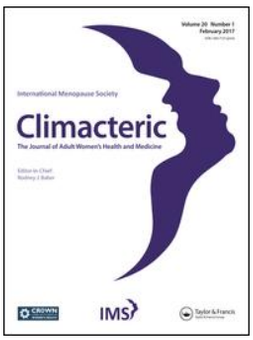

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REVIEW

Systemic lupus erythematosus and menopause

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ABSTRACT

Estrogen has been known for a long time to be a trigger on auto-immunity and may influence the course of lupus. Women experiencing systemic lupus are at high risk for premature ovarian insufficiency if using cyclophosphamide, of osteoporosis, arterial ischemic diseases and venous thrombosis at young age. In about 30% of them, an antiphospholipid/anticoagulant antibody can occur which is associated with very high risk of thrombosis. However, the severity of the disease may vary and some women with lupus could benefit from a menopausal hormone therapy (MHT). As a consequence, management of menopause symptoms needs to evaluate carefully the condition of the patient, her lupus history and cardiovascular risk. We will describe the effect of lupus on menopause, of menopause on lupus and report in detail the literature available on MHT and the risk of lupus or the risk of flares in women with lupus. Some other options than MHT for the management of climacteric symptoms will be discussed.

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Introduction

Systemic lupus erythematosus (SLE) is an auto-immune disease, concerning ten-fold more women than men. The influence of estrogens on SLE has been suggested since 1944[1]. The disease is polymorphous and various clinical presentations can occur with different level of severity. It is characterized by flares which can involve almost all of the organs including kidney and brain. The disease can be associated with antiphospholipid/anticoagulant (APL) antibodies (Abs) in about 30% of the cases which is associated with a very high risk of venous and arterial thrombosis. It is mostly a disease of premenopausal women but it can also less frequently occur after the menopause. This review will address the influence of SLE on menopause, the influence of menopause on SLE and the place of menopause hormonal treatment in women with a history of SLE.

Influence of gonadal steroids on immunity

The potential modulation of auto-immunity by estrogens (worsening), progesterone and androgens (improving) has been known for decades and reported in several recent excellent reviews[2–5]. We will not go into details in this chapter. Briefly, it is known that auto-immunity is enhanced in women compared to men whereas cellular immunity is decreased in women. Women are more prone to defend against viral and bacterial diseases than men. This is interpreted as the dual effects of estrogens and androgens on Th1 cells, and also by a genetic background since the increased number of X chromosomes is associated with a higher risk of lupus (risk high for males with Klinefelter and low for women with Turner).

Cells involved in immunity mediation (T cells, thymic epithelial cells, B cells, dendritic cells, macrophages and monocytes, NK cells, type-2 innate lymphoid cells, and granulocytes) as well as their progenitors contain estrogen receptor (ER) α, progesterone receptor (PR), and androgen receptor (AR). Estrogens can suppress T and B cell lymphopoiesis and activate B cell functions and thereby increase production of auto-Abs including APLs. It also inhibits part of NK function and enhances T helper function, inhibits AIRE gene (a key molecule in central tolerance), plays a role in dendritic cell differentiation and has anti-inflammatory or pro-inflammatory actions according to concentrations, tissues, external, environmental or internal stimuli. Progesterone and androgens display opposite properties.

Hormones and SLE

SLE is a disease mediated by Th1 immunity. There is clearly a sexual dimorphism and a deleterious effect of estrogens: before puberty, there is a sex ratio always higher for females than males, much lower before puberty, whereas after puberty, the ratio is at least 10/1 and after menopause 3/1[6]. The group of Talal, using a strain of mice developing a glomerulopathy with Abs anti-DNA, demonstrated the opposite role of estrogens and androgens on the survival of these mice[7]. Males castrated or treated by estrogen have a length of life shorter than control males and close to females which have the shorter survival. Females receiving androgens have a prolonged survival. The first report on pregnancy as worsening the course of SLE was made in 1963[8] and confirmed

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in recent publications Estrogen–progestin contraception has also been reported at risk of flares in sporadic publications with poor quality[9], but two randomized trials did not show any statistical increase in flares[10,11]. The number of drop-outs was high in these studies and criteria of inclusion selected patients with inactive or mild active disease which may have lowered the power of detecting flares. In a recent meta-analysis, the authors concluded that oral contraceptives and MHT did not affect the course of lupus activity at a clinically significant level[12]. Similarly, Khafagy *et al*. stated that MHT appears to be well tolerated in women with SLE[13]. Our clinical experience is somehow different from these publications in that some women may develop flares following a short period of contraception containing estrogens. There are no data on possible means to predict an individual sensitivity to estrogens. Given the severity of some flares, a careful evaluation of the indication is mandatory before prescribing an estrogen-containing drug.

Effect of lupus on menopause

Premature ovarian insufficiency

Premature ovarian insufficiency (POI) is associated with cyclophosphamide treatment in women with SLE. The use of cyclophosphamide is now decreasing and it is replaced by mycophenolate or aziathioprine. Among the causes of POI are auto-immune disorders. However, POI occurs in endocrine auto-immune diseases rather than in systemic auto-immune disease[14,15]. Studies on anti-Muellerian hormone (AMH) and ovarian reserve in SLE show discrepancies in their results[16–19]. All agree for a decrease in AMH in women treated by immunosuppressants. Several studies did not show an increase in POI in women with SLE who did not receive cyclophosphamide[15].

Age at menopause

Some studies suggested an earlier age at menopause associated with SLE. However, in a well-conducted study on 961 SLE women, predominantly premenopausal, after adjusting for smoking and chemotherapy, age at menopause was not different from the general population[20].

Effect of menopause on lupus

Several studies have reported that women with SLE occurring after the age of 50 years have less severe organ involvement and that flares decrease after menopause.

A French study reported on 47 patients with SLE diagnosed at or over the age of 50 years and compared them with 114 patients aged younger than 50 years at SLE diagnosis[21]. They also reported on the literature in addition to their own series. Arthritis, malar rash and nephropathy were less frequent in postmenopause, but more serositis, lung involvement and Sjögren's syndrome were observed[21–23]. More deaths occurred in postmenopausal women and this is in concordance with further studies. Outcomes are definitely not benign in older women due to comorbidity, in particular in cardiovascular events.

The question remains on the influence of menopause on the course of SLE. Two important studies have designed their studies to answer that question. A longitudinal multiethnic study, LUMINA (LUpus in MInorities, NAture versus nurture), was conducted on 518 women, 436 (84.2%) premenopausal and 82 (15.8%) postmenopausal. They were followed for 35.7 ± 33.7 months[24]. They reported less renal involvement in postmenopausal women but more vascular arterial events, more venous thrombosis (VTE) (non-significant) and more Raynaud's syndrome (non-significant)[24]. Damage accrual was higher in postmenopausal women. Damage was measured with the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index including irreversible damage in 12 different organ systems. They concluded that time rather menopausal status by itself was associated with decrease in activity. An elegant Canadian study looked at women diagnosed after the menopause, compared to women diagnosed before menopause and women going through the menopausal transition. There were 190 women with SLE diagnosed in the premenopausal years and 55 women with SLE diagnosed in the postmenopausal years, followed for at least 3 years, 49 patients followed during the menopausal transition, 3 years before and 3 years after, 193 patients followed for 6 years in the premenopausal period and 76 patients followed for 6 years in the postmenopausal period[25]. The adjusted mean SLEDAI-2K (lupus index of activity modified in 2000) was significantly higher in the premenopausal group. Among this index, vasculitis, proteinuria, rash, pericarditis, and the presence of anti-DNA antibodies were significantly greater in the premenopausal group. Activity decreased with time in all the groups. Their conclusions were similar to those of the previous study: disease activity is milder in postmenopause than premenopause but damage accrual is higher in postmenopausal women[25]. Both studies stated that the decrease in disease activity was associated with increase in disease duration rather than the menopausal status[24,25].

Specific risks at menopause in women with SLE

Cardiovascular risk

Cardiovascular (c-v) events (myocardial infarction and stroke) occur at younger age in women with SLE[26]. A study from USA reported a relative risk (RR) above 50 for myocardial infarction (MI) in women with SLE 35–44 years old. In women 55–64 years old, the RR = 4.21 (1.7–7.9) compared to the population of the Framingham study[27]. Several studies reported increase in the number of plaques in women with SLE[28]. In addition to the classical c-v risk factors, smoking, dyslipidemia, diabetes mellitus and metabolic syndrome, hypertension, central obesity, which are also more prevalent in women with SLE, other factors are involved such as inflammation and immune dysregulation leading to an imbalance between endothelial damage and atheroprotection[28,29]. Renal disease, duration of disease, APLs, cumulative dose of corticosteroid (over 36.5 g there was a 1.7-fold risk of

c-v event) whereas hydroxychloroquine decreased the risk, likely through a decrease in cholesterol and inflammation[28–31]. Mild cases of lupus are treated by antimalarial drugs and more active ones by steroids and immunosuppressants. It was also suggested that immunosuppressants such as cyclophosphamide, cyclosporine, and mycophenolate mofetil but not azathioprine exerted c-v beneficial effects on atherosclerosis[28]. As well known, POI without estrogen supplementation is as well a strong risk factor for c-v events which may concern young women with severe lupus. It is somehow difficult to evaluate which factor among those listed here is playing the main role in c-v risk: severity of the disease which could be associated with important inflammation, or specific effect of treatment, or hypoestrogenism which may concur to aggravate arterial condition.

Venous thrombosis

APLs are associated with a major risk of arterial and VTE. Even without APLs, lupus by itself is at increased risk of thrombosis to a level of 3–4-fold. The risk is major (×15-fold) during the first years following the diagnosis, but may be sustained furthermore. In addition to APLs, age, smoking, inflammation, venous insufficiency, vasculitis, severity of the disease, glucocorticoid dose and nephritis may contribute to that increased risk[32–35].

Osteoporosis

Osteoporosis is clearly a disease associated with corticosteroids. Inflammation is also a risk factor for osteoporosis and greater activity of SLE has been associated with low bone mineral density (BMD). Women with SLE receive a recommendation not to get sun exposure. Usually vitamin D and calcium are supplied to patients using corticosteroids. Low vitamin D has been reported in women with SLE and has to be monitored carefully and systematically[36]. Another major risk factor, POI, is also more prevalent in this population (see above). Several large cohort studies have confirmed that those women are at increased risk of low bone mineral density (BMD) and high risk of vertebral fractures[37–41]. In the Toronto lupus cohort, 286 patients had a BMD. In premenopausal women ($n = 173$) with a mean age 31 ± 8 years, 17.3% had a Z-score below the expected range for age. In postmenopausal women ($n = 81$) with a mean age 52 ± 10 years, 43.2% had a low BMD and 12.3% had osteoporosis. Of 769 inception patients of this cohort, 11.1% experienced fragility fractures at a mean age of 48.8 ± 18.3 years old. In a very large cohort of SLE patients from United States Medicaid, 47,709 SLE patients were matched to 190,836 non-SLE controls[41]. The mean age was 41.4 years. 41.2% of SLE patients were prescribed glucocorticoids. The incidence of any fracture among SLE patients was 4.32 per 1000 person-years and 4.60 per 1000 person-years in patients with renal involvement and 2.40 per 1000 person-years in the comparators. Pelvic fractures were the most frequent ones in SLE patients. The risk for any fractures was two-fold in SLE patients (hazard ratio [HR] 2.09 (1.85–2.37)) with increased risk in hip, pelvic, humerus and wrist fractures. In case of nephritis, the HR = 3.06 (2.24–4.17). The RR was a little attenuated after adjustment on steroid treatment[41]. The increase in the risk was about two-fold in women above 50 years. In both studies, the prevalence of treatment by bisphosphonates was low. The treatment of osteoporosis is out of the scope of this review and will not be addressed in detail, but its systematic evaluation and follow-up are mandatory in those women. The American College of Rheumatology has published guidelines for management of glucocorticoid-induced osteoporosis[42] to which one can refer.

Risk of breast cancer, endometrial and ovarian cancers

Whereas there is an increased risk in lymphoma and leukemia in patients with SLE, a meta-analysis gathering results from five large studies suggested a decrease in risk of breast and gynecological cancers in women with SLE. Among 42,171 SLE women, there were 376 breast cancers, 66 endometrial cancers, and 44 ovarian cancers. The total number of cancers observed was less than that expected, with standardized incidence ratios of 0.76 (0.69–0.85) for breast cancer, 0.71 (0.55–0.91) for endometrial cancer, and 0.66 (0.49–0.90) for ovarian cancer[43].

Risk of incident lupus in women using MHT

A meta-analysis reported an increased risk of incident lupus in women treated with MHT. The RR was 1.96 (1.51–2.56)[12]. Confirming the causal plausibility of the association, the data from the Nurses' Health Study showed an increased risk with increased duration of use. Furthermore, incident discoid lupus was as well more frequent. Interestingly, the study by Meier *et al.*[44] found a lower risk in patients treated with combined MHT compared with unopposed estrogen and similarly, in the Nurses' Health Study, in women with surgical menopause, very likely using estrogen alone, were at higher risk[45] (Table 1).

Table 1. Risk of incident SLE in women taking MHT.

	Relative risk (95% confidence interval)
Nurses' Health Study[63]	
Ever users	2.1 (1.1-4)
Current users	2.5 (1–2.5)
1 to 4 years	1.8 (0.9–3.8)
5 to 10 years	2.7 (1.2–6.4)
>11 years	3.5 (1.2–10.9)
Nurses' Health Study[45]	
Ever users	1.9 (1.2–3.1)
Surgical menopause	2.3 (1.2–4.5)
Meier *et al.*[44]	
Long-term users >2 years	2.8 (1.3–5.8)
Short-term users	2.8 (0.9–9.0)
Estrogen users	5.3 (1.5–18.6)
E + P users	2 (0.8–5.0)
Meta-analysis[12]	1.96 (1.51–2.56)

SLE, systemic lupus erythematosus; MHT, menopausal hormone therapy; E, estrogen; P, progesterone

Outcomes of clinical trials of MHT in women with SLE

Two randomized controlled trials (RCT) have studied the impact of MHT in women with SLE[46,47]. Their results are mostly reassuring but cannot be applied to all categories of lupus (Table 2).

In the first double-blind non-inferiority RCT[46], 351 postmenopausal women (mean age, 50 years) with an inactive (81.5%) or a stable-active (18.5%) disease, with prednisone dosage of 0.5 mg/kg per day or less, SLE women received conjugated estrogens (CE) and a progestin (CE = 0.625 mg/day + medroxyprogesterone acetate (MPA) = 5 mg × 10 days) or a placebo and were followed for 1 year. The primary outcome was flares. The main exclusion criteria were presence of APLs (high titer), history of arterial or VTE, an unstable HTA. Seventy women in the MHT group and 55 in the placebo group discontinued the treatment or were lost before completion of the study. Severe flares occurred in 13 of the 174 patients (7.5%) in the active group and eight of the 177 (4.5%) in the placebo group, and were not significantly increased in women taking MHT for 1 year. However, mild to moderate flares were increased in the active group: 1.14 flares/person-year for MHT and 0.86 flares/person-year for placebo, RR = 1.34 (1.07–1.66). The probability of any type of flare at 1 year was 0.64 for the MHT group and 0.51 in the placebo group. In the active group, the annual rate of severe flares was double (0.081) compared to placebo (0.049) but non-significant. Women with a stable-active lupus had a higher risk of severe flare, RR = 2.87 (1.19–6.92), especially if there was renal involvement. The rate of mild to moderate flares was significantly different, from 1.14 flares/women-year for MHT users and 0.86 flares/women-year in the placebo group (RR = 1.34 [1.07–1.66])[46] (Table 2). In the active group, one death, two VTE, one stroke and one thrombosis in an arteriovenous graft occurred and one VTE in the placebo group. The authors concluded that the benefits of MHT can counterbalance the risk of flares which remained mild.

The second RCT included 106 women in menopausal transition or postmenopausal, randomized between MHT (CE = 0.625 mg/day + MPA 5 mg/day 10 days) ($n = 52$) or a placebo ($n = 54$). The follow-up was scheduled for 2 years but 44 and 45 women were followed 1 year and 37 and 38 during 2 years, respectively[47]. The exclusion criteria were a history of thrombosis in the past 6 months, a highly active SLE (SLEDAI >30), age >65 years[47]. The presence of APLs was not an exclusion: 20 women in the active group were carriers including 14 with a lupus anticoagulant or an ab-antiβ2GP1. The main outcome was SLEDAI (index of SLE activity). The proportion of women using an anticoagulant treatment was not given. No difference was observed in the SLEDAIs within groups, expressed as mean or AUC. There was no difference for the number of flares, RR = 0.96 (0.70–1.32). Three patients in the active group developed a thrombosis: one VTE and two arterial and one arterial in the placebo group in a patient with an APL.

Raloxifene is indicated in the prevention and treatment of vertebral osteoporosis in postmenopausal women. Its antiestrogen activity could be in theory of interest in women with SLE. Its limitation is the increased risk of VTE. A RCT has followed up 30 women with SLE using raloxifene and 32 women using placebo. In that small study, the treatment was efficient on lumbar BMD and well tolerated without any thrombosis[48]. But, in addition to the risk of VTE, that treatment does not alleviate climacteric symptoms and may even worsen them.

Tibolone could also be an alternative to estrogen in women with SLE due to its mild androgenic and progestin potencies. A RCT has shown that tibolone was efficient on fracture prevention in women with osteoporosis but was associated in these aged women (mean age 67 years) with an increased risk of stroke[49]. In studies in younger women, no c-v increased risk was observed. Among SLE women, a RCT has evaluated the tolerance of tibolone in 30 women (mean age: 51.8 ± 1.9 years) vs. placebo (51.5 ± 2.3 years), with a low SLEDAI, no APL, no history of thrombosis, and followed for 1 year[50]. Treatment was efficient on climacteric symptoms and well tolerated. It is a small short-term study. It would not be advised to use it in women with the above criteria of high c-v risk.

Table 2. Risk of flares in women with SLE and using MHT.

Arden[51], UK Mean follow-up: 12 months	Retrospective study, 30 users vs. 30 non-users	No difference
Kreidstein[64], Canada Mean follow-up: 12 months	Observational prospective 16 users vs. 32 non-users	No difference
Mok[65], Hong-Kong Mean follow-up: 12 months	Observational prospective 11 users vs. 23 non-users	No difference
SELENA MHT, Buyon[46], USA 12 months Severe flares Moderate to mild flares	Randomized controlled trial CE + MPA vs. placebo	 1.75 (0.73–4.22) 1.34 (1.07–1.66)
Sanchez-Guerrerro[47], Mexico 12 months SLEDAI	Randomized controlled trial CE + MPA vs. placebo 52 vs. 54	No difference in flares, SLEDAI
Hochman[52], Canada Coronary artery disease (CAD)	Observational prospective 114 users vs. 227 non-users	No difference in CAD

CE, conjugated estrogen; MPA, medroxyprogesterone acetate; SLEDAI, index of SLE activity; SLE, systemic lupus erythematosus; MHT, menopausal hormone therapy.

Observational or retrospective studies of MHT on a small number of patients did not report any worsening of the disease or cardiovascular events (Table 2). However, some information was missing in some of the studies and selection of patients with less active disease was very likely. In the study by Arden *et al.*[51], the magnitude of change in disease activity was not mentioned as well as the exclusion criteria. In the study by Kreidstein *et al.*, there was a large difference in age between women receiving the treatment and controls (41 vs. 30 years). The study from Hochman *et al.*[52] was conducted in a subgroup of the Toronto Lupus Clinic cohort, followed prospectively. Among the cohort, 114 patients with SLE and no previous coronary heart disease were identified as having used MHT and were compared to 227 non-users of MHT. There were some differences between groups which could constitute confounding factors: age at diagnosis, 35.2 ± 10.6 years for the treated group vs. 43.8 ± 14.1 and thus duration of lupus longer in non-users (increased risk of c-v events), age at menopause younger in the active group (increase in the risk of c-v events), 43.2 ± 7.3 years vs. 46.3 ± 5.0 years, and more patients using antimalarial drugs in the active group (decrease in the risk and SLE less severe?). The usual c-v risk factors were equivalent in both groups. The follow-up after menopause was approximately 13 ± 8 years. The number of cases of coronary artery disease that occurred during the long follow-up was not different between groups, with 13 (11.4%) and 31 (13.7%), respectively[52].

Management of climacteric symptoms in women with SLE

As shown in the previous paragraph, there is no extensive information on safety of MHT in women with SLE. As a consequence, recommendations are based on what is known in non-SLE women and expert opinion. Among available treatments, transdermal estradiol (E2) is at lower risk for coagulation activation and VTE risk[53,54]. Use of micronized progesterone (P) or dydrogesterone or a close pregnane is also neutral on the risk of VTE[53]. The risk of ischemic stroke was also not increased in women using transdermal E2 in two studies, at least at usual doses (≤50 μg/patch)[55,56]. Similarly, the risk of stroke was only increased as for VTE with norpregnane progestogens. Concerning the risk of MI, there are very few data. One large study from USA also reported less c-v diseases (including stroke, coronary heart disease, angina and congestive heart failure) with transdermal than oral E2[57]. There are no specific data on the use of transdermal estradiol in women with SLE, and it is not known whether transdermal estradiol might be associated with the same risk of moderate flares than the oral route.

In women with SLE as stated above, risk of c-v and VTE events is higher than in healthy women. Thus if any MHT is decided, the type of treatment recommended should be low-dose transdermal E2 + P or dydrogesterone. Posology is adapted to clinical efficacy.

Who could benefit from MHT among SLE women?

When available, the type of MHT used was CE + MPA, known to increase more the risk of VTE and arterial thrombosis. No data are available with other types of treatment. If SLE has been severe, with renal involvement, long duration of disease, where there is a major risk of accrual damage, we can guess that MHT may worsen the evolution in those patients with severe endothelial dysfunction. Due to the risk of flares, if a MHT is initiated, a close follow-up on clinical and biological markers has to be developed. RCT have proven that MHT is as efficient as in healthy women to alleviate climacteric symptoms in women with SLE[46,47,58].

The EULAR recommendations (expert group from European League Against Rheumatism) on menopause treatment in women with SLE was 'HRT can be used for the management of severe vasomotor menopausal manifestations in SLE women with stable/inactive disease and negative aPL (1/A). The use of HRT in patients with positive aPL should be carefully weighed against the risk of thrombosis and cardiovascular disease (–/D)'[59].

When E2 is contraindicated, P may be efficient on vasomotor symptoms. In addition, P is beneficial on sleep disorders[60,61]. P and dydrogesterone are contraindicated only in case of breast cancer. We suggest to use them as a first-line therapy to treat climacteric symptoms in women with contraindication to estrogen. Topical estrogens are authorized and can be combined with P. But this treatment is not active on osteoporosis and the management of it should be monitored independently.

Selective serotonin or noradrenaline reuptake inhibitors constitute an alternative therapy used in women with contraindications to MHT such as with breast cancer[62]. These drugs are not contraindicated in women with SLE as well as the other non-hormonal alternatives.

Women have to be aware that phytoestrogens may be responsible for flares (personal data).

Life-style interventions are of major importance, as in other women. Maintaining a normal body mass index, exercising with adaptation to the clinical situation, stopping smoking, limiting alcohol consumption, and maintaining an adequate intake of calcium and vitamin D are recommended.

Conclusions

Despite the fact that women with SLE are at higher risk of POI, c-v events and osteoporosis at young age, those women are not always good candidates for MHT. Thirty percent of them may carry an APLs which can be extremely deleterious with the risk of arterial and VTE. A careful evaluation of the condition of the woman in conjunction with the expert involved in its follow-up will help to discriminate which one can benefit from MHT. If indicated, transdermal E2 at low dose combined with P or dydrogesterone can be used. Close monitoring of lupus activity is then recommended. P can alleviate climacteric symptoms and sleep disorders and can be combined with topical estrogens which are not

contraindicated even in women with APLs. Non-hormonal alternatives can always be used.

Potential conflict of interest None. I am a member of an advisory board for estetrol, Mithra, but do not speak of estetrol in this review.

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