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Estrogen in Cardiovascular Disease during Systemic Lupus Erythematosus

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Abstract

Purpose—Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease that disproportionately affects women during their childbearing years. Cardiovascular disease is the leading cause of mortality in this patient population at an age when women often have low cardiovascular risk. Hypertension is a major cardiovascular disease risk factor, and its prevalence is markedly increased in women with SLE. Estrogen has traditionally been implicated in SLE disease progression because of the prevalence of the disease in women; however, its role in cardiovascular risk factors such as hypertension is unclear. The objective of this review is to discuss evidence for the role of estrogen in both human and murine SLE with emphasis on the effect of estrogen on cardiovascular risk factors, including hypertension.

Methods—PubMed was used to search for articles with terms related to estradiol and SLE. The references of retrieved publications were also reviewed.

Findings—The potential permissive role of estrogen in SLE development is supported by studies from experimental animal models of lupus in which early removal of estrogen or its effects leads to attenuation of SLE disease parameters, including autoantibody production and renal injury. However, data about the role of estrogens in human SLE are much less clear, with most studies not reaching firm conclusions about positive or negative outcomes after hormonal manipulations involving estrogen during SLE (ie, oral contraceptives, hormone therapy). Significant gaps in knowledge remain about the effect of estrogen on cardiovascular risk factors during SLE. Studies in women with SLE were not designed to determine the effect of estrogen or hormone therapy on blood pressure even though hypertension is highly prevalent, and risk of premature ovarian failure could necessitate use of hormone therapy in women with SLE. Recent evidence from an experimental animal model of lupus found that estrogen may protect against cardiovascular risk factors in adulthood. In addition, increasing evidence suggests that estrogen may have distinct temporal effects on cardiovascular risk factors during SLE.

Implications—Data from experimental models of lupus suggest that estrogens may have an important permissive role for developing SLE early in life. However, their role in adulthood remains unclear, particularly for the effect on cardiovascular disease and its risk factors. Additional work is needed to understand the effect of estrogens in human SLE, and preclinical

studies in experimental models of SLE may contribute important mechanistic insight to further advance the field.

Keywords

estrogen; hypertension; immune; inflammation; lupus

Background

Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease of unknown cause with multiple genes, environmental factors, and sex hormones likely playing roles in its pathogenesis.¹ SLE is characterized by a loss of tolerance to self-antigens which leads to the production of autoantibodies to the nucleus, most commonly anti-double-stranded DNA (anti-dsDNA) antibodies.² These autoantibodies contribute to immune complex formation and can deposit within virtually every tissue in the body, leading to inflammation and tissue injury, thus producing the clinical symptoms experienced by patients.² Malar rash, discoid rash, photosensitivity, pleuritis, pericarditis, nonerosive arthritis, neurologic disorders such as seizures and psychosis, and hematologic disorders such as hemolytic anemia and thrombocytopenia are all clinical symptoms of SLE³ (Table I). The kidneys are commonly affected in patients with SLE with a high prevalence of immune complex-mediated glomerulonephritis, and the leading cause of mortality in these patients is cardiovascular disease.^{4,5} Although its cause is multifactorial, it is clear that SLE has a strong predilection for females, especially during their childbearing years.⁶ When disease onset occurs between menarche and menopause, the female-to-male ratio is 9:1.⁷ However, SLE diagnosis before the onset of puberty and after menopause, although still favoring women, lacks a strong female-to-male ratio.⁸ This predilection for women during their reproductive years suggests the possibility of a role for sex steroids, especially estrogen, in the pathology of SLE and contributes to the controversy surrounding manipulation of estrogen through oral contraceptives and hormone therapy (HT) in women with SLE. Although estrogens are widely perceived as contributing to SLE disease progression, the effect of estrogens on cardiovascular risk factors during SLE remains unclear.

Methods

Articles were identified through a PubMed search that used key words related to estrogen and SLE. References from retrieved publications were also examined.

Findings

Cardiovascular Disease in SLE

SLE disease is associated with a bimodal pattern of mortality.⁵ Death early in the disease often results from increased rate of infection in patients with active disease in part because of immunosuppression from conventional treatments for SLE. In contrast, death later in the course of SLE most often occurs during inactive disease and is primarily a result of

cardiovascular problems and atherosclerotic heart disease. Despite the improvement in the prognosis of SLE, cardiovascular disease has emerged as a major problem for patients with SLE at increased risk for stroke, atherosclerosis, and myocardial infarction.^{9–11} In one cohort of 9547 patients, patients with SLE had not only an increased risk of death in comparison with the general population but also an increased risk of death due to circulatory or cardiovascular disease.⁴ Studies in other cohorts of SLE also support a link between SLE and increased cardiovascular disease.^{12,13} Although the rate of mortality and the prognosis of patients with SLE have significantly improved since 1975,¹³ approximately 10% of patients with SLE still die within the first 5 years of the disease.¹⁴ Patients with SLE develop atherosclerosis prematurely, and in one cohort of patients with SLE 37% of patients presented with atherosclerosis compared with 15% of controls.¹⁵ Premature cardiovascular disease was much more common in young women with lupus than in the general population. A comparison of 498 patients with SLE at the University of Pittsburgh Medical Center and age-matched healthy controls from the Framingham study found that patients with SLE were 52 times more likely to have a myocardial infarction.¹⁶ A retrospective study of acute care hospitals in California reported that young women with SLE aged 18 to 44 years were 2.27 times more likely to be hospitalized for an acute myocardial infarction, 3.80 times more likely to be hospitalized for congestive heart failure, and 2.05 times more likely to be hospitalized for a cerebrovascular accident.¹⁷ All of these studies highlight the importance of combating cardiovascular disease in patients with SLE. More importantly, the risk factors for cardiovascular diseases, especially hypertension which is more prevalent in patients with SLE,¹⁸ need to be studied.

Prevalence of Hypertension in SLE

Traditional risk factors, such as age, smoking, hyperlipidemia, and hypertension, have all been implicated as potential reasons for the higher prevalence of cardiovascular disease in patients with SLE,¹⁰ and SLE disease itself has been suggested to be a risk factor for coronary heart disease.¹⁹ The prevalence of hypertension in women with SLE is often reported to be greater than or near 40%, with some cohorts reporting prevalence as high as 74%.^{20,21} This is much greater than the expected prevalence of approximately 8% to 10% in similarly aged healthy women.²² In one SLE cohort, the prevalence of hypertension was 36.8% with 25.8% of premenopausal patients with SLE being hypertensive.²³ Approximately 40% of female patients with SLE in the Hopkins Lupus Cohort were hypertensive, leading to the need for implementing treatment during the study.²⁴ A study of subclinical atherosclerosis in patients with SLE identified hypertension in 45% of the SLE cohort.²⁵ Sabio et al²⁶ reported that the prevalence of hypertension in female patients with SLE was almost double that of age-matched controls. Interestingly in that study, the prevalence of hypertension was four times that of age-matched controls in female patients with SLE younger than 40 years of age. Although it may be easy to attribute the prevalent hypertension to the renal damage associated with immune complex-mediated glomerulonephritis, evidence suggests a dissociation between renal injury and hypertension during SLE.²⁷ Consistent with this, 38% of patients with SLE in one study were hypertensive without evidence of glomerulonephritis.²⁸ Another SLE cohort identified that 38% of patients were hypertensive and that 47% of those hypertensive patients displayed impaired renal function as identified by creatinine >120 $\mu\text{mol/L}$ compared with impaired

renal function in only 18.5% of normotensive patients.²⁹ These studies suggest that one should be cautious in ascribing the increased risk of hypertension in SLE to kidney injury alone and underscore the need to better understand the prevalent hypertension for which the mechanisms remain unclear. Our laboratory has approached this problem by using an established mouse model of SLE (female NZBWF1 mice). Our recent studies have examined both the relation among inflammation, renal and vascular function, and hypertension by using this model of SLE.^{30–32}

Effects of Estrogen on the Immune System

Part of what makes estrogen an attractive candidate for promoting SLE disease progression in women is its ability to modulate the immune environment. Estrogen is often considered to be an anti-inflammatory agent.^{33–36} It affects target cells by binding to estrogen receptor α or β (ER- α or ER- β), members of the steroid nuclear receptor family.³⁷ On binding of estrogen, the ER activates, dimerizes, and then binds to an estrogen response element to enhance gene transcription or to interact with other coactivator proteins indirectly to affect gene expression.³⁸ ERs reside in various tissues, including human and murine thymocytes, thymic epithelial cells, B lymphocytes in the bone marrow, peripheral T and B lymphocytes, and macrophage/mononuclear cells.³⁹ Because of a growing interest in the role that inflammation and immune system has in the development of hypertension,^{40,41} it is possible that any effect of estrogen on blood pressure occurs, in part, through modulation of the immune environment.

Two cell types critical for normal immune function are the T lymphocyte and the B lymphocyte. Undifferentiated T helper cells (T_H) can be activated to form a T_H1 or T_H2 lymphocyte with each producing different cytokines. The T_H1 response leads to a paradigm with inflammatory cytokines, such as tumor necrosis factor- α , interferon- γ , and interleukin 2 (IL-2), and IL-12 predominates. In contrast, activation of T_H2 cells induces humoral (antibody-mediated) immunity and an anti-inflammatory response via production of IL-4.^{35,36}

Estrogens are generally believed to promote a T_H2 response while suppressing a T_H1 response.³⁶ Several lines of evidence contribute to this idea, including physiologic evidence from studies in both pregnant women and animal models.^{42,43} During pregnancy, serum levels of estrogen increase significantly, especially within the second and third trimesters, and lead to a shift from T_H1 to T_H2 immune responses⁴² to avoid rejection of the fetoplacental unit. In addition, in vitro studies found that 17 β -estradiol stimulates humoral immunity and production of antibodies in human peripheral blood mononuclear cells.⁴⁴ In contrast, testosterone suppresses the production of immunoglobulin G (IgG) anti-dsDNA autoantibodies in peripheral blood mononuclear cells from patients with SLE.⁴⁵

Estrogen and SLE: Humans

Because of the partiality of SLE toward women of reproductive age and the ability of estrogen to stimulate humoral immunity, estrogen has long been considered to play a role in lupus disease. Despite this common perception of a pejorative role for estrogen in SLE disease development and progression, much of the data related to estrogens and SLE in

humans is equivocal (Table II), making the exact role for estrogens an area that requires further study.

Serum Levels of Estrogen in SLE—Evidence about serum levels of estrogens in women with SLE is not as clear as expected, given the pathogenic role commonly ascribed to estrogens in SLE. In a study of 9 women and 6 men with SLE, 17 β -estradiol levels were increased, androgens were decreased, and aromatase activity was elevated compared with controls, suggesting that abnormal aromatase activity may lead to abnormal estrogen production in SLE.⁶⁰ However, a meta-analysis that examined serum levels of 17 β -estradiol in SLE did not reach a consensus about whether estrogens are consistently altered in women with SLE.⁵⁶ Similar results were noted for serum testosterone in women with SLE with some studies reporting decreased testosterone and others no differences.⁵⁶ Given that estrogens are often in the normal physiologic range in women with SLE,⁵⁶ others have focused on the ratio of estrogens to androgens and have suggested that this ratio plays a role in autoimmune disease with a high estradiol-to-low testosterone ratio correlating with disease activity.⁶¹

Oral Contraceptives and SLE—Pharmacologic studies further complicate the picture of the role of estrogen in adult women with SLE. In the Nurses' Health Study cohort, the past use of oral contraceptives was associated with a slightly elevated risk of SLE.⁶² However, several studies suggest use of oral contraceptives by women with SLE was generally tolerable.^{63,64} A double-blind, randomized, placebo-controlled clinical trial of 183 women with either inactive SLE disease or stable active disease reported no differences in mild, moderate, or severe flares between women receiving oral contraceptives (triphasic ethinyl estradiol plus norethindrone) or placebo.⁵⁸ Furthermore, women with SLE receiving ethinyl estradiol plus norethidone were found to have no increased incidence of flares compared with women on placebo. A single-blind clinical trial of 162 women with SLE found that global disease activity, incidence of flares, and time to first flare were all similar among women with SLE assigned to either combined oral contraceptives (ethinyl estradiol plus levonorgestrel), progestin-only pill (levonorgestrel), or copper intrauterine device.⁶⁵ Although the exogenous estrogens in oral contraceptives have been widely feared to exacerbate SLE disease and, therefore, have been avoided by clinicians, these studies and clinical trials especially found that oral contraceptives can be a viable and tolerable option for women with SLE with stable disease.

HT and SLE—Although considerable hope was placed in supplementation of postmenopausal women with HT to protect against cardiovascular disease, the Women's Health Initiative and Heart and Estrogen-Progestin Replacement Study I and II trials failed to find beneficial outcomes for cardiovascular risk and events, whether primary or secondary prevention.^{66–68} The conjugated equine estrogen (CEE)-only arm of the Women's Health Initiative also found that CEE increased the risk of stroke and had no effect on coronary heart disease in postmenopausal women.⁶⁹ These trials remain controversial, and further examination of these trials has indicated that HT may be more efficacious in younger postmenopausal women; although, this remains to be determined.⁷⁰

Use of exogenous estrogens by women with SLE remains controversial with some studies highlighting risks and others the benefits of HT. For example, there was a small, but significant, increase in the risk of developing mild-to-moderate flares (from 0.86 flare/person-year for women receiving placebo to 1.14 flares/person-year for women on HT) in a randomized, double-blind placebo-controlled trial of menopausal women with SLE receiving CEE and medroxyprogesterone for 12 months.⁴⁶ In a separate randomized, double-blind clinical trial of 106 women with SLE, venous thrombosis was a risk in HT users with 3 of 52 HT users developing thromboses.⁷¹ Therefore, HT should be avoided in women with SLE at risk for thrombosis.

However, several studies suggest that HT can be tolerable and beneficial for women with SLE. For example, in women with SLE who undergo premature ovarian failure (POF) or early menopause after treatment with cyclophosphamide, HT may be beneficial to treat menopausal symptoms.⁷² Although the elevated estrogen level caused by HT has been feared to risk exacerbation of SLE disease, several studies found that HT use is tolerable in women with SLE. In one randomized, double-blind placebo-controlled trial, the risk of developing a severe flare was not significantly increased in menopausal women with SLE on HT (CEE plus medroxyprogesterone) compared with women receiving placebo.⁴⁶ In another prospective study of 34 women with SLE, Mok et al⁴⁷ concluded that HT was tolerable in postmenopausal women with SLE. Total SLE disease activity index scores during flares were similar between HT users and nonusers, and the rate of flare was not increased. Similarly, in a cohort of 16 women with SLE on HT for at least a year, rate of lupus flares was not increased compared with 32 age-matched women with SLE.⁴⁸ A randomized, double-blind clinical trial of 106 women with SLE found that postmenopausal HT did not alter disease activity as assessed by SLE disease activity index scores during 2 years of treatment.⁷¹ These studies suggest that use of HT by women with SLE does not predispose to exacerbation of disease flare.

HT has also provided some benefits to postmenopausal women with SLE while not increasing disease flares. For example, estrogen plus progestin (CEE plus medroxyprogesterone) improved vasomotor symptoms in postmenopausal women with SLE.⁷³ The LUPus in MINorities NATURE versus nurture study in a multiethnic US cohort found that use of HT by postmenopausal women with SLE was not associated with vascular arterial events.⁷⁴ Hochman et al⁴⁹ examined the effects of HT and risk of cardiovascular disease in postmenopausal women with SLE. In that study, the incidence of coronary artery disease was similar between HT users at 11.4% (13 of 114) and 13.7% (31 of 227) in nonusers. That study suggested that HT does not predispose to coronary artery disease in postmenopausal women with SLE. Cardiovascular disease is highly prevalent in women with SLE; therefore, these data are encouraging in that women with SLE can use HT to alleviate menopausal symptoms while not increasing cardiovascular risk. Although the cohort was small, that study found that short-term courses of HT may be useful to alleviate menopausal symptoms.

These studies together suggest that HT does not exacerbate lupus flares or disease activity in postmenopausal women with SLE. Importantly, randomized clinical trials have found that severe flares are not increased in women with lupus. Although careful monitoring and

counseling of individual women with SLE is needed, short-term courses of HT can be beneficial to relieve some menopausal symptoms, especially vasomotor symptoms, in women with SLE. Because women with SLE frequently experience POF, these studies are significant because women with SLE may require longer exposure to HT after POF. In addition, there is a significant gap in knowledge in relation to the effects of HT on blood pressure in SLE. Given that hypertension is a major cardiovascular risk factor, further studies are required to assess the effect of HT on blood pressure in women with SLE.

Estrogen and SLE: Animal Models

Although the role of estrogens in both women and men with SLE remains uncertain, studies in animal models of lupus disease were conducted to enhance our understanding of the role that estrogen plays in lupus progression. Some of the most definitive and illuminating evidence for the role of estrogen in lupus development comes from a study in ER- α knockout (KO) NZBWF1 mice.⁷⁵ ER- α KO NZBWF1 female mice exhibited reduced development of anti-dsDNA IgG autoantibodies, glomerulonephritis, and albuminuria and exhibited increased survival time. Male ER- α KO NZBWF1 mice survived longer and developed less anti-dsDNA antibodies. These results implicate estrogen in lupus disease through interaction with ER- α . Studies in ER- α -deficient NZM2410 lupus-susceptible mice further link estrogen to lupus development through ER- α .⁷⁶ Similar to ER- α KO NZBWF1 female mice, NZM2410 female mice exhibited reduced proteinuria and glomerulonephritis with increased survival time. A study of NZBWF1 mice that underwent ovariectomy at 6 weeks of age and treated with propyl pyrazole triol, a selective ER- α agonist, supports the involvement of estrogen in SLE disease development via ER- α activation. These mice had reduced survival time, earlier development of albuminuria, and increased levels of anti-DNA IgG subtype-specific antibodies.⁷⁷ These three studies strongly suggest that estrogen contributes to SLE disease progression through ER- α . Although studies have yet to be conducted in ER- β KO NZBWF1 mice, ovariectomized female NZBWF1 mice, treated with an ER- β -selective agonist, had reduced production of anti-DNA IgG_{2b} autoantibodies. Other anti-DNA IgG subclasses and total IgG concentration were not altered, and albuminuria and survival did not improve.⁷⁷ Therefore, ER- β may have a slight immunosuppressive role in SLE, whereas ER- α likely plays the predominant role.

Early studies detailing ovariectomy and subsequent sex hormone treatment in NZBWF1 mice found that female mice, undergoing ovariectomy at 2 weeks of age and supplemented with estradiol, experienced greatly enhanced mortality, earlier production of anti-nucleic acid antibodies, and worsened glomerulonephritis compared with sham-operated and ovariectomized females supplemented with 5- α -dihydrotestosterone.⁷⁸ Likewise, young male NZBWF1 mice, castrated at 2 weeks of age and given 17 β -estradiol, had a worsened disease course with increased mortality, anti-nucleic acid antibodies, and more evidence of glomerulonephritis. Castration followed by androgen treatment led to opposite findings. Female NZBWF1 mice, undergoing ovariectomy at 2 weeks of age and given androgen powder (6–7mg in silastic tubing), had decreased mortality along with improved proteinuria and less autoantibody formation.⁷⁹ Another study found that female NZBWF1 mice treated with flutamide, an androgen receptor blocker, beginning at 6 weeks of age, led to accelerated mortality; however, albuminuria and anti-DNA autoantibodies were not

altered.⁸⁰ In NZBWF1 mice undergoing ovariectomy at 6 to 8 weeks of age, the development of renal disease was significantly delayed, and proteinuria was reduced.⁸¹ These studies further support an important role for estrogens to contribute to SLE disease development. Whether an altered estradiol-to-testosterone ratio is an important factor that mediates these effects in mice has not been directly tested.

In light of evidence that early-life ovariectomy ameliorated SLE disease progression and improved survival in NZBWF1 mice, the effects of selective ER modulators on SLE disease have been examined in several studies. NZBWF1 mice treated subcutaneously with tamoxifen every 2 weeks for 5 months developed less severe albuminuria and exhibited increased survival.⁸² Tamoxifen did not affect levels of anti-dsDNA antibodies. Another study of NZBWF1 mice treated twice a week with tamoxifen, beginning at 8 weeks of age, reported similar beneficial effects, notably increased survival, reduced proteinuria, and reduced immune complex glomerular deposits.⁸³ In contrast to the previous study, SLE disease improvement was associated with a significant reduction in IgG₃ autoantibodies.⁸³ Taken together, several studies that used the NZBWF1 model suggest that estrogens contribute to SLE disease progression; however, the role that estrogens have in the prevalent hypertension associated with SLE has not been carefully examined.

On the basis of the studies suggesting that estrogens contribute to SLE disease progression in NZBWF1 mice, we initially hypothesized that estrogens might also contribute to the progression of hypertension. Unexpectedly, our recent work in adult female NZBWF1 mice found that estradiol plays a protective role against the progression of hypertension and albuminuria in SLE during adulthood (Figure) without affecting autoantibody production.⁸⁴ When ovariectomy was performed in early life, as done previously by others, we could replicate the delay in developing autoantibodies and albuminuria; however, blood pressure was not different between ovariectomized and sham-operated animals when they reached adulthood (unpublished observations). When considered in the context of previously published work, we interpreted these data to suggest that estrogen has distinct temporal effects during SLE (Table III), perhaps with early life exposure to estrogens having a permissive role for developing SLE while exhibiting a protective role in adulthood through reducing tissue inflammation. Although studies are limited, some evidence supports the concept that timing of estrogen administration or treatment can affect the course of other diseases, including Alzheimer disease,^{85–87} experimental autoimmune encephalomyelitis,^{88,89} and myasthenia gravis.⁹⁰ One possibility that could help to explain the disparate temporal effects of estradiol on blood pressure in our studies may be differences in ER expression over time.^{91–93} It is also possible that epigenetic effects of estrogens may influence SLE disease progression.⁹⁴ The mechanisms that lead to the distinct temporal actions of estrogen during autoimmune disease will be important to explore to have a more complete understanding of the pathogenesis of SLE.

The effect of ovariectomy on autoimmune disease in the MRL mouse strain has been investigated, although its effect on glomerulonephritis remains to be elucidated. One study of MRL/+ mice undergoing ovariectomy at 4 weeks of age found that ovariectomy led to increased serum anti-dsDNA antibodies and an accelerated development of autoimmune lesions in the parotid, submandibular, and lacrimal glands.⁹⁵ Another study of MRL/lpr

mice found similar pejorative effects on disease progression when mice underwent ovariectomy at 4 weeks of age.⁹⁶ These mice developed severe autoimmune arthritis at a younger age, and subsequent administration of estrogen reversed the autoimmune lesions. When MRL/lpr mice were treated with LY139478, an analog of the selective ER modulator raloxifene, they survived longer and had attenuated glomerular nephritis.⁹⁷ In the same study, MRL/lpr mice administered 17 α -ethinylestradiol did not have prolonged survival, but treatment reduced glomerular nephritis. Anti-dsDNA antibody levels were not affected by either treatment. Interestingly, the MRL strains do not exhibit a sex-specific phenotype (both male and female MRL/lpr mice are affected with SLE disease to a similar degree), nor do they develop hypertension.⁹⁸ In contrast, the development of SLE in the NZBWF1 mice occurs earlier and is more pronounced in the female mice than in the male mice. Therefore, careful selection of experimental models for examining the effect of estrogens on blood pressure and SLE progression should be an important consideration.

Conclusion

Over the past several decades, studies in experimental animal models of SLE have implicated a detrimental role for estrogen in developing lupus disease. This body of work finds that early life removal of estrogens or absence of ERs delays the onset of SLE. These studies report the effect that estrogens have on developing autoantibodies and on developing SLE. However, it is also important to consider the effect of estrogens in adulthood during SLE, given that the peak onset of SLE in women typically occurs in the third and fourth decades of life.^{99,100} The role of estrogens in human SLE, whether related to oral contraceptive use, pregnancy, or HT, is far less certain than what is commonly presumed. New evidence indicates that removal of estrogens in adult mice with SLE does not afford any protection and actually exacerbates the hypertension and renal injury associated with SLE.⁸⁴ These findings suggest a more complex role for estrogens in SLE disease progression and support the need for carefully designed studies in both humans and experimental models to better delineate the effect of estrogens on SLE and its cardiovascular risk factors such as hypertension.

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Figure.

(A) Effect of OVX in adulthood on MAP in SLE mice. MAP was significantly higher in SLE mice than had undergone OVX ($n = 11$) than in sham-operated mice ($n = 16$). Repletion of E_2 prevented the OVX-induced increase in MAP in SLE mice ($n = 6$). Treatment with Etan blunted the exaggerated increase in MAP in SLE mice that had undergone OVX ($n = 6$). $*P < 0.05$ vs SLE sham. (B) Effect of OVX in adulthood on urine albumin in control and SLE mice. Weekly percentage of SLE mice with positive urinary albumin as measured by dipstick assay of 24-hour urine samples ($n = 8$ /group). No control mice developed albuminuria. Etan = etanercept; E_2 = estradiol; MAP = mean arterial pressure; OVX = ovariectomy; SLE = systemic lupus erythematosus. Reprinted with permission from Gilbert EL, Mathis KW, Ryan MJ. 17β -Estradiol protects against the progression of hypertension during adulthood in a mouse model of systemic lupus erythematosus. *Hypertension*. 2014;63:616-623.⁸⁴

Table I

Diagnostic criteria for SLE.

Criterion	Description
Malar rash	Erythema over the malar eminence (characteristic butterfly rash)
Discoid rash	Erythematous patches
Photosensitivity	Skin rash on exposure to sunlight
Oral ulcers	Oral or nasopharyngeal ulceration
Serositis	Pleuritis, pericarditis, pleural effusion, friction rub
Renal disorder	Proteinuria >0.5 g/d, immune complex-mediated glomerulonephritis
Neurologic disorder	Psychosis, seizures
Hematologic disorder	Hemolytic anemia, leukopenia, thrombocytopenia
Immunologic disorder	Anti-dsDNA antibody, anti-Smith antibody, lupus anticoagulant
Positive ANA	Abnormal titer of ANA

Four of 11 diagnostic criteria are required for diagnosis of SLE.

ANA = antinuclear antibody; Anti-dsDNA = anti-double-stranded DNA; anti-Smith = anti Smith; SLE = systemic lupus erythematosus.

Table II

Studies in humans with SLE are less clear about the role of estrogens than what is commonly presumed.

Study	Finding	Effect
Buyon et al ⁴⁶	HRT is associated with small risk (0.64 vs 0.51) of flare in pm women with SLE	↑
Mok et al ⁴⁷	HRT well tolerated in pm women with SLE; benefit may outweigh risks	↔
Kreidstein et al ⁴⁸	HRT does not increase flares in pm women with SLE, 1-year follow-up	↔
Hochman et al ⁴⁹	HRT delayed time until coronary event in women with SLE	↓
Moroni et al ⁵⁰	Incidence of renal flares before and during pregnancy in women with SLE not different	↔
Tandon et al ⁵¹	Renal disease/function similar between nonpregnant and pregnant women with SLE	↔
Doria et al ⁵²	Increased flare second trimester, decreased flare in third trimester of pregnancy	↑↓
Sturgess et al ⁵³	Tamoxifen did not ameliorate indices of SLE in 11 women (renal, leukocytes, Ab, C, IC)	↔
Mok et al ⁵⁴	Raloxifene did not affect lupus flares in pm women with SLE	↔
Lu et al ⁵⁵	ERα polymorphisms associate with IL-10, IL-4, IL-2, IFN-γ in women with SLE	↑
McMurray and May ⁵⁶	Meta-analysis of 20 studies that measured serum estradiol in patients with SLE	↑↓
Rider et al ⁵⁷	Estradiol stimulates calcineurin pathway in T cells isolated from women with SLE	↑
Petri et al ⁵⁸	No effect of oral contraception on SLE disease course	↔
Colangelo et al ⁵⁹	Self-reported SLE disease activity increased during menses but not hormone surge	↓

Ab = antibody; C = complement; HRT = hormone replacement therapy; IC = immune complex; IFN-γ = interferon γ; IL = interleukin; pm = postmenopausal; SLE = systemic lupus erythematosus; ↑ = exacerbates symptoms of SLE; ↔ = no significant effect on symptoms of SLE; ↓ = alleviates symptoms of SLE.

Table III
Effect of ovariectomy on SLE in an established mouse model (female NZBWF1 mice)

	Ovariectomy in adulthood	Early life ovariectomy
Urinary albumin excretion	↑	↓
Plasma autoantibodies	↔	↓
Mean arterial pressure	↑	↔

↑ = exacerbates symptoms of SLE; ↔ = no significant effect on symptoms of SLE; ↓ = alleviates symptoms of SLE.