Role of Estrogen in the Flaring up of Lupus Nephritis

Samir Kamal Abdul Hamid, Ashraf Anwar El Shazly, Hager Zanaty Abd Elroaf*

Internal Medicine Department, Faculty of Medicine, Assiut University, Assiut, Egypt

*Corresponding author: Hager Zanaty Abd Elroaf; E-mail: hager.znaty.abd@gmail.com

Abstract

Systemic lupus erythematous (SLE) is an autoimmune disease that induces chronic inflammation of the major body systems. This disease induces autoantibodies production, causing immune complex formation and deposition in tissue, which result in inflammation and multi-organs damage. Among the common SLE complications is the development of lupus nephritis (LN) in which inflammation and damage to the kidneys occur. In the current study we aimed to evaluate the effect of administrating pulse therapy on LN patients during ovulation period (period of high estrogen level) in menstruating patients and during full moon period in non-menstruating group.

This was a one year prospective cross-sectional study, included 101 LN female patients in the reproductive age attended Nephrology Department, Assiut University Hospital. They was divided into; Group A (menstruating group) that was subdivided into; Group A1: included 36 patients received pulse therapy during ovulation, Group A2: included 15 patients served as controls and received pulse therapy during any time (n=15). Group B (non-menstruating) that was subdivided into; Group B1: included 35 patients received pulse therapy during moon period, and Group B2: included 15 patients served as controls and received pulse therapy during any time. Patient's response was evaluated to determine the best time for receiving the pulse therapy. In menstruating women, the degree of reduction in blood urea nitrogen (P=0.033, after three months of follow up), protein/ creatinine ratios (P=0.016, after two months of follow up, and P=0.005, after three months of follow up), and increase in hemoglobin level (P=0.006, after two months of follow up, and P=0.016, after three months of follow up) were significantly higher among patients who received pulse therapy during the period of ovulation. In non-menstruating women, receiving pulse therapy during full moon period enhanced and augmented its effect.

In conclusion, estrogen hormone may play a major role in the female predominance of autoimmune disease, particularly systemic lupus erythematous.

Keywords: Lupus Nephritis, estrogen hormone, flaring.

Introduction:

Systemic lupus erythematous (SLE) is an autoimmune disease with overall age-adjusted incidence rate of 5.5 per 100,000 persons [1]. It is characterized by lymphoproliferation, loss of tolerance against nuclear autoantigens, immune complex disease, polyclonal autoantibody production, and multi-organ inflammation [2, 3]. About 50.0% of SLE patients have some degree of renal involvement, and about 20% advance to end-stage renal illness [4].

Lupus nephritis (LN) is distinguished by the production of anti-nuclear antibodies, the deposition of immune complexes, and immune mediated kidney damage. LN development remains a poor prognostic indicator and a significant cause of morbidity and mortality [5].

The significance of the sex hormones estrogens in this disease is of particular importance because 9 out of 10 SLE patients are female. Estrogen signal through two estrogen receptors (ERa) and (ERb) [6]. Contrary to estrogen receptor b, which is only found in female reproductive organs, ERa is present in both male and female kidney, liver, heart, and lungs in addition to being strongly expressed on the majority of immune cells [7]. However, the kidney is thought to be the most estrogenic non-reproductive organ. The suggestion that estrogens or other reproductive hormones drive the development of lupus is supported by the overwhelming female preponderance of SLE, which starts around puberty and lasts until menopause. This idea is further supported by reports of SLE flare-ups throughout the menstrual cycle [8], disease aggravations caused by the use of oral contraceptives [9, 10] or administration of estrogen [11, 12], and lupus induction caused by ovulation regimens [13, 14].

There is evidence that fibroblasts and blood lymphocytes from SLE patients are particularly vulnerable to the cytotoxic effects of ultraviolet (UV) light radiation, suggesting that ultraviolet rays have a role in the flare-up of SLE. The production of RNA and proteins is also impacted by UV radiation. The reasons why the human menstrual cycle duration evolved to be so near to the lunar cycle's length are the subject of various evolutionary theories. Numerous cultures and mythologies also contain

stories and beliefs that link the two. Menstruation and menses are derived from Latin and Greek words that mean month (menses) and moon (mene) respectively [15].

The main goal of the current study was to evaluate the effect of administrating the pulse therapy on LN in patients during ovulation period in menstruating women and during full moon period in non-menstruating women.

Material and methods

Study population

The present study was a one year prospective cross-sectional study conducted at one of the major tertiary health care hospitals, Assiut University Hospital, Egypt during the period from January 2020 to December 2020. The study included 101 LN female patients in the reproductive age. The study participants were divided into two groups: Group A (menstruating group) that was subdivided into; Group A1: included 36 patients received pulse therapy during ovulation, Group A2: included 15 patients served as controls and received pulse therapy during any time (n=15). Group B (non-menstruating) that was subdivided into; Group B1: included 35 patients received pulse therapy during moon period, and Group B2: included 15 patients served as controls and received pulse therapy during any time.

The primary outcome was the evaluation of the best time for administrating the pulse therapy for LN female patients.

Exclusion criteria

Patients with other autoimmune diseases as (rheumatoid arthritis erythematous, polyarthritis nodosa, dermatomyositis, and/or scleroderma), pregnant, lactating, menopausal women, those with primary amenorrhea, or on current administration of oral contraceptive agents, women received pulse therapy during the study period were all excluded from the study.

Demographic, clinical and laboratory characteristics

Detailed history was taking, including age, residence, occupation, disease duration, history of present illness, drug intake, and age of disease onset.

This was followed by full clinical examination prior to inclusion in the present study.

Venous blood samples were collected for complete blood counts (CBC) and blood chemistries. For the first group: serum estrogen [Enhanced Estradiol (eE2)] and urinary Protein creatinine (P/C) ratio in the first day, fourteenth day of menstrual cycle, and for the second group: serum estrogen and urinary P/C ratio in the first day, fourteenth day of lunar cycle.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Science (SPSS) program, version 20, (IBM, and Armonk, New York). Qualitative data were statistically described in the form of mean ± SD, and median (range) while qualitative data were statistically described in form of number (percentage). Comparison of quantitative variables was done using the student t test for normally distributed data and the Mann Whitney U test for non- normally distributed data. The Friedman test was used for comparing quantitative variables in the same group overtime. For comparing categorical data, the Exact test was used instead of Chi square ($\chi 2$) test as the expected frequency was less than 5. Significance was considered at $p<0.05$.

Results

Table 1 shows that both studied groups were comparable with no significant difference between them as regard age, disease duration, systolic and diastolic blood pressure, degree of lower limb edema, and the class of renal biopsy ($p>0.05$, for all).

Table 1 Demographic and clinical data of Group A (menstruating group) and Group B (non-menstruating).

	Group A (n=51)			**Group B (n=50)**		
Variable name	**Group A1 (n=36)**	**Group A2 (n=15)**	***p value*[1]**	**Group B1 (n=35)**	**Group B2 (n=15)**	***p value*[2]**
Age (years)			0.826			0.405
• Mean ± SD	26.25 ± 3.62	26.27 ± 3.17		26.03 ± 3.16	26.60 ± 2.75	
• Median (range)	26 (18 – 35)	26 (20 – 35)		26 (20 – 35)	27 (22 – 32)	
Duration of disease (years)			0.689			0.622
• Mean ± SD	3.72 ± 2.54	3.83 ± 2.04		3.60 ± 1.89	3.93 ± 2.12	

• Median (range)	3.5 (1 mon – 9 yrs)		3.5 (1 – 8)			3 (1 – 7)		4 (1 – 8)	
Systolic blood pressure (mmHg)					0.951				0.286
• Mean ± SD	139.50 ± 9.39		139.67 ± 9.73			137.14 ± 10.17		140.67 ± 9.04	
• Median (range)	140 (120 – 160)		140 (120 – 160)			140 (120 – 160)		140 (130 – 160)	
Diastolic blood pressure (mmHg)					0.597				0.828
• Mean ± SD	83.75 ± 4.49		83.67 ± 5.40			83.14 ± 4.39		84.00 ± 6.04	
• Median (range)	85 (80 – 100)		80 (80 – 100)			85 (80 – 95)		80 (80 – 100)	
Lower limb					0.193				1
• Mild	2	(5.6)	1	(6.7)		2	(5.7)	0	(0.0)
• Moderate	22	(61.1)	8	(53.3)		16	(45.7)	8	(53.3)
• Severe	12	(33.3)	6	(40.0)		17	(48.6)	7	(46.7)
Renal Biopsy					0.913				0.619
• Class 3	19	(52.8)	5	(33.3)		16	(45.7)	7	(46.7)
• Class 4	8	(22.2)	6	(40.0)		11	(31.4)	3	(20.0)
• Class 5	9	(25.0)	4	(26.7)		8	(22.9)	5	(33.3)

Quantitative data are presented as mean ± SD and median (range), qualitative data are presented as number (percentage). Significant at p≤0.05.
Group A1: Received pulse therapy during ovulation.
Group A2: Received pulse therapy during any time "controls"
Group B1: Received pulse therapy during moon period.
Group B2: Received pulse therapy during any time "controls"

Data in table 2 show that both studied groups had significant reduction in blood urea nitrogen (BUN) levels from baseline to 3 months of follow up (p<0.001, for both). However, in Group A patients who received the pulse therapy during ovulation had significant reduction of BUN after 3 months of follow up compared to controls (p=0.033).

Table 2 Comparison of blood urea nitrogen level from baseline to 3 months of follow up

	Ovulation period			**First half**		
Blood urea nitrogen	**Group A1 (n=36)**	**Group A2 (n=15)**	***p value*[1]**	**Group B1 (n=35)**	**Group B2 (n=15)**	***p value*[2]**
First month			0.610			0.377
• Mean ± SD	28.94 ± 6.03	29.40 ± 4.55		36.83 ± 4.31	38.60 ± 4.22	
• Median (range)	29 (17.8 – 40.0)	30 (22 – 35)		37 (28 – 45)	39 (33 – 45)	
Second month			0.560			0.115
• Mean ± SD	24.11 ± 5.72	24.67 ± 2.58		28.86 ± 3.20	31.40 ± 4.84	
• Median (range)	24.5 (15 – 35)	25 (20 – 28)		29 (22 – 36)	32 (24 – 38)	
Third month			**0.033***			0.140
• Mean ± SD	16.44 ± 3.21	18.27 ± 1.62		22.49 ± 3.26	24.33 ± 4.06	
• Median (range)	16 (11 – 22)	18 (15 – 20)		22 (17 – 30)	25 (18 – 30)	
***p value*[3]**	**<0.001***	**<0.001***		**<0.001***	**<0.001***	

BUN: blood urea nitrogen. Quantitative data are presented as mean ± SD and median (range). Significant at p≤0.05.
Group A1: Received pulse therapy during ovulation.
Group A2: Received pulse therapy during any time "controls"
Group B1: Received pulse therapy during moon period.
Group B2: Received pulse therapy during any time "controls"
p value[1]: for comparing both studied groups at the ovulation time. p value[2]: for comparing both studied groups at the first half. p value[3]: for comparing the same group overtime.

Data in table 3 show that both studied groups had significant reduction in serum creatinine level from level at baseline to 3 months of follow up (p<0.001, for both).

Table 3 Comparison of creatinine from baseline to 3 months of follow up

	Ovulation period			**First half**		
Creatinine	**Group A1 (n=36)**	**Group A2 (n=15)**	***p value[1]***	**Group B1 (n=35)**	**Group B2 (n=15)**	***p value[2]***
First month			0.918			0.076
• Mean ± SD	352.00 ± 110.37	346.67 ± 93.78		348.03 ± 84.26	402.00 ± 121.19	
• Median (range)	330 (175 – 600)	320 (210 – 500)		355 (190 – 520)	400 (250 – 620)	
Second month			0.828			0.058
• Mean ± SD	270.39 ± 88.18	275.53 ± 83.98		301.63 ± 83.77	358.13 ± 116.18	
• Median (range)	258 (139 – 450)	260 (160 – 417)		290 (140 – 465)	350 (212 – 577)	
Third month			0.569			0.057
• Mean ± SD	205.61 ± 69.05	221.00 ± 74.37		261.80 ± 81.93	316.87 ± 111.58	
• Median (range)	200 (120 – 360)	192 (124 – 347)		250 (117 – 420)	300 (170 – 530)	
p value[3]	**<0.001***	**<0.001***		**<0.001***	**<0.001***	

Quantitative data are presented as mean ± SD and median (range). Significant at p≤0.05.
Group A1: Received pulse therapy during ovulation.
Group A2: Received pulse therapy during any time "controls"
Group B1: Received pulse therapy during moon period.
Group B2: Received pulse therapy during any time "controls"
p value[1]: for comparing both studied groups at the ovulation time. p value[2]: for comparing both studied groups at the first half. p value[3]: for comparing the same group overtime.

Data in table 4 show that both studied groups had significant reduction in serum estrogen levels from level at baseline to 3 months of follow up (p<0.001, for both).

Table 4 Comparison of estrogen from baseline to 3 months of follow up

	Ovulation period			**First half**		
Estrogen	**Group A1 (n=36)**	**Group A2 (n=15)**	***p value[1]***	**Group B1 (n=35)**	**Group B2 (n=15)**	***p value[2]***
First month			0.663			0.130
• Mean ± SD	238.16 ± 37.77	243.36 ± 31.23		209.51 ± 39.76	178.27 ± 44.13	
• Median (range)	245 (180 – 300)	245 (178 – 280)		200 (175 – 350)	200 (92 – 221)	
Second month			0.243			0.175

• Mean ± SD	199.97 ± 24.76	170.87 ± 54.74		190.66 ± 14.44	169.27 ± 40.61	
• Median (range)	200 (160 – 250)	200 (80 – 220)		189 (170 – 230)	180 (88 – 200)	
Third month			0.075			0.477
• Mean ± SD	195.31 ± 20.92	165.80 ± 49.35		190.63 ± 13.81	171.40 ± 40.83	
• Median (range)	195 (160 – 235)	188 (79 – 215)		193 (169 – 225)	194 (90 – 205)	
p value[3]	**<0.001***	**<0.001***		**<0.001***	**<0.001***	

Quantitative data are presented as mean ± SD and median (range). Significant at p≤0.05.
Group A1: Received pulse therapy during ovulation.
Group A2: Received pulse therapy during any time "controls"
Group B1: Received pulse therapy during moon period.
Group B2: Received pulse therapy during any time "controls"
p value1: for comparing both studied groups at the ovulation time. p value[2]: for comparing both studied groups at the first half. p value[3]: for comparing the same group overtime

Data in table 5 show that both studied groups had significant reduction in P/C ratio from baseline to 3 months of follow up (p<0.001, for both). However, in Group A patients who received the pulse therapy during ovulation had significant reduction of P/C ratio after 3 months of follow up compared to controls (p=0.005).

Table 5 Comparison of protein/creatinine ratio from baseline to 3 months of follow up

	Ovulation period			**First half**		
P/C ratio	**Group A1 (n=36)**	**Group A2 (n=15)**	***p value[1]***	**Group B1 (n=35)**	**Group B2 (n=15)**	***p value[2]***
First month			0.868			0.188
• Mean ± SD	3.03 ± 0.83	2.96 ± 0.82		3.49 ± 0.94	3.87 ± 0.90	
• Median (range)	2.9 (2 – 5)	3 (1.2 – 4.0)		3.4 (2 – 5)	4 (2.5 – 5.0)	
Second month			**0.016***			0.131
• Mean ± SD	1.75 ± 0.36	2.13 ± 0.71		2.87 ± 0.98	3.32 ± 0.89	
• Median (range)	1.9 (1.0 – 2.2)	2.1 (0.8 – 3.5)		2.9 (1.2 – 4.4)	3.5 (1.9 – 4.5)	
Third month			**0.005***			0.156
• Mean ± SD	0.94 ± 0.32	1.36 ± 0.52		2.31 ± 0.99	2.74 ± 0.89	
• Median (range)	0.9 (0.5 – 1.8)	1.4 (0.3 – 2.1)		2.4 (0.6 – 3.8)	2.9 (1.2 – 3.9)	
p value[3]	**<0.001***	**<0.001***		**<0.001***	**<0.001***	

P/C ratio; protein/creatinine ratio. Quantitative data are presented as mean ± SD and median (range). Significant at p≤0.05.
Group A1: Received pulse therapy during ovulation.
Group A2: Received pulse therapy during any time "controls"
Group B1: Received pulse therapy during moon period.
Group B2: Received pulse therapy during any time "controls"
p value1: for comparing both studied groups at the ovulation time. p value[2]: for comparing both studied groups at the first half. p value[3]: for comparing the same group overtime

Data in table 6 shows that both studied groups had significant increase in hemoglobin level from baseline to 3 months of follow up ($p<0.001$, for both). However, in Group A patients who received the pulse therapy during ovulation had significantly higher hemoglobin level after 3 months of follow up compared to controls ($p=0.016$) The same result was observed in Group B where patients who received the pulse therapy during moon period had significantly higher hemoglobin level after 3 months of follow up compared to controls ($p=0.033$).

Table 6 Comparison of Hemoglobin level from baseline to 3 months of follow up

	Ovulation period			**First half**		
Hemoglobin	**Group A1 (n=36)**	**Group A2 (n=15)**	***p value*[1]**	**Group B1 (n=35)**	**Group B2 (n=15)**	***p value*[2]**
First month			0.064			**0.006***
• Mean ± SD	10.58 ± 1.38	9.91 ± 1.41		10.57 ± 0.83	10.02 ± 0.59	
• Median (range)	10.5 (9 – 13.5)	10 (8.5 – 14.3)		10.8 (8.7 – 12.0)	10 (9 – 10.8)	
Second month			**0.006***			**0.007***
• Mean ± SD	10.80 ± 1.03	9.85 ± 0.76		10.91 ± 0.72	10.37 ± 0.58	
• Median (range)	10.8 (9.5 – 12.9)	10 (8 – 11.2)		11.2 (9.4 – 11.8)	10.5 (9.3 – 11.3)	
Third month			**0.016***			**0.033***
• Mean ± SD	11.25 ± 0.91	10.50 ± 0.51		11.16 ± 0.62	11.36 ± 0.59	
• Median (range)	11 (10 – 12.8)	10.5 (9.4 – 11.4)		11 (9.7 – 11.8)	11.5 (10.3 – 12.2)	
***p value*[3]**	**<0.001***	**<0.001***		**<0.001***	**<0.001***	

Quantitative data are presented as mean ± SD and median (range). Significant at $p\leq0.05$.
Group A1: Received pulse therapy during ovulation.
Group A2: Received pulse therapy during any time "controls"
Group B1: Received pulse therapy during moon period.
Group B2: Received pulse therapy during any time "controls"
p value1: for comparing both studied groups at the ovulation time. p value[2]: for comparing both studied groups at the first half. p value[3]: for comparing the same group overtime.

Discussion

The present study prospective cross-sectional study was aimed to detect the role of estrogen and environmental factors (lunar cycle) in the flaring up of lupus nephritis among female patients in the reproductive age attended Nephrology Department, Assiut University Hospital. The present study included 101 patients with LN [divided into Group A, menstruating group (n=51), and Group B, non-menstruating (n=50)]. We analyze each group separately.

The primary hypothesis is that receiving the ovulation time (13th, 14th, and 15th days from beginning of menstruation) is the best time to for receiving pulse therapy in LN female patients. To confirm this hypothesis we divide Group A into two subgroups; Group A1 included 36 patients and received pulse therapy during the ovulation period, and Group A2 included 15 patients served as controls and received pulse therapy during any time. Both studied groups were comparable with no significant difference regarding to their age, disease duration, systolic and diastolic blood pressure, degree of lower limb edema, and the class of renal biopsy.

Additionally, at the beginning of the study, all laboratory data (BUN, serum creatinine, estrogen, P/C ratio, and hemoglobin level) were more or less comparable between both studied subgroups. However by comparing the laboratory data throughout the period of the study "three consecutive months" we observed that; both studied subgroups showed significant reduction in all studied laboratory data (BUN, serum creatinine, estrogen, and P/C ratio), and significant increase in hemoglobin level from baseline to 3 months of follow up. Surprisingly we observed that the degree of reduction in BUN and P/C ratio, and increase in hemoglobin level were significantly higher among Group A1 who received pulse therapy during the period of ovulation which support our hypothesis that pulse therapy should be given during the ovulation period for better outcome.

The current finding was supported by finding of the study by Stojan and Baer. 2012 which stated that lupus flares during pregnancy are generally attributed to the progressive increase in serum estrogen levels during pregnancy, particularly in the 3rd trimester. Estrogens increase immunologic reactivity, which is often cited as the reason for women's increased risk of autoimmune disease. Thus, increased estrogen levels during pregnancy are thought to increase the risk of lupus flares [16].

Pregnancy and SLE are inextricably linked, and the human body can either favors pregnancy or result in fetal complications (miscarriage, intrauterine growth retardation, preterm birth, and/or neonatal lupus) or maternal complications (activation of SLE; mainly of lupus nephritis, preeclampsia)

[17]. This highlights the need for further studies to determine the role of estrogen hormone and the progression of SLE both throughout the pregnancy and the post-partum period.

Research using experimental lupus animal models also suggests that estrogen may have a permissive role in the development of SLE. These studies show that early elimination of estrogen or its effects can attenuate SLE illness symptoms such autoantibody production and kidney damage [18]. In addition; Xue et al. 2016 and Corradetti et al. 2018 stated that estrogen through estrogen receptor alpha (ERα) accelerate the LN progression. As a result, ER signalling affects metabolic function in the kidneys to encourage immune-mediated nephropathy and has consequences for LN [19, 20]. And recently Graham et al. (2020) based on mouse models reported that estrogens, acting through ERα, stimulate the development of lupus and greatly contribute to the female gender bias seen in this illness [21].

However, information about the function of estrogens in human LN is significantly less clear, with the majority of research failing to draw definitive conclusions about the effectiveness of hormonal interventions including estrogen in course of treatment of LN. There are still substantial knowledge gaps regarding the optimal time for treatment of lupus nephritis. As studies in women with LN were not designed to determine the optimal time for receiving their pulse therapy. Our study is unique one which clarify that ovulation time is the best time to receive pulse therapy to women with LN as it is associated with better outcome. Further prospective studies with larger sample size and on wider scale including pre and post-menopausal women are needed to clarify our finding.

Although the majority of these suggested lunar consequences on human physiology have not been able to be statistically proven, this hypothesis is predicated on the idea that there are lunar effects on human biology, including psychosis, violent conduct, birth, and menstruation [22]. By the end of the 20th century, interest in the theory that the moon cycle controlled the menstrual cycle had returned [23]. To confirm this hypothesis

we divide Group B (non-menstruating) into two groups; Group B1: included 35 patients received pulse therapy during moon period, and Group B2: included 15 patients served as controls and received pulse therapy during any time. Both studied groups were comparable with no significant difference between them as regard age, disease duration, systolic and diastolic blood pressure, degree of lower limb edema, and the class of renal biopsy.

At the baseline of the study, all laboratory data (BUN, serum creatinine, estrogen, P/C ratio, and hemoglobin level) were more or less comparable between both studied subgroups (Group B1 and Group B2). And by comparing the laboratory data in each studied sub-group separately "throughout three consecutive months" we observed significant reduction in BUN, serum creatinine, estrogen, P/C ratio, and significant increase in hemoglobin level from baseline to after 3 months of follow up in both studied subgroups. However the degree of improvement was much better in Group B1 than Group B2, however it did not reach statistically significance. Based on our findings we suggest that the effect of moon illumination has decreased recently due to excessive use of artificial lightening.

Our study supported by the previous study of Law, 1986 on 826 volunteers females aged from 16 to 25 years who had regular menstrual cycles. The author observed that the majority of menstruations took place around the new moon [24].

On the other hand, a study using four distinct prospectively obtained sets of data from various years and seasons is provided. It was shown that these women typically menstruate at the full moon, with the likelihood of menstruation beginning decreasing as the distance from the full moon rises [25].

Also recently, according to long-term menstrual records of specific women using different techniques for biological rhythm analysis suggested that menstrual cycles appeared to be sporadic synchronized with the luminescence and/or gravimetric cycles of the moon [26].

However no previous studies have addressed the same issue to compare our finding with. Our study seems to be the first one which tries to link the proper time for receiving the pulse therapy with the moon cycle in non-menstruating women with LN. Further studies are needed to provide the optimal time for receiving the pulse therapy in non-menstruating women with LN, in order to improving their outcomes.

Finally, we could say that pulse therapy given during the ovulation period for menstruating SLE women, and during the full moon period for non-menstruating SLE women could result in better outcome.

Author Contributions

SKA contributed to the study design, and supervision. HZA contributed to writing the original draft, material preparation, collection, and analysis of data. AAE contributed to the study design, concept, and methodology, and provided clinical supervision. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

Regarding the research, writing, and/or publication of this paper, the author(s) reported that they had no potential conflicts of interest.

Ethical approval

The study protocol was reviewed and approved by the Medical Ethics Committee, Faculty of Medicine, Assiut University in Assiut, Egypt (Dated February 2020). The study was recorded under the NCT04468438 ID on ClinicalTrials.gov.

Informed consent

Before being enrolled in the study, each subject gave their written informed consent.

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References

1. Somers EC, Marder W, Cagnoli P, et al. Population-based incidence and prevalence of systemic lupus erythematosus: the Michigan Lupus Epidemiology and Surveillance program. Arthritis & rheumatology 2014;66(2):369-78.
2. Liu Z, Davidson AJNm. Taming lupus—a new understanding of pathogenesis is leading to clinical advances. 2012;18(6):871-82.
3. Moulton VR, Tsokos GCJAr, therapy. Abnormalities of T cell signaling in systemic lupus erythematosus. 2011;13(2):1-10.
4. Korbet SM, Schwartz MM, Evans J, et al. Severe lupus nephritis: racial differences in presentation and outcome. 2007;18(1):244-54.
5. Schwartz N, Goilav B, Putterman CJCoir. The pathogenesis, diagnosis and treatment of lupus nephritis. 2014;26(5):502.
6. Hughes GC, Choubey DJNRR. Modulation of autoimmune rheumatic diseases by oestrogen and progesterone. 2014;10(12):740.
7. Cunningham M, Gilkeson GJCria, immunology. Estrogen receptors in immunity and autoimmunity. 2011;40(1):66-73.
8. ROSE E, PILLSBURY DMJAoIM. Lupus erythematosus (erythematodes) and ovarian function: observations on a possible relationship, with report of six cases. 1944;21(6):1022-34.
9. Petri M, Robinson WCJA, rheumatism. Oral contraceptives and systemic lupus erythematosus. 1997;40(5):797-803.
10. Buyon J, ed Oral contraceptives in women with systemic lupus erythematosus. Annales de medecine interne; 1996.
11. Yang L, Huang W, Chen W, et al. Does parenteral oestrogen therapy flare up disease activity in patients with systemic lupus erythematosus complicated by haemorrhagic cystitis? 1999;38(4):372-3.
12. Barrett C, Neylon N, Snaith MJR. Oestrogen-induced systemic lupus erythematosus. 1986;25(3):300-1.
13. Ben-Chetrit A, Ben-Chetrit EJA, Rheumatology ROJotACo. Systemic lupus erythematosus induced by ovulation induction treatment. 1994;37(11):1614-7.
14. Casoli P, Tumiati B, La Sala GJTJor. Fatal exacerbation of systemic lupus erythematosus after induction of ovulation. 1997;24(8):1639-40.
15. Tan DA, Haththotuwa R, Fraser IS. Cultural aspects and mythologies surrounding menstruation and abnormal uterine bleeding. Best Practice & Research Clinical Obstetrics & Gynaecology 2017;40:121-33.
16. Stojan G, Baer AN. Flares of systemic lupus erythematosus during pregnancy and the puerperium: prevention, diagnosis and management. Expert review of clinical immunology 2012;8(5):439-53. doi: 10.1586/eci.12.36.
17. Gluhovschi C, Gluhovschi G, Petrica L, et al. Pregnancy Associated with Systemic Lupus Erythematosus: Immune Tolerance in Pregnancy and Its Deficiency in Systemic Lupus Erythematosus—An Immunological Dilemma. Journal of Immunology Research 2015;2015:241547. doi: 10.1155/2015/241547.
18. Gilbert EL, Ryan MJ. Estrogen in cardiovascular disease during systemic lupus erythematosus. Clinical therapeutics 2014;36(12):1901-12. doi: 10.1016/j.clinthera.2014.07.021.
19. Xue L, Liu Z, Hu J, et al. Estrogen-induced expression of tumor necrosis factor-like weak inducer of apoptosis through ERα accelerates the progression of lupus nephritis. Rheumatology (Oxford, England) 2016;55(10):1880-8. doi: 10.1093/rheumatology/kew248.

20. Corradetti C, Jog NR, Cesaroni M, et al. Estrogen Receptor α Signaling Exacerbates Immune-Mediated Nephropathies through Alteration of Metabolic Activity. Journal of immunology (Baltimore, Md : 1950) 2018;200(2):512-22. doi: 10.4049/jimmunol.1700770.
21. Graham JH, Yoachim SD, Gould KA. Estrogen Receptor Alpha Signaling Is Responsible for the Female Sex Bias in the Loss of Tolerance and Immune Cell Activation Induced by the Lupus Susceptibility Locus Sle1b. Frontiers in immunology 2020;11:582214. doi: 10.3389/fimmu.2020.582214.
22. Foster RG, Roenneberg T. Human responses to the geophysical daily, annual and lunar cycles. Current biology : CB 2008;18(17):R784-r94. doi: 10.1016/j.cub.2008.07.003.
23. Lemmer B. No correlation between lunar and menstrual cycle - an early report by the french physician J. A. Murat in 1806. Chronobiology international 2019;36(5):587-90. doi: 10.1080/07420528.2019.1583669.
24. Law SP. The regulation of menstrual cycle and its relationship to the moon. Acta obstetricia et gynecologica Scandinavica 1986;65(1):45-8.
25. Cutler WB, Schleidt WM, Friedmann E, et al. Lunar influences on the reproductive cycle in women. Human biology 1987;59(6):959-72.
26. Helfrich-Förster C, Monecke S, Spiousas I, et al. Women temporarily synchronize their menstrual cycles with the luminance and gravimetric cycles of the Moon. Science advances 2021;7(5). doi: 10.1126/sciadv.abe1358.