

# Safety of Hormone Replacement Therapy (HRT) in Systemic Lupus Erythematosus (SLE)

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Despite its obvious benefits, many physicians are reluctant to prescribe HRT to patients with SLE. We have performed a retrospective study in 60 postmenopausal women with SLE including 30 HRT users and 30 never users. The patients were studied for 12 months after the initiation of HRT. The two groups were well matched for disease characteristics. The HRT users experienced significant improvements in general well being, libido and depression. There was no significant difference in any other parameter measured. There was no increase in the number of thrombo-embolic events in the user group despite 7 patients having a positive thrombophilia screen. In conclusion, in stable postmenopausal SLE HRT appears well tolerated and safe.

**Key Words:** Systemic lupus erythematosus Hormone replacement therapy Thromboembolic events

## Introduction

Hormone replacement therapy (HRT) is widely accepted as the treatment of choice for menopausal vasomotor symptoms, the prevention and treatment of postmenopausal osteoporosis<sup>1</sup> and has proven efficacy in the management of steroid-induced osteoporosis<sup>2</sup>. It has also been shown to reduce the incidence of ischaemic heart disease (IHD) by up to 60% in current users<sup>3</sup>. Women with SLE have an increased risk of osteoporosis due to a combination of long-term corticosteroid use, ovarian dysfunction and the increased incidence of premature menopause. They also have an increased incidence of and mortality from IHD<sup>4</sup>. SLE is regarded by most physicians as a relative contraindication to HRT as it is believed to be an oestrogen-dependent disease. It predominantly affects females of childbearing age and the oral contraceptive pill is said to cause flares in SLE<sup>5</sup> although the literature on this topic is controversial<sup>6</sup>. Individual case reports suggest that postmenopausal HRT can act in a similar fashion<sup>7</sup>. There is also concern about the potential thrombotic tendency of oestrogens<sup>8</sup>, particularly in patients at high risk of thromboembolic events related to the antiphospholipid syndrome<sup>9</sup>.

## Subjects and methods

We performed a retrospective telephone questionnaire with hospital record validation. The names of all women with SLE aged 34-60 years were obtained from the St. Thomas' Hospital Lupus Register. Of the 165 names identified, 137 were contacted by telephone of whom 35 were HRT ever users and 30 HRT never users. The files of all patients from

the lupus death register were examined and revealed that no patient had been on HRT within 1 year of their death. Each HRT user was paired with the best available age matched never user and both patients were questioned about the 12 month period following the initiation of HRT in the user. Information was obtained via a standardized telephone questionnaire relating to: HRT compliance and reasons for discontinuation, changes in general disease activity, cutaneous manifestations, hypertension, thromboembolic events, arthritis, depression and migraines, general well-being, libido, changes in drug treatment and admission to hospital and several control symptoms (bowel habit, hearing and visual acuity). The medical records were inspected to validate these results and to record changes in laboratory variables. Parametric variables were analysed using the paired Student's *t*-test and non-parametric variables using the chi-squared test. The two groups were well matched with no significant difference in racial origin (92% Caucasian), disease duration, years postmenopause, clinical disease characteristics (especially renal and neurological complications), laboratory variables, serology, smoking and steroid use (Table I). The HRT never users were older (50.9 vs. 48.2 years,  $P = 0.045$ ), had a later menopause (46.6 vs. 43.8 years,  $P = 0.023$ ) and were less likely to have ever reported symptoms of depression (38% vs. 65.5%,  $P < 0.05$ ).

## Results

The average duration of HRT use at the time of the survey was 23.7 (range 1-132) months with 21 of 30 being current users. Of the nine ex-users, five stopped due to known side-effects of HRT and one due to lack of efficacy. Two stopped due to symptoms attributable to SLE (arthralgia and general malaise). In one patient this was attributed

**Table 1** Patient characteristics.

	HRT users (n = 30)	HRT never users (n = 30)	Significance
Disease duration (years) (SD)	15.7 (10.2)	18.0 (11.1)	NS
Years postmenopause (SD)	4.5 (4.9)	4.3 (3.9)	NS
Antinuclear antibody (n)	26 (86)	26 (86)	NS
Anti-Ro antibody (n)	11 (38)	11 (38)	NS
Lupus anticoagulant (n)	3 (11)	5 (17)	NS
Anticardiolipin antibody (n)	5 (17)	8 (27)	NS
Previous thromboembolic events (n)	8 (27)	9 (30)	NS

Values in parentheses are percentages unless indicated otherwise.  
NS: not significant.

to HRT as symptoms resolved on discontinuation. In the second, the flare coincided with cessation of all SLE medication including prednisolone and hydroxychloroquine. The final patient, who was African with marked discoid lesions, stopped due to increasing skin pigmentation. However, this continued to progress after the withdrawal of HRT and was probably unrelated.

The HRT users were significantly improved in terms of symptoms of depression ( $P < 0.005$ ), general well-being ( $P < 0.001$ ) and libido ( $P = 0.01$ ). There was no significant difference between the two groups in the number of flares of disease activity as assessed by patient reported flares, change in ESR or number of hospital admissions. Even though no significant differences were noted in changes in lupus therapy, in the user group less patients increased medication and more decreased medication (Table II). No differences were reported for the control symptoms. There was only one thromboembolic event in the HRT users which was a transient ischaemic attack (TIA) occurring 5 weeks after the discontinuation of HRT in a woman with a negative thrombophilia screen. In the HRT never users, there were three thromboembolic events: one thrombotic cerebrovascular accident in a patient with anticardiolipin antibodies, one TIA and one pulmonary embolus in patients with a negative thrombophilia screen. There were no thromboembolic events in the seven HRT users with a positive thrombophilia screen.

**Table 2** Changes in medication, ESR and admissions

	Ever users (n = 30)	Never users (n = 30)	Significance
Changes in ESR over 1 year	-13%	-9%	NS
Decrease in medication (n)	9 (30)	4 (13)	NS
Increase in medication (n)	3 (11)	5 (17)	NS
New medication (n)	0	1 (3)	NS
Hospital admissions (n)	2 (7)	5 (17)	NS

Values in parentheses are percentages.  
NS: not significant.

## Discussion

The two groups in the study were well matched in terms of disease characteristics. Most patients had relatively stable disease in accordance with the view that postmenopausal lupus is a relatively mild disease. The HRT compliance rate of 70% at 1 year compares favourably with studies of community-based compliance studies which suggests rates as low as 40% at 1 year<sup>10</sup>. As expected there was an improvement in general well-being, libido and depressive symptoms as in other groups of postmenopausal women. There were two disease flares in the user group compared with six in the never user group. In the two patients documented to have flared on HRT (one from our study and one from the case report<sup>7</sup>), withdrawal of the HRT resulted in clinical remission with no obvious long-term sequelae. Although no significant difference was found between the two groups in any other measured parameter, in most parameters the user group compared favourably with the never user group.

There was only one thromboembolic event in the user group, which occurred 5 weeks after discontinuation of HRT, despite there being seven patients in the group with a positive thrombophilia screen. This is in agreement with the recent literature which suggests that the low-dose conjugated oestrogens used in HRT do not carry a significantly increased risk of thrombosis, even in high risk patients<sup>11</sup>.

Retrospective studies are potentially liable to recall and surveillance bias. Both biases usually act by exaggerating adverse events in the exposed group and thus tending to overestimate the side-effects and obscure any benefits of HRT. Another problem is inaccurate recall; this problem was minimized by validation from hospital files and the use of hard data including ESR, changes in treatment and hospital admissions. Nevertheless, in view of these problems and the need to more accurately quantify the risks and benefits, a prospective study is now being performed.

In conclusion, in patients with relatively stable disease HRT appears to be well tolerated and safe. A positive thrombophilia screen per se should not be regarded as a contraindication to HRT but more research is needed in patients with a previous thromboembolic event. Stable postmenopausal patients with SLE, who are at a high risk of osteoporosis and cardiovascular disease, should not be denied the undoubted benefits of HRT.

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