Premature ovarian failure in patients affected by systemic lupus erythematosus: a cross-sectional study

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Abstract

Objective

We evaluated age at natural menopause and the prevalence of premature ovarian failure (POF) in a monocentric Caucasian cohort of patients with systemic lupus erythematosus (SLE).

Methods

In this cross-sectional study, we enrolled women affected by SLE compared with healthy controls (HC) to investigate data about natural menopause (amenorrhoea for at least 12 months at ≥40 years) and POF (amenorrhoea for at least 12 months at <40 years).

Results

We enrolled 196 SLE (median age 47.0 years, IQR 16.7; median disease duration 132 months, IQR 180) and 90 HC (median age 49.9 years, IQR 15.0). Ninety-four SLE (48.0%) and 26 HC (23.4%) were menopausal: median age at onset was significantly lower in SLE than HC (47 years, IQR 8.0 vs. 50.5 years, IQR 4; p=0.0001). POF was registered in 17% of the SLE, and in none of the HC (p<0.0001). POF was significantly associated with anti-Sm (p=0.0004), anti-RNP (p=0.02), anti-cardiolipin (p=0.0008), lupus anticoagulant (p=0.0002), treatment with cyclophosphamide (p=0.0001), azathioprine (p=0.0001), mycophenolate mofetil (p=0.0001), cyclosporine A (p=0.007).

Conclusion

SLE patients develop menopause at a younger age; moreover, a higher POF frequency was observed in SLE patients in comparison with HC. POF is associated with specific SLE-related autoantibodies and the use of immunosuppressant drugs, in particular cyclophosphamide.

Key words

systemic lupus erythematosus, menopause, menopausal status, antibodies, premature ovarian failure, autoimmunity

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Introduction

Natural menopause is defined as the permanent interruption of menstruation due to loss of ovarian follicular activity; it occurs after 12 consecutive months of amenorrhoea, without a pathologic aetiology (1).

The age at natural menopause seems to be mainly influenced by genetic factors; moreover, several studies reported an association between menopausal age and socio-economic status, ethnicity and lifestyle background. Women suffering from autoimmune diseases, such as systemic lupus erythematosus (SLE), seem to develop menopause at younger age. Indeed, hormonal factors play a fundamental role in SLE development, as also demonstrated by the prevalent involvement of women of reproductive age (2-6).

Furthermore, a higher frequency of ovarian dysfunction has been described in SLE: these patients could experience increased menstrual flow, oligomenorrhoea, temporary amenorrhoea, earlier menopause and premature ovarian failure (POF), defined as the permanent interruption of menstruation before the age of 40 years (7-10). The presence of a cause-effect link between the disease and such modifications remains poorly understood. The role of disease activity and chronic damage, together with the administration of immunosuppressant drugs, has been suggested (8).

In particular, it is well known that cyclophosphamide (CYC) treatment may cause ovarian insufficiency, with a prevalence ranging from 11% to 59% of treated patients; the risk seems to be associated with patients' age and cumulative drug dosage (11).

Conversely, few data are available concerning POF development in non-CYC treated patients. In this setting, a prevalence similar to general population (0.6–2.7%) has been described in SLE. Nevertheless, an association with disease activity and anti-corpus luteum antibodies has been observed, suggesting an autoimmune aetiology (7, 12, 13). Moreover, data from the LUMINA cohort showed an association between POF and Texan-Hispanic ethnicity, regardless of CYC treatment (14).

Moving from these premises, we performed a cross-sectional study in a large monocentric Caucasian SLE cohort in order to evaluate the prevalence of POF and its associations with disease features.

Patients and methods

We enrolled consecutive women with SLE referring to the Lupus Clinic of the Rheumatology Unit, Sapienza University of Rome (*Sapienza Lupus Cohort*). Patients were classified according to the revised 1997 American College of Rheumatology criteria (15). Healthy women without any autoimmune disease referring to the Gynaecology Department of Sapienza University of Rome were consecutively enrolled as the control group. Both patients and controls provided written informed consent at the time of the enrollment. The study was approved by the ethics committee of Policlinico Umberto I, Rome.

For each SLE patient, the clinical and serological data, including demographics, past medical history with the date of diagnosis and treatments, were collected in a standardised, computerised, and electronically filled form. The study protocol included the determination of autoantibodies and the evaluation of C3 and C4 serum levels. Antinuclear antibodies (ANA) were determined by indirect immunofluorescence (IIF) on HEp-2 (titre ≥1:160 or ++ on a scale from + to ++++), anti-double-stranded DNA (ds-DNA) with IIF on Crithidia Luciliae (titre ≥1:10), ENA (including anti-Ro/SSA, anti-La/SSB, anti-Sm, and anti-RNP) were analyed by enzyme-linked immunosorbent assay (ELISA) considering titres above the cut-off of the reference laboratory, anti-cardiolipin (aCL) (IgG/IgM isotype) were analysed by ELISA, in serum or plasma, at medium or high titres (*e.g.* >40 GPL or MPL or above the 99th percentile), anti-β2 glycoprotein-I (anti-β2GPI) (IgG/IgM isotype) analysed by ELISA, in serum (above the 99th percentile), and lupus anticoagulant (LA), according to the guidelines of the International Society on Thrombosis and Hemostasis. Finally, C3 and C4 serum levels were determined by radial immunodiffusion.

By interview, obstetric and gynaecological features were investigated in

both patients and controls: in particular, we registered age at menarche, occurrence and age of menopause, history of hysterectomy. Natural menopause was defined as the absence of menses for at least 12 months in women aged ≥40 years. As above reported, POF was defined as amenorrhoea for at least 12 months in women <40 years.

In SLE patients, at the time of enrolment we assessed chronic damage by a modified SLICC Damage Index (SDI) (16), excluding the item regarding premature gonadal failure.

Statistical analysis

Categorical variables are summarised as frequencies and percentages, while continuous variables are presented as means and standard deviation (SD) or median (range) and interquartile range (IQR), if normally or non-normally distributed, respectively. Mann-Whitney test was performed when appropriate. Univariate comparisons between nominal variables were calculated using chi-square test or Fisher's exact-test, where appropriate.

Multivariate analysis was performed using binary logistic regression. The results are presented as ORs with their 95% CIs. In order to perform the multivariate analysis, we used a step-forward model including, progressively, those variables with $p<0.1$ (so also those that showed a trend of an association) to have a stronger model. *p*-values less than 0.05 were considered significant. We used version 13.0 of the SPSS statistical package.

Table I. Demographic, clinical, laboratory and gynaecological characteristics, and treatment history of 196 SLE women enrolled in the study.

	SLE women (n=196)	Menopausal SLE women (n=94)
Demographic features		
Median age, IQR (years)	47.0, 16.7	49.0,11.0
Median disease duration, IQR (months)	132.0, 180.0	138.0, 228.0
Median SDI, IQR	0, 1	0, 1
SDI ≥1, n (%)	63 (32.1)	36 (38.3)
Current smoking, n (%)	54 (27.5)	29 (30.8)
Past smoking, n (%)	35 (17.8)	18 (19.1)
Median BMI, IQR	23.3, 5.3	23.1, 6.4
Antiphospholipid syndrome, n (%)	40 (20.4)	19 (20.2)
Autoimmune disease, n (%)	41 (20.9)	21 (22.3)
Gynaecological characteristics		
Mean age at menarche ± SD	12 ± 1.4	12.1 ± 1.4
Menses in previous 12 mts		
Present, n (%)	102 (51.5)	0
Absent, n (%)	94 (48)	94 (100)
History of hysterectomy, n (%)	7 3.5)	7 (7.4)
Clinical manifestations, n (%)		
Malar rash	147 (75)	72 (76.6)
Discoid rash	8 (4.1)	5 (5.3)
Joint involvement	169 (86)	86 (91.4)
Serositis	40 (20.4)	20 (21.2)
Renal involvement	50 (25.5)	22 (23.4)
Neuropsychiatric involvement	26 (13.2)	16 (17)
Haematological manifestations	106 (54.1)	45 (47.9)
Low C3/C4 level	117 (59.7)	51 (54.2)
Laboratory manifestations, n (%)		
ANA	196 (100)	94 (100)
Anti-dsDNA	97 (49.5)	38 (40.4)
Anti-SSA	67 (34.2)	33 (35.1)
Anti-RNP	29 (14.8)	14 (14.9)
Anti-Sm	27 (13.7)	13 (13.8)
Anti-SSB	26 (13.2)	11 (11.7)
Anti-cardiolipin IgG/IgM	58 (29.5)	29 (30.8)
Anti-β2Glicoprotein I IgG/IgM	32 (16.3)	16 (17)
Lupus anticoagulant	44 (22.4)	20 (21.2)
Treatments, n (%)		
Glucocorticoids	196 (100)	94 (100)
Hydroxychloroquine	185 (94.3)	87 (92.5)
Mycophenolate mofetil	51 (26)	24 (25.5)
Methotrexate	43 (21.9)	27 (28.7)
Azathioprine	67 (34.1)	34 (36.1)
Cyclosporine A	44 (22.4)	21 (22.3)
Cyclophosphamide	33 (16.8)	18 (19.1)

Results

We consecutively enrolled 196 Caucasian women with SLE (median age 47.0 years, IQR 16.7; median disease duration 132 months, IQR 180). Table I reports the demographic, clinical, laboratory and gynaecological features, and treatment during disease course.

As controls, we enrolled 90 HC (median age 49.9 years, IQR 15.0). Ninety-four SLE patients (48.0%) and 26 HC (23.4%) were in menopausal status: the median age at occurrence was significantly lower in SLE than HC (47 years, IQR 8.0 *vs*. 50.5 years, IQR 4; $p=0.0001$; Fig. 1).

Among the SLE patients, a natural menopause was observed in 70 subjects (74.4%), surgical in 7 (7.4%), iatrogenic (specifically drug-induced) in 17 (18.1%). In particular, 13 (13.8%) SLE patients referred the occurrence of menopause after CYC exposure. The median age at the time of CYC exposure was 29 years (IQR 15.5), the median interval between treatment and menopause occurrence was 5.5 years (IQR 10.7).

For further evaluation, we excluded SLE patients with POF due to surgical procedures. Thus, POF was reported by 16/87 patients (18.4%); this prevalence was significantly higher in comparison with HC group, in which none of subjects experienced POF ($p=0.0001$).

By comparing SLE patients with and without POF, a significantly higher frequency in the prevalence of anti-Sm (31.2% *vs*. 10.2%; $p=0.0004$), anti-RNP (25.0% *vs*. 12.8%; $p=0.02$), aCL (50.0% *vs*. 26.9%; $p=0.0008$) and LAC (37.5% *vs*. 17.9%; $p=0.002$) was observed. Concerning the association with treatment, as expected, CYC was more frequently taken in patients who developed POF (56.0% *vs*. 11.0%; $p=0.0001$).

Moreover, these subjects showed a

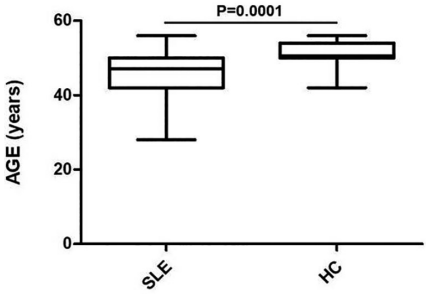

Fig. 1. Box and whiskers plot (median, quartiles, range) representing age at the menopause onset in systemic lupus erythematosus - SLE (n=94) and healthy controls - HC (n=26).

significant more frequent history of treatment with azathioprine (62.5% *vs*. 30.7; *p*=0.0001), mycophenolate mofetil (50% *vs*. 20.5%; *p*=0.0001) and cyclosporine A (37.5% *vs*. 19.2%; *p*=007). No significant differences were found in terms of clinical manifestations and mean SDI.

A multivariate analysis to evaluate the factors associated with POF occurrence was performed. The logistic regression confirmed the association between POF and CYC exposure (*p*=0.007, OR 6.6, 95%CI 1.6–26.4).

Discussion

In the present study, performed on a large Caucasian SLE cohort, we observed a significantly lower age at menopause in SLE patients in comparison with HC; in addition, a significantly higher frequency of non-surgical POF was observed.

Since SLE occurs mostly in women of child-bearing age, the reproductive health is an important topic, significantly influencing patient's quality of life. Pregnancy planning could be difficult for SLE patients not only due to disease activity and treatments, but also due to decrease in fertility and shortness of fertile period (17, 18). Furthermore, it should be considered the relationship between menopause and complications of SLE, especially osteoporosis and premature atherosclerosis. In fact, SLE as well as menopause are risk factors for osteoporosis and fragility fracture (19). Moreover, the risk of cardiovascular disease, the most common cause of death in SLE patient, can be increased by POF occurrence (20).

We moved from a review of data published so far in the literature concerning menopause in SLE cohorts: the main results are summarised in Table II. Only two studies specifically evaluated the age at menopause occurrence. Our results are in agreement with the study conducted in a Finnish cohort by Ekblom-Kullberg and colleagues, showing a mean age at menopause of 44.9 years (18). Conversely, Alpizar-Rodriguez and colleagues observed higher mean age in a Mexican population (46.4 years) (1). These results could suggest a possible role of ethnicity in determining the age at menopause. Moving on POF occurrence, we identified a prevalence of 18.4% in our cohort. This was higher compared with HC and previously assessed cohorts. Similarly to menopausal age, we hypothesised the possible role of ethnicity. In fact, all the studies – except for the analysis conducted by Ekblom-Kullberg and colleagues – evaluated other-than Caucasian cohorts, with a prevalence of POF ranging from 5.4% to 12.0% (18).

As previously described, we observed a significant association between POF and CYC treatment, confirmed at multivariate analysis. Data from literature described a prevalence of POF in CYC-exposed SLE patients ranging from 11% to 59%, depending on the study design, drug dosage and patients' features (23-29). In particular, the risk of CYC-related POF seems to be associated with patient's age and cumulative drug dosage (11).

Moreover, in our cohort we identified at univariate analysis a significant association between POF and other immunosuppressive agents, in particular, mycophenolate mofetil, azathioprine and cyclosporine A. This association has not been previously observed in the literature. We can speculate the role of a more severe disease course requiring immunosuppressive therapy, as suggested by the lack of association at multivariate analysis. Indeed, several studies suggested that SLE disease activity is involved in the development of ovarian dysfunctions (8).

In this context, we could explain the association between POF and positivity for anti-Sm and anti-RNP autoantibodies. In particular, anti-Sm can be detected in 5–30% of SLE patients (31-32) and seem associated with disease activity and the occurrence of disease flares (33, 34).

Finally, we found an association between POF and antiphospholipid (aPL) antibodies, specifically aCL antibodies. These antibodies are associated with thrombotic events, including ovarian vein thrombosis and reproductive failure in women with SLE or primary aPL syndrome (35-37). By evaluating a large cohort of POF patients, Chernyshov *et al*. observed a higher frequency of aCL in comparison with healthy

Table II. Studies on menopause in SLE cohorts.

Study	n	Ethnicity	Mean age at menopause (years)	POF (%)	Identified risk factors
Medeiros, 2001[21]	71	NS	NS	11.3	Olderage, CYC
Gonzalez, 2008[14]	316	Hispanic, Afro-American	NS	11.7	Disease activity, Texan-Hispanic ethnicity, CYC
Ekblom-Kullberg, 2009[18]	206	Finnish	44.9	13.1	NS
Alpizar-Rodriguez, 2014[1]	961	Mexican	46.4	NS	Age at SLE diagnosis
Akawatcharangura, 2015[21]	92	Thai	NS	12.0	CYC, duration of disease
Mayorga, 2016[7]	961	Mexican	NS	5.4	Disease activity, CYC

NS: not specified; CYC: cyclophosphamide; POF: premature ovarian failure.

controls (38). In addition, aCL positivity have been associated with lower estradiol levels in premenopausal SLE patients (39). These evidences, together with our results, could suggest a possible role of aPL, in particular aCL, in POF development.

Certainly, the present study shows some limitations, in particular the small sample size of both menopausal SLE patients and controls and the retrospective nature of the study. Moreover, a recalling bias could influence the results. Further studies, with larger SLE cohorts and a prospective design should be performed in order to confirm our results.

In conclusion, our study provides information about the menopausal age and POF occurrence in a SLE Caucasian cohort. In particular, we identified a higher prevalence of POF associated with specific SLE-associated antibodies and immunosuppressant treatment.

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