



Estrogen, progesterone, and testosterone: Can they be used to treat autoimmune diseases?

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- **BACKGROUND** Sex hormones have marked immunomodulatory properties and may play important roles in the etiology of various autoimmune diseases.
- **OBJECTIVE** To review the immunomodulatory effects of sex hormones, their roles in the etiology of autoimmune diseases, and their potential therapeutic applications.
- **DISCUSSION** Progesterone and androgens suppress the immune system, prolactin stimulates it, and estrogens can do either. Rheumatoid arthritis tends to improve during pregnancy, during estrogen replacement therapy, and during treatment with estrogen-containing oral contraceptives. Systemic lupus erythematosus is aggravated by pregnancy and probably by estrogens. Therapy of rheumatoid arthritis with estrogens has not been promising, but testosterone replacement in men has shown modest benefits. In lupus, 19-nortestosterone has had little or no benefit, but danazol has been helpful in some patients, and encouraging preliminary results were obtained with dehydroepiandrosterone.
- **CONCLUSIONS** We strongly recommend estrogen replacement therapy to prevent postmenopausal osteoporosis in women with rheumatoid arthritis. Younger women with rheumatoid arthritis can undergo pregnancy or use estrogen-containing contraceptives. Estrogens can be used in lupus only with great caution. Recommendations regarding other hormones and other diseases are less firm, but research is continuing in this area.

■ **INDEX TERMS:** SEX HORMONES; AUTOIMMUNE DISEASES; IMMUNE SYSTEM
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MANY RHEUMATIC diseases show marked gender predilections, suggesting that sex hormones play a role in the multifactorial etiopathogenesis of rheumatoid arthritis, systemic lupus erythematosus (SLE), Takayasu's arteritis, scleroderma, and other such diseases. Moreover, many sex steroids possess powerful immunoregulatory and anti-inflammatory properties, suggesting that the underlying immunological processes and the resulting inflammatory activity may be modulated by sex steroids.

As a result of these observations, researchers are poised to achieve a more complete understanding of the etiology and pathogenesis of diseases such as rheumatoid arthritis and SLE through studies of immunoendocrinological function in humans and in animals. This understanding will help clinicians to predict whether a patient will get better or worse during states of natural or iatrogenic modulation of sex hormone status (ie, pregnancy, estrogen replacement therapy) and to use sex steroids as adjunctive therapeutic agents.

This review discusses the immunomodulatory properties of the

most prominent sex steroids, the role that sex steroids play in rheumatoid arthritis, SLE, scleroderma, and other diseases, the current recommendations for treatment with sex hormones, and possible future applications of these compounds.

IMMUNOLOGICAL EFFECTS OF SEX STEROIDS

The varied immunological effects of sex steroids do not allow for simple generalizations. Furthermore, much of the data on these effects come from in vitro studies; the results of such research do not necessarily apply to in vivo functioning. Nevertheless, the following observations can be made, as outlined in *Table 1*.

Estrogens

Estrogens as a group have both immunosuppressive and immunostimulatory properties. Thus, in vitro studies have revealed that estrogens increase T-cell proliferation in response to allogeneic cells¹ and increase the number of plaque-forming cells (plasma cells) when B cells are activated with pokeweed mitogen.² In experimental animals, estrogen administration increases the number of CD4⁺ T cells³ and shortens the survival of bone marrow grafts.⁴ On the other hand, estrogens also decrease T-cell and natural killer cell responses⁵⁻⁷ and prolong survival of organ grafts in animals.⁸ Moreover, mitogen-induced T-cell proliferation in healthy women taking oral contraceptives containing ethinyl estradiol is significantly lower than in women not taking estrogens.⁹ Estrogens also down-regulate neutrophil function.^{10,11}

As an example of the complexity of the immunological effects of estrogens, Carlsten et al¹² showed that in MRL/lpr mice (a model of lupus), estrogen therapy increased polyclonal B-cell activation and raised the level of anti-DNA antibodies and circulat-

TABLE 1
IMMUNOMODULATORY PROPERTIES OF SEX HORMONES

Hormone	Action	Examples
Estrogens	Immunostimulatory	Increased mixed-lymphocyte reaction Increased plaque-forming cells Increased CD4 ⁺ cells
	Immunosuppressive	Decreased bone marrow graft survival Prolonged graft survival Decreased phytohemagglutinin antigen and concanavalin A responses Decreased natural killer cell function Decreased cell-mediated immunity Suppressed neutrophil function
Progesterone	Immunosuppressive	Decreased phytohemagglutinin antigen and concanavalin A responses Decreased immunity during pregnancy Increased CD8 ⁺ cells
Androgens	Immunosuppressive	Lowered resistance to viral infections Decreased phytohemagglutinin antigen responses Decreased immunoglobulin A expression Decreased gammaglobulin synthesis Decreased graft rejection
		Increased interleukin-2 Increased granulocyte-macrophage colony-stimulating factor (human) Decreased interleukin-4, interleukin-5, interleukin-6 (murine)
Dehydroepiandrosterone	Immunomodulatory	

ing immune complexes, leading to a more severe immune-complex glomerulonephritis. However, the same animals had *decreases* in T-cell-mediated periarthritic inflammation, renal vasculitis, and sialoadenitis. These results were interpreted as evidence that estrogens stimulate B-cell-mediated immunity but suppress T-cell-mediated immunity.

Classic studies^{13,14} have shown that humoral immune responses are stronger in female than in male mice. On the basis of the findings just mentioned, one could argue that estrogens mediate this effect. However, other factors such as genetic determinants encoded on the X or Y chromosome may also be implicated.

Progesterone

Less intensively studied than estrogens, progesterone tends to suppress the immune system. Thus, in vitro, progesterone down-regulates T-cell proliferative responses to mitogens.¹⁵⁻¹⁷ In vivo, the number of CD8⁺ T cells increases after administration of progesterone.³ Clement and associates¹⁵ have suggested that progesterone is responsible for the decreased immune responses observed during pregnancy. The natural role of this immune-suppressed state might be to facilitate the survival of the pla-

centa and fetus, which carry strongly immunogenic and allogeneic epitopes.

Prolactin

The immunological effects of prolactin have been reviewed by Buskila et al.¹⁸ and Jara et al.¹⁹ Prolactin increases levels of antibodies, expression of interleukin-2 receptors, secretion of interleukin-2,²⁰ and responses of T cells to mitogens *in vivo*.²¹ Thus, prolactin appears to mostly stimulate the immune system. Prolactin levels fluctuate with the menstrual cycle, are higher in pregnant women with SLE than in pregnant controls,²² and are elevated in men with SLE²³ and, possibly, also in a subset of women with SLE.²⁴ In rheumatoid arthritis and fibromyalgia, there is increased prolactin secretion in response to thyrotropin-releasing hormone,¹⁹ and in rheumatoid arthritis, the bioactivity of circulating prolactin may be reduced.²⁵ Although the diseases themselves may cause some of these abnormalities of prolactin regulation, abnormal levels of prolactin may contribute to autoimmune diseases.

Androgens

Androgens have been studied extensively, and almost all of their effects on the immune system are suppressive.²⁶ *In vitro*, androgens decrease proliferation of T cells in response to mitogens and decrease the production of gamma-globulin by activated B cells.^{27–29} The latter finding in particular could be important in the therapeutic application of androgens in antibody-mediated diseases. In animals, androgens decrease resistance to viral infection and allow organ grafts to survive longer.^{4,26} Androgens also down-regulate expression of major histocompatibility complex class II genes.³⁰

Various androgens may have different activities. Testosterone increases CD4+ T-cell proliferation after *in vitro* stimulation with interleukin-2.²⁰ The weakly androgenic adrenal steroid hormone dehydroepiandrosterone (DHEA) possesses a number of unique immunomodulatory properties. *In vitro*, DHEA causes activated murine T lymphocytes to secrete more interleukin-2 and less interleukin-4, -5, and -6.³¹ In human systems, T cells stimulated with anti-CD3 also secrete more interleukin-2 after *in vitro* DHEA treatment.³² Our own studies indicate that DHEA administration to human subjects may also increase granulocyte-macrophage colony-stimulating factor production by activated T cells (unpublished data). The precise significance of

these findings remains to be determined. Daynes and Araneo³³ have suggested that DHEA plays a role in directing CD4+ T-cell differentiation into the T helper type 1 or type 2 subsets. Type 1 cells secrete interleukin-2 and gamma-interferon; type 2 cells secrete interleukin-4 and interleukin-5.³⁴

Relaxin

Relaxin³⁵ reaches high serum levels in the third trimester of pregnancy.³⁶ It is considered responsible for cervical “ripening” and, at least in rodents, for loosening of the pelvic ligaments. Relaxin has important effects on collagen synthesis and metabolism³⁷ and may have a role in certain connective tissue diseases.

STUDIES IN ANIMALS

Sex steroids modulate various autoimmune and rheumatic diseases in animals. Thus, in the non-obese diabetic mouse, the incidence of autoimmune diabetes is much higher in females than in males. This sex predilection can be reversed by castration, hormone treatment in either gender, or both.³⁸ Testosterone protects against experimental autoimmune thyroiditis in rats.^{39,40} Likewise, estrogens aggravate streptococcal cell-wall-induced arthritis, but androgens ameliorate it.⁴¹ The SLE-like disease induced in non-lupus-prone mice by immunization with human anti-DNA antibody can be prevented by testosterone administration in female mice; in male mice, orchiectomy, estrogen administration, or both increase susceptibility to the disease.^{29,42} The dichotomous effects of estrogens in the MRL/lpr mouse model of lupus⁹ were described above.

In the most widely studied animal model of SLE, the NZB/NZW F1 mouse, the parental NZB strain shows late-onset, mild autoimmune manifestations, but the NZW strain is phenotypically normal. The F1 offspring, however, spontaneously acquire anti-DNA antibodies and membranoproliferative glomerulonephritis at age 3 to 6 months, leading to proteinuria and death by age 6 to 9 months. The disease develops earlier and at a higher frequency in female F1 mice than in males. It has been firmly established that this gender predilection is mediated by sex hormones. Thus, androgens protect against SLE in this model, and estrogens aggravate it.^{29,43,44} Hyperprolactinemia also develops after estrogen administration and may contribute to worsening of SLE.⁴⁴ DHEA at high dosages protects against SLE

in the NZB/NZW model,⁴⁵ but even in lower dosages some amelioration is seen.⁴⁶ In the latter setting, decreased spontaneous B-cell proliferation and increased interleukin-2 secretion follow DHEA treatment, provided such treatment begins before the age of 3 months.

The tight-skin mouse has allowed various endocrinological and immunological interventions for scleroderma to be studied in animals, unfortunately with few remarkable results so far.^{47,48} However, recent studies have suggested that relaxin may be of benefit in this model (Amento EP, personal communication, 1993).

CLINICAL OBSERVATIONS

Rheumatoid arthritis

Rheumatoid arthritis is three to four times as frequent in women as in men, and in women it tends to fluctuate in severity with the menstrual cycle.⁴⁹ Rheumatoid arthritis develops less frequently during pregnancy, but incidence increases in the postpartum period.^{50,51} This at-risk period lasts from 3 to 12 months postpartum. Similarly, the disease commonly remits during pregnancy but frequently relapses to pregravid severity in the postpartum period. It is not known if these changes are mediated by estrogens, progesterone, or specific protein hormones of pregnancy such as alpha-2-pregnancy-associated globulin,⁵² relaxin,³⁵ or prolactin. Moreover, cortisol levels increase during pregnancy. Thus, pregnancy is not contraindicated in patients with rheumatoid arthritis, although the practical problem of how to manage the arthritis medications deserves attention, as reviewed by Spector and Da Silva.⁵³ Similarly, nulliparity appears to be a risk factor for the later development of rheumatoid arthritis, although a weak one.⁵⁴

Men with rheumatoid arthritis may be relatively deficient in androgens, as demonstrated during flares of disease activity.⁵⁵ A small study of testosterone therapy in men with rheumatoid arthritis showed modest benefits (see below).⁵⁶

Whether oral contraceptive therapy protects against rheumatoid arthritis is controversial.⁵⁷ Some studies have found an overall protective effect,^{58,59} while others have found contraceptives to protect against rheumatoid arthritis only before age 35.⁵⁴ Women who were currently taking contraceptives were not protected in one study,⁶⁰ but they were in the much bigger cohort of Hazes and colleagues.⁶¹

The latter study also confirmed that the effect was greatest between ages 30 and 40 (which may correspond to peak onset) and showed that contraceptive use earlier in life protected against rheumatoid arthritis better than current use did. A meta-analysis of earlier studies also confirmed the modest protective effect of contraceptives in rheumatoid arthritis.⁶² Thus, estrogen-containing contraceptives can be strongly recommended as birth control in women with rheumatoid arthritis. A caveat: very rarely, contraceptives can cause symptoms and serologic abnormalities suggestive of rheumatic disease^{63,64} and, more commonly, carpal tunnel syndrome. Insufficient data exist regarding the possible benefits of "progesterone-only" contraceptives in rheumatoid arthritis.

Because of the apparent beneficial effects of estrogens in rheumatoid arthritis and the known high risk of osteoporosis in such patients, we recommend estrogen replacement therapy for all postmenopausal women with rheumatoid arthritis, except when absolute contraindications are present (eg, history of breast or endometrial carcinoma), irrespective of whether the patient has received corticosteroids.

The logical extension of these observations, namely, treatment of rheumatoid arthritis with estrogens, has been reported in only one study so far.⁶⁵ Administration of lynestrenol plus ethinyl estradiol to 10 women with rheumatoid arthritis for 6 months produced little if any improvement, and therapy had to be prematurely stopped for lack of efficacy in one third of patients. The investigators concluded that this regimen was not effective in rheumatoid arthritis. Whether other estrogens would be more effective remains to be determined. In our opinion, a large study comparing conventional agents with and without estrogens is warranted despite the negative results in this very small study.

Systemic lupus erythematosus

SLE affects women much more frequently than men,⁶⁶ and various abnormalities of sex-hormone metabolism may contribute to the cause and development of this disease. For example, patients with SLE have abnormal estrogen metabolism with increased formation of the more immunologically active alpha-2-hydroxylated compounds than do healthy controls.⁶⁷ This metabolic anomaly is not found in the NZB/NZW mouse model of lupus.⁶⁸ Furthermore, patients with SLE have low levels of progesterone⁶⁹ and consistently low levels of most

androgens,⁷⁰ even before corticosteroid therapy and irrespective of disease activity. Pregnancy in SLE patients is associated with well-documented increases in disease activity and risk of flare,⁷¹⁻⁷³ although the magnitude of this risk and the clinical implications remain subjects of intense debate.⁷³ Oral contraceptive therapy precipitated increased lupus activity in one study,⁷⁴ but not all studies confirmed this.⁷⁵ Nevertheless, estrogen-containing contraceptives are generally felt to be inappropriate for most lupus patients.⁷⁶

Because of the potential beneficial effects of androgens in SLE, danazol was used in a number of trials, particularly in SLE with thrombocytopenia.⁷⁷⁻⁷⁹ Unfortunately, the results in these trials showed only modest benefits at best. A long-term, open study of 19-nortestosterone in SLE showed no benefits in women, and the clinical status of men deteriorated.⁸⁰ The latter finding might be explained by 19-nortestosterone exerting disproportionate negative feedback on the pituitary gland. This would cause the pituitary gland to secrete less follicle-stimulating hormone and luteinizing hormone and the gonads to produce less androgens, resulting in lower overall androgen levels in treated patients.

In an open study conducted at Stanford University, 10 women with SLE took DHEA 200 mg daily by mouth for 3 to 6 months.⁸¹ Other medications were adjusted as clinically indicated. Most patients improved and their corticosteroid requirements decreased. The average SLE disease-activity index decreased from 10 to 4.9, the patients' overall assessment of disease activity decreased from an index of 35.1 to 14.1, and the average daily dose of prednisone decreased from 14.8 mg to 5.6 mg (unpublished observations).

We recently completed a double-blind, placebo-controlled trial of DHEA in 30 women with mild to moderate SLE. Overall disease-activity scores improved in the DHEA group but remained stable or worsened in the placebo group; however, most differences did not reach statistical significance. DHEA-treated patients also needed less prednisone. DHEA was generally well tolerated, although acne occurred frequently (unpublished observations).

Progressive systemic sclerosis

As in rheumatoid arthritis, more women than men acquire progressive systemic sclerosis. However, very little is known about the role of sex hormones in

this disease. One study showed that estrogens can down-regulate collagen type III synthesis by dermal fibroblasts in normal individuals but not in patients with progressive systemic sclerosis.⁸² Abnormal estrogen-receptor metabolism was implicated in this study. Male patients had elevated levels of testosterone and estrogens, but the significance of these results remains unclear.⁸³ Flares of disease activity during pregnancy have been documented,⁸⁴ but no controlled studies have been done to determine the relative risk for such a flare. Consequently, recommendations concerning pregnancy and oral contraceptive use cannot easily be made at this time.

Other rheumatic diseases

The down-regulatory effects of relaxin on collagen synthesis by fibroblasts suggest a possible role for this hormone in the treatment of scleroderma. We have recently begun clinical studies of such treatment.

Notable among the rheumatic diseases, ankylosing spondylitis and the seronegative spondyloarthropathies develop more often in men than in women. The underlying mechanisms and sex-hormone status in these patients are not well characterized. In one study, high luteinizing hormone levels and inverted estrogen-to-testosterone ratios were noted in 10 men with ankylosing spondylitis⁸⁵; in women, estradiol levels were lower during active disease and correlated inversely with the erythrocyte sedimentation rate.⁸⁶ Worsening of ankylosing spondylitis during pregnancy has been described.⁸⁷

Dermatomyositis⁸⁸ and mixed connective tissue disease⁸⁹ reportedly flare during pregnancy, and pregnancy in patients with Takayasu's arteritis may pose significant risks to the mother and fetus, mostly related to cardiovascular morbidity.⁹⁰ However, the magnitude of such risks has not been assessed, and, consequently, whether this can be translated into practical advice for such patients remains to be determined.

CURRENT RECOMMENDATIONS FOR CONTRACEPTION AND ESTROGEN REPLACEMENT THERAPY

Clearly, any possible recommendations are somewhat tentative, and further investigation is needed in many of these areas. Nevertheless, when a woman with rheumatoid arthritis desires contraception, estrogen-containing contraceptives can be recommended with some confidence.

TABLE 2
RECOMMENDED USE OF SEX HORMONES IN RHEUMATIC DISEASES

Disease	Hormone intervention	Recommendations and observations
Rheumatoid arthritis	Estrogen-containing oral contraceptive therapy	Recommended
	Estrogen replacement therapy	Strongly recommended
	Therapeutic use of estrogen	Investigational
	Therapeutic use of testosterone	Investigational; might be considered in men with low serum testosterone
Systemic lupus erythematosus	Estrogen-containing oral contraceptive therapy	To be avoided, or used with caution under close monitoring
	Progesterone-only oral contraceptive therapy	Recommended, except when hypercoagulability or history of thromboembolic disease exist
	Estrogen replacement therapy	May be used in most patients; relatively contraindicated in active systemic lupus erythematosus but cautiously recommended in inactive systemic lupus erythematosus
	Danazol	Modest benefits in systemic lupus erythematosus-related cytopenias
	Nortestosterone	Not indicated in men; investigational in women, probably no benefit
	Dehydroepiandrosterone	No studies to date in men; investigational in women, probable benefit
Ankylosing spondylitis	Human chorionic gonadotropin	Investigational, possible benefit for men
	Estrogen	Investigational, possible benefit for women
	Bromocriptine	Investigational, possible benefit

In SLE, unfortunately, the situation is considerably more complicated. In view of the importance of adequate contraception in many SLE patients, highly reliable contraceptives should be given preference. However, estrogen-containing agents, generally the most effective ones, may be objectionable both on theoretical grounds and from the available patient data. Patients with mild SLE and patients in or near remission, for whom contraceptives are desirable, can undergo such therapy under close monitoring for a 3- to 6-month trial period, using the lowest-dose preparations available. For patients with active or severe lupus, however, the progesterone-only contraceptives (eg, the "mini-pill," medroxyprogesterone injections, levonorgestrel implants) might be more suitable, although a lack of adverse effects in SLE would be notoriously hard to ascertain and cannot therefore be completely ruled out. In addition, progesterone is a moderate procoagulant, and some case reports have suggested thrombotic complications during use of progesterone-only contraceptives in patients with the antiphospholipid antibody syndrome.⁹¹ Although it is unclear if a causal connection exists, it would seem prudent to avoid the progesterone-only contraceptives in patients who have the antiphospholipid antibody syndrome or SLE with a history of thromboembolic disease. Thus, for many SLE patients the safest form of contraception remains the meticulous use of barrier methods.

No strong recommendations regarding specific

modes of contraception in the other rheumatic diseases can be made at this time.

Estrogen replacement therapy is very strongly indicated in postmenopausal women with rheumatoid arthritis, in view of their high risk for osteoporosis and the potential benefits of such therapy for the arthritic disease process. In SLE patients this is a far more difficult decision and should be individualized. Some authors categorically recommend against estrogen replacement therapy in SLE.^{92,93} However, because many SLE patients are at high risk for osteoporosis and for premature arteriosclerosis and because of the beneficial metabolic and cardiovascular effects of estrogen replacement therapy, we generally favor giving it, albeit no more than 0.625 mg per day. Also, we would avoid starting this treatment during a phase of disease activity. In the other rheumatic diseases, we feel that estrogen replacement therapy can be strongly recommended.

TREATMENT OF RHEUMATIC DISEASES WITH SEX STEROIDS

As mentioned earlier, treatment of rheumatoid arthritis with lynestrenol plus ethinyl estradiol in 10 women was not very encouraging.⁶⁵ Nevertheless, we feel that this avenue deserves to be explored further in clinical trials. In view of the low progesterone levels seen in rheumatoid arthritis, the use of combined estrogen-progesterone preparations would be a logical investigational treatment.

Of more immediate interest, seven men with rheumatoid arthritis took oral testosterone undecanoate in a study lasting 6 months.⁵⁶ These patients, who had abnormally low baseline testosterone levels, had modest but statistically significant decreases in the number of affected joints and concurrently prescribed nonsteroidal anti-inflammatory drugs and in rheumatoid factor titer. Although the results were not impressive, this treatment might have a role as adjunctive therapy. On the basis of this study, one could cautiously recommend measuring testosterone levels in men with rheumatoid arthritis and supplementing this hormone in patients with low levels. However, the method used for supplementation in this study, oral testosterone undecanoate, is unusual, and other preparations or routes of administration may be preferred; we tend to give testosterone undecanoate 200 mg intramuscularly every 2 to 3 weeks.

In SLE, treatment with the androgen danazol was only modestly helpful,⁷⁷⁻⁷⁹ and 19-nortestosterone⁸⁰ did not show any benefit. Paradoxically, the anti-androgen cyproterone acetate reportedly had modest long-term beneficial effects in one cohort of patients with SLE.⁹⁴ If confirmed, this result might be explained on the basis of the pro-androgenic and progestational effects that this synthetic hormone also possesses.⁹⁵ The use of gonadotropin-releasing

hormone agonists is also under investigation.⁹⁶ Our own studies of DHEA in the treatment of SLE have been very encouraging and are currently being continued. Whether there is a role for testosterone replacement in men with SLE analogous to the situation in rheumatoid arthritis remains unclear.

Tapia-Serrano et al^{85,86} reported that biweekly injections of human chorionic gonadotropin for 10 weeks abated symptoms of ankylosing spondylitis and lowered the erythrocyte sedimentation rate in 10 men; seven women had similar benefits following treatment with estrogen. These authors have also noted improvement using the prolactin antagonist bromocriptine (personal communication). Recommendations for the use of sex hormones in rheumatic diseases are summarized in Table 2.

CONCLUSION

Although sex hormones apparently do not cause autoimmune disease, they may significantly influence immunological and inflammatory responses and, consequently, the expression and severity of illness. As researchers gain understanding of these relationships, they are beginning to identify treatment opportunities that may diminish immunoinflammatory events and improve the course and outcome of autoimmune diseases.

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