FEMALE SEX HORMONES AT THE ONSET OF SYSTEMIC LUPUS ERYTHEMATOSUS AFFECT SURVIVAL

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SUMMARY
Female sex hormones affect susceptibility to systemic lupus erythematosus (SLE). To determine the effect of female sex hormones at onset of SLE on the survival of these patients, a retrospective survey was performed. The charts of 168 female SLE patients were evaluated to study the disease course, in particular the presence and kind of SLE criteria. Patients were classified as either belonging to the ‘high female sex hormone at onset (HH)’ or ‘low female sex hormone at onset (LH)’ group according to age at diagnosis. The statistics of the Dutch population, matched for age, were used to control for differences in life expectancy in these groups. A Cox regression model revealed that the relative mortality risk of HH patients vs HH controls was 4.2 times higher than the relative mortality risk of LH patients compared to LH controls. No differences in the frequency of SLE criteria between HH and LH patients were found that could explain the observed difference in mortality risk.

KEY WORDS: Systemic lupus erythematosus, Survival, Sex hormones.

SEVERAL observations suggest that oestrogens influence the incidence and disease course of systemic lupus erythematosus (SLE). The female to male ratio of SLE patients is 9:1 in the reproductive years, but much lower in the prepubertal period [1]. Oral contraceptives induced a 1.9 times higher chance of developing SLE in a prospective cohort study of 121 645 women [2]. It has been reported that 16α-hydroxylation of oestradiol is enhanced in patients with SLE, resulting in an increased concentration of relatively potent oestrogens like oestriol [3]. An extensive review summarizes the studies performed to elucidate the possible pathogenesis of the influence of oestrogens on autoimmunity [4]. Oestrogen receptors are identified on thymocytes, macrophages and endothelial cells. Furthermore, oestrogens influence cytokine production and the expression of genes involved in apoptosis [4].

In summary, there is ample evidence that female sex hormones affect the incidence and disease course of SLE. However, the influence of female sex hormones at the onset of disease on prognosis has been scarcely described. Although a number of studies report a worse prognosis in male lupus patients [5–9], the presence of androgens in these patients is likely to be of influence as well [10, 11]. Hence, the objective of this study is to investigate whether life expectancy differs between females who have high and low concentrations of female sex hormones at the onset of SLE.

PATIENTS AND METHODS
The charts of 168 consecutive female SLE patients who visited the out-patient departments of the Leiden University Hospital, Sophia Children’s Hospital in Rotterdam and Juliana Children’s Hospital in The Hague during the years 1985–1995 were studied. The date of diagnosis of SLE and SLE criteria present at diagnosis or developing during disease course were noted. Patients were followed until the last known contact with their physician or the time of death. Patients were classified as either belonging to the ‘high female sex hormone at onset (HH)’ or ‘low female sex hormone at onset (LH)’ group according to age at diagnosis. LH patients were women aged <14 yr, while HH patients aged ≥14–47 yr. Twelve female patients, 15–16 and 48–50 yr of age, were excluded because of possible doubt about their hormonal status. Life table analysis was performed with Dutch health statistics, matched for age, serving as the control. Hazard rates were calculated using Cox’s regression model with hormonal status, the presence or absence of SLE and the interaction term between these variables as variates.

RESULTS
Baseline characteristics of both groups are depicted in Table I. A total of 114 HH patients (mean age 29.3 yr, mean follow-up time 8.3 yr) were compared to 42 LH patients (24 patients ≤14 yr, mean age 11.3; ≥51 yr of age, 60.8 Mean age of patients ≥51 yr of age

<table>
<thead>
<tr>
<th>TABLE I</th>
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<tbody>
<tr>
<td><strong>High female sex hormones at onset</strong></td>
</tr>
<tr>
<td>Baseline characteristics</td>
</tr>
<tr>
<td>Mean age (yr)</td>
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<tr>
<td>Mean duration of follow-up (yr)</td>
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<tr>
<td><strong>Low female sex hormones at onset</strong></td>
</tr>
<tr>
<td>Baseline characteristics</td>
</tr>
<tr>
<td>Mean age of patients ≤14 yr of age</td>
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<tr>
<td>Number of patients ≥51 yr of age</td>
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<td>Mean age of patients ≥51 yr of age</td>
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<tr>
<td>Mean duration of follow-up (yr)</td>
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18 patients \( \geq 51 \) yr, mean age 60.8; mean follow-up
time for both groups 7.6 yr). SLE criteria that emerged
at diagnosis or during follow-up are shown in Table II. For
Although the difference in frequencies of photosensitivity and
leucopenia reached statistical significance, none remained
significance after correction for multiple testing
according to Bonferroni.

In the comparison between Dutch controls and SLE
patients, Cox regression analysis resulted in the following
relative mortality risks: LH SLE patients vs LH
to HH controls, 2.5; HH SLE patients vs HH controls, 10.5.
Thus, the relative mortality risk of HH patients vs HH
controls was 4.2 times higher than the relative mortality
risk of LH patients compared to LH controls
\( (P < 0.05) \).

**DISCUSSION**

The objective of this study was to investigate the
influence of female sex hormones at the time of diag-
nosis on the survival of SLE patients. In order to
achieve this goal, the patient population was divided
into a HH group, consisting of female SLE patients
who were in their reproductive years at the time of
diagnosis (17–47 yr), and an LH group, consisting of
female SLE patients \( \leq 14 \) yr or \( \geq 51 \) yr at diagnosis.
Considering the fact that the HH and LH patients
different life expectancies, the statistics for the
Dutch population, matched for age, were added to the
data set to control for this effect. Cox regression
analysis revealed that patients who developed SLE
during the reproductive years have a 4.2 times higher
relative mortality risk during any time of follow-up
compared to the controls than LH patients.

Given the retrospective character of this study, a
few remarks have to be made. Misclassification
of patients cannot be ruled out since the patients were
assigned to one of either groups based on epidemio-
logical grounds and not laboratory testing. In an
attempt to avoid misclassification, patients of 15–16
and 48–50 yr of age were excluded.

The survival of SLE patients mentioned here is an
overestimation of the true survival. The patients
included in this study visited the out-patient clinics
during the years 1985–1995. Hence, in some patients,
the diagnosis of SLE was made before 1985. On
average, these patients probably have less severe dis-
ease, because the severe SLE cases diagnosed before
1985 are more likely to have died during the years
from onset of SLE until 1985. However, no indication
is present that the time from diagnosis to entering the
study period differs between the two sex hormone
groups.

Furthermore, there might be additional confounding
factors not controlled for that can affect survival. For
instance, some SLE manifestations might influence
prognosis. In a cohort of 408 SLE patients, mortality
was associated with nephritis and seizures [12].
Nevertheless, in this study, the frequencies of SLE
criteria including nephritis and seizures did not differ
significantly between the two groups.

The frequency of leucopenia, however, differed
between groups. In the LH group, more patients had
leucopenia than in the HH group. After Bonferroni
correction for multiple testing, only a trend remained.
This is most likely caused by a difference in frequency
of neutropenia, since the frequency of lymphopenia
did not differ. It has not been previously reported that
neutropenia occurs more often in certain age groups.
A possible explanation for this phenomenon might be
that patients in the LH group have more active disease
than those in the HH group. However, more active
disease would probably lead to a higher mortality.
This is in contradiction with the fact that HH patients
have a higher mortality risk than LH patients.

**TABLE II**

<table>
<thead>
<tr>
<th>SLE criteria</th>
<th>LH group</th>
<th>HH group</th>
<th>( P^* )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis during disease course</td>
<td>92.9% (39/42)</td>
<td>95.6% (109/114)</td>
<td>0.49</td>
</tr>
<tr>
<td>Malar rash</td>
<td>59.5% (25/42)</td>
<td>47.4% (54/114)</td>
<td>0.11</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>26.2% (11/42)</td>
<td>50.9% (58/114)</td>
<td>0.006</td>
</tr>
<tr>
<td>Discoid lupus</td>
<td>16.7% (7/42)</td>
<td>27.2% (31/114)</td>
<td>0.17</td>
</tr>
<tr>
<td>Oral ulcers</td>
<td>45.2% (19/42)</td>
<td>40.4% (46/114)</td>
<td>0.58</td>
</tr>
<tr>
<td>Cellular casts</td>
<td>54.8% (23/42)</td>
<td>59.6% (68/114)</td>
<td>0.58</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>47.6% (20/42)</td>
<td>47.4% (54/114)</td>
<td>0.98</td>
</tr>
<tr>
<td>Serositis</td>
<td>69.0% (29/42)</td>
<td>62.3% (71/114)</td>
<td>0.43</td>
</tr>
<tr>
<td>Pleuritis</td>
<td>61.9% (26/42)</td>
<td>56.1% (64/114)</td>
<td>0.52</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>23.8% (10/42)</td>
<td>39.8% (45/113)</td>
<td>0.06</td>
</tr>
<tr>
<td>Seizures</td>
<td>16.7% (7/42)</td>
<td>18.4% (21/114)</td>
<td>0.80</td>
</tr>
<tr>
<td>Psychosis</td>
<td>11.9% (5/42)</td>
<td>5.2% (6/114)</td>
<td>0.15</td>
</tr>
<tr>
<td>Anaemia</td>
<td>76.2% (32/42)</td>
<td>59.6% (68/114)</td>
<td>0.06</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>52.4% (22/42)</td>
<td>38.6% (44/114)</td>
<td>0.12</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>75.6% (31/41)</td>
<td>49.1% (56/114)</td>
<td>0.003</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>19.5% (8/41)</td>
<td>28.9% (33/114)</td>
<td>0.24</td>
</tr>
<tr>
<td>Antinuclear antibodies</td>
<td>100% (42/42)</td>
<td>100% (114/114)</td>
<td></td>
</tr>
<tr>
<td>Anti-DNA</td>
<td>72.5% (29/40)</td>
<td>72.9% (78/107)</td>
<td>0.96</td>
</tr>
<tr>
<td>Anti-Sm</td>
<td>35.7% (5/14)</td>
<td>33.3% (8/24)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

*Without Bonferroni correction for multiple testing.*
Moreover, other parameters for SLE activity do not differ between groups.

Oestradiol augments the binding of anti-SS-A/Ro and anti-SS-B/La to the cell surface of human keratinocytes. Binding of these antibodies to keratinocytes has been implicated in the pathogenesis of photosensitivity in subacute cutaneous lupus erythematosus and neonatal lupus erythematosus [13]. In line with this hypothesis, the frequency of the presence of photosensitivity in the HH group exceeded that in the LH group (50.9% vs 26.2%, not significant after Bonferroni correction). It is unlikely that this difference could explain the observed increase in mortality risk in the HH group.

In conclusion, a significantly higher mortality risk is observed in patients who have developed SLE during the reproductive years than in patients who have developed SLE during the non-reproductive years, using Dutch health statistics to control for age differences in survival.

References