidence of autoimmune disorders in women taking estrogen-containing contraceptive pills. The current practice of using smaller doses of estrogen ($<50\text{ }\mu\text{g}$) in combination pills probably accounts for the apparent decrease in lupus-like side effects noted in the past three decades [14].

Based on the findings that estrogen-containing oral contraceptives could stimulate autoantibodies, the question arose that using the pills could give rise to new SLE. Sanchez-Guerrero [18] did find that oral contraceptives were associated with a small risk of *de novo* SLE in a cohort of women in the Nurses' Health Study who were followed every 2 years (1976–1990). When oral contraceptive users were compared with those who never used oral contraceptives, the relative risk for developing SLE was 1.9. In metropolitan Philadelphia, however, oral contraceptives were not associated with new-onset SLE in patients diagnosed between 1985 and 1987 [19].

The possibility that combination oral contraceptive pills would activate preexisting SLE was addressed in the

prospective multicenter Safety of Estrogens in Lupus Erythematosus-National Assessment (SELENA) trial, in which 183 women with inactive or stable active disease took either oral contraceptive pills containing triphasic ethinyl estradiol, $35\text{ }\mu\text{g}$, plus norethindrone, 0.5 to 1.0 mg, or placebo for 1 year. Severe lupus flares occurred in 7.7% of women taking oral contraceptives compared with flares in 7.6% of controls, and it was concluded that oral contraceptives did not increase the risk of flare in women with stable SLE [20]. In another study, 162 women with SLE were assigned randomly to combined oral contraceptive pills, progestin-only pills, or a copper intrauterine device. Severe flares occurred, respectively, in 4%, 10%, and 5% of subjects in each group [21].

Routine use of hormone replacement therapy after the menopause is not recommended by the US Preventive Services Task Force [22] because "the harmful effects of combined estrogen and progestin are likely to exceed the chronic disease prevention benefits in most women." Earlier reports of women taking estrogen after the menopause did suggest that hormone replacement predisposed to developing SLE. Women in the Nurses' Health Study who had taken hormone replacement had an increased risk of developing SLE *de novo*, and the risk was positively related to duration of therapy [23].

Postmenopausal hormone replacement was thought to stimulate preexisting lupus in isolated cases [24]. Two recent studies with small groups of subjects showed no significant increase in lupus activity but suggested that thrombosis was a hazard [25, 26]. The SELENA trial affirmed that postmenopausal hormone replacement (0.625 mg of conjugated estrogen daily, plus 5 mg of medroxyprogesterone 12 days a month) contributed to flares of SLE. Severe flares were observed in 7.5% of women receiving hormone replacement and 4.5% of the placebo group, but the difference was not significant. In contrast, 59% of hormone-treated SLE patients had mild to moderate flares with an overall incidence rate (taking into account multiple flares of any type) of 1.25 flares per person-year. Flares did occur in 50% of patients taking placebo, but the incidence rate of flares was significantly lower (0.93 flare per person-year, $p=0.006$) [27]. The trial was stopped in 2002 after all 351 patients were enrolled, based upon results of the Heart and Estrogen/Progestin Replacement Study [28] and the Women's Health Initiative trial [29], showing that patients receiving replacement estrogen-progestin replacement were at risk for severe vascular incidents.

The hazards of assisted reproduction in the setting of SLE may be associated with the very high concentrations of circulating estrogen stimulated by hormonal manipulation. Ovulation induction (OI) increased circulating estradiol to ten times the concentration found in nonpregnant women,

and OI was associated with new-onset SLE in at least five women (reviewed in [14]). In women with established SLE, OI appeared to cause moderate flares [30] and a fatal exacerbation of SLE [31]. Increased lupus activity was observed in 25% of OI/in vitro fertilization cycles in SLE patients, and 13% were complicated by the ovarian hyperstimulation syndrome [32]. In another series, the rate of lupus flares was higher after gonadotropin induction (27%) compared to clomiphene induction (6%) [33].

The mean age of menarche was delayed in young women with SLE (13.5 years) compared to healthy adolescents (12.5 years), but most young women with SLE had normal ovarian function and were expected to be fertile [34]. Lupus was not associated with abnormally high levels of estrogen. In fact, 25% of 94 women with SLE had reduced estrogen levels [35]. Metabolism of estrogen, however, was abnormal in SLE. In women with SLE, metabolism of estradiol-17 β and estrone was shifted to favor production of 16-hydroxyestrone and estriol, and these metabolites were increased significantly compared with normal women. The 16 metabolites are potent mitogens that have the potential to stimulate inflammation [36]. In men with SLE, imbalances in estrogens and androgens could contribute to increased susceptibility to active disease. Estradiol levels have been reported to be increased, normal, or low in male SLE patients. Males with lupus had elevated serum 16-hydroxyestrone and estrone concentrations [14].

Current knowledge of the immunostimulating properties of estrogens has led to attempts to treat SLE by hormonal manipulation. Diet was used to treat NZB/NZW mice that spontaneously develop SLE. Indole-3-carbinol is abundant in cruciferous vegetables and can shift estrogen metabolism away from mitogenic 16 α -hydroxyestrone towards less estrogenic metabolites. When indole-3-carbinol was fed to female NZB/NZW mice soon after weaning, 80% of treated mice were alive at 1 year of age compared to 10% of controls [37]. Inhibitors of estrogen have also been successful in treating murine models of lupus. The selective estrogen modifier (SERM) LY139478 increased survival in autoimmune MRL/*lpr/lpr* mice [38], and the SERM, tamoxifen, suppressed autoimmune disease in NZB/NZW females [39] and prevented autoimmunity in the estrogen-sensitive R4A- γ 2b BALB/c transgenic mouse model [40]. The aromatase inhibitor 4-hydroxyandrostenedione, which blocks conversion of androgen precursors to estrogen, suppressed glomerular inflammation in autoimmune MRL/Mp-*lpr/lpr* mice [41].

Estrogen-limiting treatments have produced varied results in treating human SLE. In the era before corticosteroids, improvement was noted after surgical removal of the uterus and ovaries or treatment with testosterone.

Irradiation of the ovaries, however, did not change the course of disease [42]. Aromatase inhibitors are used widely as adjuvant treatment for breast cancer. This class of drugs would appear to be useful for treating SLE. Instead, aromatase inhibitor treatment of breast cancer patients resulted in autoimmune syndromes. Twenty-four women taking aromatase inhibitors were referred for rheumatological evaluation because of joint pain. Pain in multiple joints and synovitis of the proximal interphalangeal and metacarpophalangeal joints were found in 79% of cases, 67% had sicca symptoms, and one (4%) had definite Sjogren's syndrome. Nine patients were positive for antinuclear antibodies [43].

Routine long-term hormone replacement with estrogen and progesterone is no longer advised for postmenopausal women whether or not SLE is present [22], and some patients resort to alternative treatments such as over-the-counter phytoestrogens, which should be viewed with concern. A 55-year-old SLE patient with partial reduction in protein S, taking prophylactic aspirin, developed retinal vein thrombosis 3 days after starting a preparation of black cohosh, dong quai, red clover, and wild Mexican yam [44].

Other forms of estrogen treatment have been attempted in the postmenopausal lupus patient in order to address the problem of osteoporosis. Transdermal estrogen (50 mg 17 β -estradiol) was given to 15 postmenopausal SLE patients for a period of 1 year. Lumbar spine density was preserved, and there were no lupus flares. Notable, however, was the dropout rate of 53% [45].

Treatment with SERMs was beneficial for treating lupus-like disease in autoimmune mice but was not successful in treating human SLE. Tamoxifen was given to 11 women with stable SLE in a crossover trial. Two subjects deteriorated, and there was no improvement in clinical or serologic indices of disease activity [46]. Raloxifene prevented osteoporosis in patients with inactive SLE over a period of 12 months. Mild and moderate flares occurred in 25% of treated patients compared to 35% of controls, and it was concluded that raloxifene did not adversely affect lupus activity [47].

The amount of alpha estrogen receptors on T cells from lupus patients appeared to be less than T cells from normals [48], and specific polymorphisms of the alpha estrogen receptor gene have been associated with the age of SLE onset [49] and severity of disease [50]. Estrogen receptors were targeted in a recent experiment in which the selective estrogen receptor antagonist, fulvestrant, was given to ten premenopausal SLE patients in 12 monthly intramuscular injections. SLEDAI-assessed disease activity improved significantly, and the mean dose of prednisone decreased from 5.75 to 2.5 mg daily (not significant) [51].

Box 2. Estrogen and rheumatoid arthritis

Stimulatory effects of estrogen not established
Serum estrogen concentration elevated
Estrogen increased in synovial fluid
Reproduction in RA:
Oral contraceptives retard progress of mild RA
Pregnancy protects against RA activity
Exogenous estrogen, no increase in flares
Postmenopausal hormone replacement
RA improved, osteoporosis decreased

Rheumatoid arthritis

The role of estrogen and its metabolites in the pathogenesis of RA is open to question, as estrogenic hormones have properties that can both suppress and stimulate chronic inflammatory arthritis. In experimental models of rheumatoid arthritis, estrogen had beneficial effects. Estrogen protected against development of collagen-induced arthritis in DBA/1LacJ mice and Lewis rats [52], and the naturally occurring antiangiogenic estrogen metabolite, 2-methoxyestradiol, was protective in LOU rats [53].

The role of estrogen in human RA is controversial [54, 55]. RA is typically more common in women compared to men, and RA in women may be more severe. The QUEST-RA multinational study cohort of 6,004 RA patients was 79% female, and women had higher disease activity scores than men [56]. Serum 17beta-estradiol concentrations in 13 postmenopausal women with long-standing RA were significantly higher compared to controls [57].

Inside rheumatoid joints, elevated levels of estrogen may influence inflammation directly. In women and men with RA, the concentration of estrogen in synovial fluid from knee joints was 2–2.5 times greater compared to osteoarthritis patients of the same sex [58]. The hydroxylated metabolites of estrogen, 16-hydroxyestrone and 2-hydroxyestradiol, stimulated proliferation of human monocytes *in vitro* at both low and high concentrations [59]. It has been proposed that intra-articular monocytes, which carry both alpha and beta estrogen receptors [60], become stimulated inside RA joints and contribute to synovial inflammation and hyperplasia [52].

Paradoxically, clinical RA in humans is suppressed by estrogen. Women with RA are protected from disease activity during pregnancy, a benefit that may be regulated by excessive estrogen or by the presence of the pregnancy steroid, estriol, which predominates through much of gestation [52]. The Royal College of General Practitioners reported in 1978 that the oral contraceptives of that era

protected women from developing RA. A meta-analysis that included the Royal College report, plus six additional case-controlled studies and two prospective studies, suggested that oral contraceptive pills did not protect against developing new RA but instead prevented mild disease from progressing to severe disease [61].

Hormone replacement had beneficial effects on postmenopausal osteoporosis in RA, without activating the underlying rheumatic disease. Results of two trials published in 1994 emphasized that hormone replacement therapy did not flare RA [62, 63]. In 40 postmenopausal RA patients, treatment with transdermal estradiol twice weekly plus norethisterone tablets when clinically indicated resulted in increased lumbar spine bone mineral density. In addition, the Nottingham Health Care Profile and the articular index improved significantly between entry and the end of the 48-week treatment period [62]. Another group of 77 postmenopausal women with RA received transdermal estradiol, 50 µg daily for 6 months, without evidence of deterioration. Patients with the highest concentrations of serum estradiol had improved articular index and pain index compared to controls [63].

A longer period of treatment was tested by Forsblad d'Elia and associates [64] in 88 women with active RA who were randomized to take hormone replacement plus vitamin D3 plus supplemental calcium or vitamin D3 and calcium alone for 2 years. The 41 women in the hormone replacement group received one of three replacement protocols: estradiol 2 mg plus noretisterone acetate 1 mg daily, estradiol cycled with noretisterone, or (in women with a previous hysterectomy), estradiol only. During hormone replacement, the erythrocyte sedimentation rate was suppressed, the Disease Activity Score decreased, and progression of bone destruction was retarded [64]. Hormone replacement was associated with significantly increased insulin-like growth factor I and decreased soluble IL-6 receptor [65], but standard measures of humoral and cell-mediated immune responses were not affected [66].

Whereas a 2-year period of hormone replacement was beneficial for RA, the risks of hormone treatment in a population predisposed to coronary heart disease [67] preclude long-term replacement with estrogen and a progestogen for the majority of postmenopausal RA patients [22, 27, 28]. Interest has turned to estrogen receptor modifiers and estrogen receptor ligands to treat osteoporosis and modify RA. Ovariectomized mice with established collagen-induced arthritis responded favorably to treatment with raloxifene, showing sustained suppression of arthritis progression and failure to develop new joint involvement. Treated mice were deprived of estrogen and had inflammatory disease, yet bone mineral density was sustained [68]. New compounds are being investigated that bind selectively to alpha or beta estrogen receptors or act outside traditional pathways and capture the beneficial anti-inflammatory effects

of estrogen without stimulating cell proliferation in the breast and uterus [69, 70].

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