The Egyptian Rheumatologist 42 (2020) 207–211

Contents lists available at ScienceDirect

The Egyptian Rheumatologist

journal homepage: www.elsevier.com/locate/ejr

Original Article

Impact of cyclophosphamide on gonadotropins in menopausal systemic lupus erythematosus patients: Relation to disease activity and damage

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ARTICLE INFO

Article history:
Received 30 May 2020
Accepted 4 June 2020
Available online 24 June 2020

Keywords:
SLE
Menopause
Damage
Disease activity
Gonadotropins

ABSTRACT

Background: Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease that affects females at reproductive age, where lupus patients experience menopause at younger age. It is debated whether early menopause in lupus patients results from gonadotoxic effect of cyclophosphamide treatment or an autoimmune mediated ovarian injury.

Aim of the work: To identify menopausal symptoms and characteristics in an Egyptian cohort of SLE females and its relation to disease activity, disease damage, lupus nephritis and treatment.

Patients and methods: 120 consecutive SLE female patients above the age of 35 were studied. Disease activity was assessed by SLE Disease Activity Index (SLEDAI), and accumulated damage by Systemic Lupus International Collaborative Clinics-Damage Index (SLICC-DI). Laboratory assessment was done including follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels.

Results: The mean age of the patients was 45.1 ± 8.2 years (35–63 years) and the age at menopause was 45.2 ± 7.3 years (26–54 years). Their mean disease duration was 5.1 ± 5.7 years (1 month to 21 years). The mean SLEDAI was 4.7 ± 3.5 and SLICC-DI was 0.63 ± 0.82. 24 (20%) of patients had premature menopause, 29.2% had natural menopause and 50.8% were menstruating. There was a significant negative correlation between LH and SLEDAI. There was a significant correlation of FSH and LH with the cumulative cyclophosphamide dose.

Conclusion: SLE patients have early mean age of menopause at 45 years. High LH is associated with lower disease activity. High cumulative cyclophosphamide dose is associated with high FSH and LH. cyclophosphamide is potentially associated with premature menopause.

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1. Introduction

Systemic lupus erythematosus (SLE) is a chronic inflammatory autoimmune disease affecting many systems in which both antibodies and auto-reactive T cells are responsible for widespread immunological complications [1,2]. Although SLE still remains of unknown origin, a strong genetic predisposition has been recognized, this also accompanied by environmental and hormonal factors in which female gender is considered to be the most important risk factor [3]. The disease affects women about 10 times more commonly than men with onset typically in the third or fourth decade of life [4]. Although occurring mainly in the child-bearing age, the disease often persists into the postmenopausal period [5].

Systemic lupus erythematosus is associated with a disrupted sex hormone balance characterized by lower amounts of androgens and dramatically higher levels of the estrogen metabolite, 16-hydroxyestrone [6]. Pregnancy worsens the disease [7]; incidence of SLE diminishes after menopause [8]. Menstrual irregularities; oligo-menorrhea, menorrhagia or even amenorrhea are common in female lupus patients and was attributed to higher levels of prolactin, disease activity, lower progesterone and use of immunosuppressive agents [9–11].

Natural menopause was defined as the permanent cessation of menstruation caused by the loss of ovarian follicular activity. It corresponds to the last menstrual period (LMP) and is recognized to have occurred after 12 consecutive months of amenorrhoea for which there is no other obvious pathological or physiological cause [12]. Premature menopause is defined as the menopause that occurs at an age less than two standard deviations below the mean estimate for the reference population. In Practice, in the absence of reliable estimates of the distribution of age at natural menopause in developing countries, the age of 40 years is frequently used as a cut-off point, below which the menopause is said to be premature [12].

Peer review under responsibility of Egyptian Society of Rheumatic Diseases.
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https://doi.org/10.1016/j.ejr.2020.06.001
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Menopause occurs naturally around the age of 50 years. There is a plenty of data concerning the relationship of early menopause and premature ovarian failure to rheumatic diseases, especially SLE [13,14]. It is not yet determined whether the occurrence of menopause at a younger age in SLE patients occurs due to the gonadotoxic effects of cyclophosphamide treatment or as a consequence of autoimmune-mediated ovarian injury [1]. On the other hand, women who develop SLE in their postmenopausal stage have been reported to have less active disease where incidence of lupus nephritis is reduced compared to premenopausal women but with more accrual damage of organs affected by individual flares [15–17].

Understanding the timing of natural menopause and its determinants in SLE patients with better knowledge of the effects that the disease itself may exert on the ovaries will improve counselling and health care quality. This study was performed to identify menopausal symptoms and characteristics in an Egyptian cohort of SLE females and its relation to disease activity, damage, lupus nephritis and treatment.

2. Patients and methods

In this cross-sectional study 120 female SLE patients diagnosed according to 2012 American College of Rheumatology/Systemic Lupus International Collaborating Clinics (ACR/SLICC) criteria [18] were consequently recruited from Ain Shams University Hospital; Rheumatology Department and Out-patients' Clinic. All patients were above 35 years of age. Excluded from the study were patients who had hysterectomy, severe chronic kidney disease which is defined as creatinine clearance <30 ml/min/1.73 m^2 [1], chronic liver disease or with primary amenorrhea which is defined as the absence of menstruation by age of 16 regardless of the development of secondary sexual characteristics [19]. Patients were recruited from April 2017 to September 2018. An informed consent was obtained from each participant after explanation of the study aim and procedures. Study protocol gained approval of local ethical committee of Ain Shams University.

Full history taking was done with emphasis on symptoms of disease activity, organ damage, medications, menstrual and menopausal symptoms. SLE Disease Activity Index (SLEDAI) [20] and Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index. (SLICC/ACR-DI) [21] were assessed. Patients were grouped as (A) premature menopause, (B) natural menopause and (C) menstruating.

Routine laboratory investigations were done including complete blood picture using Coulter (T660), erythrocyte sedimentation rate (ESR) first hour using Westergren method, C-reactive protein (CRP) with titre by Latex agglutination test, liver enzymes; aspartate aminotransferase (AST) and alanine aminotransferase (ALT), kidney function test and simple urine analysis. Protein creatinine ratio in morning urine sample was estimated to evaluate proteinuria. Antinuclear antibody (ANA) and anti-double stranded DNA (Anti-dsDNA) with titre using immunofluorescence and serum complement 3 and 4 were measured. Follicle stimulating hormone (FSH) and luteinizing hormone (LH) blood levels were also assessed.

2.1. Statistical analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 20. Qualitative data were presented as number and percentages while quantitative data were presented as mean, standard deviations and ranges. The comparison between 2 qualitative data groups was by *Chi-square test* and by *t-test* or ANOVA for quantitative data. Correlation was done by using *Pearson test*. Regression analysis was done to detect the predictors of premature menopause using logistic multi-regression analysis. p-value < 0.05 was considered significant.

3. Results

One hundred and twenty SLE female patients were studied. Their mean age was 45.1 ± 8.2 years (35–63 years) and mean disease duration was 5.1 ± 5.7 years (1 month to 21 years). The most common clinical finding was mucocutaneous and the least common was minor vasculitis (as skin rash or fingertip ulcerations). 36 patients underwent renal biopsy and only 14 renal biopsy reports were available. 24 patients had premature menopause (group A), 35 had natural menopause (group B) and 61 were still menstruating (group C) (Table 1). Age at menopause was 45.2 ± 7.3 years (26–54 years). The mean SLEDAI was 4.7 ± 3.5 (0–14), and SLICC-DI 0.6 ± 0.8 (0–3). According to SLEDAI, 27 (22.5%) patients had no disease activity, 45 (37.5%) had mild, 42 (35%) had moderate and 6 (5%) had high activity. Regarding the menopausal symptoms, 5 (4.17%) had hot flashes, 27 (22.5%) had vaginal dryness, 5 (4.17%) had mood changes, 1 (0.83%) had urinary incontinence and 6 (5%) had breast pains. None of the patients had urinary urgency or night sweats. Regarding medications, 118 (98.33%) patients were on oral corticosteroids. 30 (25%) had history of receiving 6 cycles and 3 (2.5%) had received 12 cycles of cyclophosphamide previously while 87 (72.5%) were receiving cyclophosphamide at the time of the study.

There was a significant difference between the three groups as regard their age ($p < 0.001$) with more elder patients in those with natural rather than premature menopause and the youngest were menstruating, while there was no significant difference between the three groups as regard the disease duration ($p = 0.516$). There was no significant difference between the three groups as regard all clinical manifestations ($p > 0.05$) as well as SLEDAI and SLICC/-DI ($p = 0.290$ and $p = 0.452$ respectively). Patients with natural menopause had significant anemia than those with premature menopause and significant thrombocytopenia than those still menstruating. ESR was significantly higher in menstruating patients. FSH and LH were significantly higher in menopausal patients. The anti-dsDNA positivity was significantly more frequent in menstruating patients and the lowest in premature meno-

Table 1
Clinical findings, renal biopsy and menstrual status in systemic lupus erythematosus patients.

Parameter n (%)	SLE patients (n = 120)	
Mucocutaneous	112	(93.3)
Nephritis	100	(83.3)
Venous thrombosis	15	(12.5)
Neuropsychiatric	14	(11.7)
Arterial thrombosis	3	(2.5)
Major vasculitis	2	(1.7)
Myocarditis	2	(1.7)
Minor vasculitis	1	(0.8)
Classes of renal biopsy:		
Class I	0	(0)
Class II	1	(6.7)
Class III	4	(26.7)
Class IV	6	(40)
Class V	1	(6.7)
Class VI	2	(13.3)
Menstrual status:		
Premature menopause	24	(20)
Natural menopause	35	(29.2)
Menstruating	61	(50.8)

SLE: systemic lupus erythematosus.

Table 2
Comparative study between premature menopausal, natural menopausal and menstruating systemic lupus erythematosus patients.

Paramete)	SLE patients (n = 120)			p
mean ± SD (range)	Premature menopause (n = 24)	Natural menopause (n = 35)	Menstruating (n = 61)	
WBC (10^3/μl)	7 ± 3.2 (2–15.7)	7.6 ± 2.7 (2.5–12)	6.7 ± 3 (1.3–16.3)	0.34
Hb (g/dl)	10.8 ± 1.4 (9–14.2)	9.8 ± 0.9 (8–11.6)	10.1 ± 1.4 (7–13.4)	**0.03**
Pl (10^3/μl)	212.9 ± 76.9 (70–356)	175 ± 48.8 (62–284)	226.2 ± 95.7 (45–628)	**0.01**
ESR (mm/1st h)	38.2 ± 19.5 (5–80)	46.3 ± 25.9 (12–135)	57.1 ± 32.1 (10–145)	**0.02**
C3 (mg/dl)	88 ± 19 (40–120)	89.3 ± 28.6 (50–205)	89.2 ± 37.7 (40–220)	0.98
C4 (mg/dl)	30.2 ± 20.9 (3–70)	35.1 ± 29.7 (5–89)	31 ± 25.6 (6–90)	0.7
P:C	1.8 ± 2.6 (0.1–11.9)	0.8 ± 0.6 (0.2–2.5)	1.2 ± 1.7 (0.01–10.5)	0.1
FSH (mIU/ml)	42.8 ± 28.6 (2–110)	47 ± 26.7 (2–100)	20.3 ± 29 (1–160)	**<0.001**
LH (mIU/ml)	46.5 ± 33.2 (4–155)	37.1 ± 35 (0.5–195)	16.6 ± 18.7 (0.5–80)	**<0.001**
ANA	24 (1 0 0)	35 (1 0 0)	60 (98.36)	0.61
Anti-dsDNA	22 (91.67)	26 (74.29)	58 (95.08)	**0.008**

SLE: systemic lupus erythematosus, WBC: White blood cells, Hb: hemoglobin, Pl: Platelets, ESR: erythrocyte sedimentation rate, C: complement, P:C: protein/creatinine ratio, FSH: follicular stimulating hormone, LH: luteinizing hormone, ANA: antinuclear antibody, Anti-dsDNA: anti-double stranded DNA. Bold values are significant at p < 0.05

Table 3
Comparison between systemic lupus erythematosus patients with and without lupus nephritis as regards the laboratory investigations.

Parameter	SLE patients (n = 120)		
mean ± SD	LN (n = 100)	Without (n = 20)	p
ESR (mm/h)	49.5 ± 28.7	53.6 ± 31.1	0.56
C3 (mg/dl)	87.8 ± 30.3	94.9 ± 38.7	0.37
C4 (mg/dl)	31.5 ± 26	34.8 ± 25.6	0.61
FSH (mIU/ml)	35.9 ± 31.3	16.1 ± 22.2	**0.008**
LH (mIU/ml)	30.2 ± 31.8	20.3 ± 16.7	0.18

ESR: erythrocyte sedimentation rate, C: complement, FSH: follicular stimulating hormone, LH: luteinizing hormone. Bold values are significant at p < 0.05

pause (Table 2). FSH levels were significantly higher in patients with nephritis than those without (Table 3).

There was a tendency to a significant negative correlation between LH and SLEDAI (p < 0.052) (Table 4). FSH and LH significantly correlated with the cumulative cyclophosphamide dose. Multi-regression analysis showed that both cyclophosphamide treatment and cumulative dose are the most sensitive independent predictors for premature menopause (F-ratio = 4.3, p < 0.05).

4. Discussion

The current study was designed to evaluate menopausal symptoms and characteristics in an Egyptian cohort of SLE females and its relation to disease activity, disease damage, lupus nephritis and treatment. This study showed that the mucocutaneous manifestations were the most common followed by nephritis, venous thrombosis, neuropsychiatric, and the least in frequency were myocarditis and minor vasculitis. This agrees with *Ferucci et al.* [4], who found that some clinical manifestations as malar rash, photosensitivity and oral ulcers were common among Native American. However, *Tomczyk-Socha et al.* [22], who found that the most common initial manifestations of SLE were musculoskeletal, cutaneous and fever while the main symptoms later throughout the course of the disease for the same patients were neurological, musculoskeletal changes and general symptoms.

It was demonstrated that the most common menopausal symptom in the patients was vaginal dryness. This was similar to *Sánchez-Guerrero* [23], who found that the symptoms associated with menopause in SLE, were identical to the symptoms associated with menopause in the general population. The symptoms were highly prevalent in the postmenopausal women and were also very common among the premenopausal women. Vaginal dryness, hot flashes and night sweats–were present in at least one of every five females interviewed.

The menstrual status did not significantly correlate with renal affection. This agrees with *Mok et al.* [24], who showed no significant difference as regard renal affection between premenopausal and postmenopausal SLE patients. On the other hand, *Urowitz et al.* [16], showed that renal affection was significantly greater in the premenopausal patients.

There was no significant difference among the premenopausal, natural menopausal and menstruating patients as regard all clinical manifestations and that agrees with *Mok, et al.* [24],. While *Urowitz et al.* [16], found that vasculitis, proteinuria, rash and pericarditis were significantly greater in the premenopausal than postmenopausal.

Table 4
Correlation study between follicular stimulating hormone and luteinizing hormone with different clinical and laboratory variables.

Parameter	SLE patients (n = 120)			
r (p)	FSH (mIU/ml)		LH (mIU/ml)	
Disease duration (years)	−0.18	(0.05)	0.05	(0.57)
SLEDAI	−0.03	(0.76)	−0.18	**(0.05)**
SLICC-DI	−0.15	(0.1)	−0.04	(0.64)
Steroid dose (mg)	−0.09	(0.33)	0.1	(0.29)
CYC dose (mg)	0.04	(0.76)	−0.03	(0.82)
CYC cumm. Dose	0.44	(**<0.001**)	0.21	(**0.046**)
C3 (mg/dl)	−0.08	(0.42)	−0.02	(0.86)
C4 (mg/dl)	−0.07	(0.46)	0.08	(0.37)
ESR(mm/1st r)	−0.17	(0.06)	−0.18	(0.06)

FSH: Follicular stimulating hormone, LH: luteinizing hormone, SLEDAI: systemic lupus erythematosus disease activity index, SLICC-DI: Systemic Lupus International Collaborative Clinics-damage index, CYC: cyclophosphamide, C: complement, ESR: erythrocyte sedimentation rate. Bold values are significant at p < 0.05

In the current study, there was no significant difference among the premenopausal, natural menopausal and menstruating patients as regard SLEDAI which is in agreement with *Sanchez-Guerrero* [23]. On the other hand, *Mok et al.* [24], found significantly fewer flares in patients with ovarian failure compared with normally menstruating SLE women. Furthermore, *Urowitz et al.* [16], found that premenopausal SLE women have more disease activity than postmenopausal. As an explanation, most of the current menopause patients were older in age and those with mild disease activity did not show up frequently in the clinic and most of them were recruited from the inpatients admitted due to high disease activity.

The SLICC-DI did not differ between premature menopause, natural menopause and menstruating patients. However, *Urowitz et al.* [16], found greater damage in postmenopausal women and *González et al.* [17], found that in postmenopausal, damage scores were higher and might be attributed to longer disease duration. However, in this work the disease duration was comparable.

The FSH and LH were significantly higher in premature and natural menopause than menstruating patients. According to the normal physiology of ovarian functions, with menopause ovarian hormones decrease and thus FSH and LH become higher. In accordance, *Shabanova et al.* [9], found that the elevation of FSH and LH concentration is an early marker of ovarian failure in SLE patients and *Oktem et al.* [25], stated that higher FSH levels are an indicator of decreased ovarian reserve in SLE patients.

Lupus nephritis is one of the most common and severe clinical manifestation of SLE and renal biopsy is considered the gold standard investigation in confirming the diagnosis [26]. FSH levels were significantly higher in patients with nephritis than those without and this agrees with *Wen and Li* [27], who found that serum FSH were much higher than normal in patients with lupus nephritis. This could be the effect of cyclophosphamide as a treatment for lupus nephritis or the effect of the disease activity.

As it is known, the elevation of FSH and LH concentration is an early marker of ovarian failure. In this study it was found that there was a significant negative correlation between LH and SLEDAI and thus higher LH (ovarian failure) is associated with lower disease activity. This agrees with *Mok et al.* [24], who found that a hypoestrogenic state is protective against lupus flares. While that was different from *Shabanova et al.* [9], who found that the SLEDAI had a significantly correlation with ovarian failure in non-treated SLE patients with steroids or cyclophosphamide, and found that active SLE might be considered as a risk factor for altered ovarian function. *Pasoto et al.* [28], also showed that menstrual disorders and ovarian dysfunction in SLE patients is related to disease activity.

There was a significant correlation of FSH and LH with the cumulative cyclophosphamide dose which means that ovarian failure is significantly associated. This agrees with Medeiros *et al.* [29], who found that cyclophosphamide administration was associated with ovarian failure. This is readily explained by the local cytotoxic side effects of cyclophosphamide on the ovarian function. Whereas it is important to mention that *Silva et al.* [30], found no significant correlation between gonadal function and cyclophosphamide, and this difference could be explained by a different study population as her study was on Juvenile SLE patients.

In conclusion, SLE have a reproductive and hormonal impact on female patients. SLE patients have early mean age of menopause at 45 years. High LH is associated with lower disease activity. High cumulative cyclophosphamide dose is associated with high FSH and LH. Cyclophosphamide treatment and cumulative dose are predictors for premature menopause. It is still a point of debate whether the effect is a result of disease activity or due to pharmacological adverse effects. Larger randomized study is needed to further evaluate this area.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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