Sexual function and reproductive health in adolescent females with systemic lupus erythematosus

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ABSTRACT

Objective: To evaluate the reproductive health of female adolescents with Juvenile Systemic Lupus Erythematosus (JSLE) and compare them with a control group. **Patients and Methods:** The demographic data, sexual function, gynecologic exam, menstrual cycle, cervicovaginal cytology, clinical characteristics, and treatment of 52 female patients with JSLE were evaluated. The control group was composed of 52 women matched for age. **Results:** The mean age of patients with JSLE was similar to that of the control group (16.7 ± 1.94 versus 16.13 ± 2.16 years, P = 0.92). The mean age of menarche was higher in JSLE patients (12.82 ± 1.62 versus 11.55 ± 1.45 years, P = 0.0004). The frequency of sex activity was significantly lower in patients with JSLE (23% *versus* 60%, P = 0.0003). In contrast, the percentage of sexual dysfunction, reduced vaginal lubrication, decreased performance, reduced orgasm, and dissatisfaction with one's sex life were significantly higher in JSLE patents (58% versus 23%, P = 0.03; 50% *versus* 16%, P = 0.046; 58% versus 23%, P = 0.03; 50% versus 26%, P = 0.046, respectively). On the other hand, demographic data, pubertal changes, abnormalities in menstrual cycle, and cervicovaginal cytology were similar in JSLE patients and the control group (P > 0.05). Demographic data, pubertal changes, abnormalities in menstrual cycle, cervicovaginal cytology, disease activity, cumulative damage, and treatment did not differ between JSLE patients with and without sexual dysfunction (P > 0.05). C**onclusion:** This is the first study to identify sexual dysfunction in female adolescents with JSLE. Sexuality-related aspects require special attention from health care professionals who treat adolescents with lupus.

Keywords: reproductive health, sexual function, adolescent, hormone, juvenile systemic lupus erythematosus, female gender.

INTRODUCTION

Juvenile Systemic Lupus Erythematosus (JSLE) is an autoimmune disorder more prevalent in women, who are usually affected during the reproductive years.[1] New therapeutic options have improved prognosis and the quality of life of adolescents with this disease, including aspects related to reproductive health and sexual function.[1-3]

Menarche marks the onset of the menstrual cycle and pubertal development. Studies have demonstrated that menarche is delayed in adolescents with JSLE when compared to healthy individuals.[4-6] Menstrual abnormalities after the first menstruation and longer cycles were also more common in JSLE patients, and amenorrhea was observed in 11.7% of patients with JSLE in a recent multicentric Brazilian study.[7]

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The possibility of vaginitis, human papillomavirus (HPV)-related dysplasia and cervicovaginal tumors represent other relevant aspects of the reproductive health of adolescents with JSLE.[6]

With the prognostic improvement of patients with JSLE, pediatric rheumatologists have to deal with matters specific to adolescence, and, among them, sexuality should be mentioned. Sexual function of youngsters with JSLE has been the subject of few studies that usually have a small population of patients of both genders.[3,6,8] However, studies evaluating sexual function and reproductive health that include a control group with healthy adolescents matched for age have not been undertaken.

The objective of the present study was to evaluate sexual function and reproductive health of adolescents with JSLE, comparing them with a control group matched for age.

PATIENTES AND METHODS

Study population

Fifty-five consecutive female patients with JSLE, ages 10 to 19 years, followed-up at the Pediatric Rheumatology Unit and Rheumatology Department of the Hospital das Clínicas (HC) of the Medical School of Universidade de São Paulo (FMUSP) were selected for this study. All patients fulfilled the diagnostic criteria for JSLE of the American College of Rheumatology.[9] Presence of menarche was the inclusion criterion. Patients were not pregnant, did not have diabetes mellitus, were not on hormonal contraceptive drugs, and they were not receiving gonadotropin-releasing hormone analogues (GnRH-a) associated with the intravenous infusion of cyclophosphamide. Three patients refused to participate in the study. The final study population consisted of 52 JSLE patients. The control group was composed of 52 healthy female adolescents, matched for age, evaluated for the first time at the Gynecology Preventive Outpatient Clinic of HC-FMUSP. This study was approved by the Ethics on Research Committee of HC-FMUSP (CAPPesq 019/04) and the patients, or their legal guardians, signed an informed consent.

Methods

The following data were collected:

Demographic and socio-economic-cultural data: demographic (onset of the disease, duration of JSLE, and current age) and socio-economic-cultural (schooling, economic class, and professional activity) data. Socio-economic class was evaluated according to the classification of the Brazilian Association of Market Research Institutes.[10]

Pubertal markers: Pubertal markers were determined according to the age of the first menstruation (menarche) and the criteria proposed by Tanner (characteristics of the breasts and distribution of pubic hair).[11]

Sexual function: Evaluation of the sexual function was based on the clinical history: presence of sexual activity; age of the first sexual relationship; number of sexual relationships in the last month; number of sex partners in the last month; masturbation; presence of desire and sexual excitement; vaginal lubrication and orgasm; dissatisfaction with one's sex life; use of contraceptives during sex (condoms); and prior pregnancy. In the present study, sexual dysfunction was defined as changes in one or more of the following sexual functions: desire, excitement, vaginal lubrication and/or reduced performance and/or absence of orgasm (anorgasmia).

Gynecological exam: The same gynecologist performed the clinical exam of the genitalia and it included evaluation of the vulva, hymen, vagina, and uterine cervix. Cervical samples in the follicular and menstrual phases of the cycle were also collected.[4]

Menstrual cycle: The menstrual cycle of at least six consecutive months was evaluated. Normal cycles were defined as an interval of 25 to 35 days with three to seven days of menstrual blood flow, as previously described in the Brazilian population.[3,5] Amenorrhea was defined as the interruption of menstruation for more than four consecutive months after menarche. Premature ovarian failure (POF) was defined as the presence of amenorrhea for more than 12 months and FSH > 40 IU/l (fluoroimmunoassay using DELPHIA® kits, WALLAC, Turku, Finland).[1,3,5,7]

Cervicovaginal cytology: Samples for Pap smear were collect from virgin adolescents with a Cytobrush®. The brush was inserted on the border of the vaginal opening and gently rotated between 90° and 180°, and immediately rolled on the external third of a glass slide. In sexually active adolescents, after introduction of the speculum, the Cytobrush® and Ayre spatula were used to collect the sample. The uterine cervix was visualized and the Ayre spatula was inserted in the cervical orifice and rotated 360° with a slight pressure; afterwards, the Cytobrush® was inserted two thirds into the endocervical canal and rotated 90° to 180°. The material on the Cytobrush® was rolled over the external third of the glass slide and a fine layer of the material from the Ayre spatula was spread on the mid third of the slide. After fixation by immersion in 95% alcohol, the material was transported to the laboratory.[6,12]

All smears were evaluated by the same cytopathologist of the colposcopy Service of the Gynecology Department of FMUSP who was unaware of the results of the gynecologic

exam. Smears were classified, according to the 2001 Bethesda System, in five patterns, with and without HPV infection: normal (benign changes), inflammatory changes, atypical squamous cells of unknown significance (ASC-US), low or high degree squamous intraepithelial lesions (LSIL or HSIL), and carcinoma *in situ*. The presence of *Trichomonas vaginalis, Candida spp,* bacterial vaginosis, *Actinomyces pp* and herpes simplex virus infection was also evaluated.[13]

Evaluation of JSLE activity, cumulative damage, and treatment: All patients were evaluated regarding disease activity and cumulative JSLE damage, at the beginning of the study, using the Systemic Lupus Erythematosus Activity Index (SLEDAI)[14] and Systemic Lupus International Collaborating Clinics/ACR-Damage Index (SLICC/ACR-DI) scales, respectively.[15] Data on treatment with prednisone, chloroquine, cyclophosphamide, azathioprine, and methotrexate were also evaluated.

Statistical analysis

Results are presented as median (variation) or mean±standard deviation, for continuous parameters, and number (%), for categorical parameters. Non-paired *t* test and Mann-Whitney test were used to compare continuous parameters to determine the differences between JSLE patients and the control group and JSLE patients with and without sexual dysfunction. Fisher's exact test was used to analyze categorical parameters. Values of $P < 0.05$ were considered statistically significant.

RESULTS

Adolescents with JSLE versus the control group

Mean current age and number of school years of JSLE patients were similar to that of the control group (16.7 ± 1.94 versus 16.13 ± 2.16 years, P = 0.92; 9.51±1.78 versus 9.7 ± 1.62 years, P = 0.57; respectively). The percentage of patients in social-economic classes C or D and professional activities were also similar in both groups. Table I shows the demographic and socio-economic-cultural data, pubertal landmarks, sexual function, menstrual cycle, and cervicovaginal cytology of JSLE patients and the control group.

Mean age of menarche was statistically higher in JSLE patients than in the control group (12.82 ± 1.62 versus 11.54 ± 1.45 years, P = 0.00004). Tanner pubertal stages B4P4 and B5P5[11] predominated in both groups (75% versus 73%, P = 1.0).

The frequency of sexually active individuals was statistically lower among JSLE patients than in the control group (23% *versus* 60%, P = 0.0003). Sexual dysfunction (the presence of reduced desire, excitation, vaginal lubrication and/or performance and/or anorgasmia) and dissatisfaction with one's sex life were reported by 58% of JSLE patients *versus* 23% in the control group (P = 0.03). Besides, the incidence of reduced vaginal lubrication and performance, as well as anorgasmia, was statistically higher in JSLE patients than in the control group (50% versus 16%, P = 0.046; 58% versus 23%, P = 0.03; 50% versus 16%, P = 0.046, respectively). The age of the first sexual relationship, number of sexual activities, and number of partners in the last month, as well as the use of condoms and prior pregnancy, were not statistically different between both groups (P > 0.05) (Table I).

Irregularities in the duration and/or interval of the menstrual cycle and amenorrhea were similar in JSLE patients and in the control group (23% versus 11%, P = 0.19; 6% versus 0%, P = 0.19, respectively). None of the patients had POF. Inflammatory cervicovaginal cytology was present in 48% of JSLE patients *versus* 46% in the control group (P = 1.0). Only 2% of JSLE patients and 4% of the patients in the control group had cervical dysplasia (LSIL) with HPV infection (P = 1.0). The presence of a higher, and statistically significant, frequency of vaginal candidiasis in JSLE patients when compared to the control group (14% *versus* 0%, P = 0.01) was an interesting aspect. A significant difference in the prevalence of *Gardnerella vaginalis* vaginosis was not observed between both groups (P = 0.11) (Table I).

Adolescents with JSLE with and without sexual dysfunction

Table 2 shows the demographic and socio-economic-cultural data, pubertal landmarks, sexual function, menstrual cycle, and cervicovaginal cytology of the 12 adolescents with JSLE sexually active regarding the presence or absence of sexual dysfunction.

Median age of onset of the disease (12 versus 15 years, P = 0.18), current age (18 versus 17 years, P = 0.795), and number of school years (11 versus 11 years, P = 0.66) were similar in JSLE patients with and without sexual dysfunction. Statistically significant differences in disease duration, age of menarche, number of school years, socio-economic class, professional activity, and Tanner pubertal stages were not observed between both groups (P > 0.05) (Table 2).

Statistically significant differences were not observed between JSLE patients with and without sexual dysfunction regarding: use of condoms, prior pregnancy, and irregularity

Table 1. Demographic and socio-economic-cultural data, pubertal landmarks, sexual function, menstrual cycle, and cervicovaginal cytology of adolescents with juvenile systemic lupus erythematosus (JSLE) and the control group

Parameters	JSLE (n = 52)	Control (n = 52)	P
Demographic and socio-economic-cultural data			
Current age, years ***	16.7 ± 1.94	16.13 ± 2.16	0.92
Number of school years***	9.51 ± 1.78	9.7 ± 1.62	0.57
Economic class, C or D*	38 (73)	41 (79)	0.64
Professional activity*	3 (6)	10 (19)	0.07
Pubertal landmarks			
Age of menarche, years***	12.82 ± 1.62	11.54 ± 1.45	0.00004
Tanner Pubertal stage B4P4 or B5P5*	39 (75)	38 (73)	1.0
Sexual function			
Sexual activity*	12/52 (23)	31/52 (60)	0.0003
Age of onset of sexual activity, years***	15.3 ± 1.72	14.87 ± 1.99	0.48
Sexual activity in the last month*	10/12 (83)	28/31 (90)	0.60
Number of sexual activities in the last month***	4.33 ± 4.73	5.45 ± 4.02	0.44
Number of sex partners in the last month**	1 (1-5)	1 (1-10)	1.0
Masturbation*	0/12 (0)	2/31 (6)	1.0
Sexual dysfunction*	7/12 (58)	7/31 (23)	0.03
Reduced desire*	4/12 (33)	3/31 (10)	0.08
Reduced excitation*	4/12 (33)	3/31 (10)	0.08
Reduced lubrication*	6/12 (50)	5/31 (16)	0.046
Reduced performance*	7/12 (58)	7/31 (23)	0.03
Anorgasmia*	6/12 (50)	5/31 (16)	0.046
Complains with sex life*	7/12 (58)	7/31 (23)	0.035
Use of condoms*	10/12 (83)	28/31 (90)	0.60
History of pregnancy*	1/12 (8)	4/31 (13)	1.0
Menstrual cycle			
Irregularities in duration and/or interval*	12 (23)	6 (11)	0.19
Amenorrhea*	3 (6)	0 (0)	0.24
Cervicovaginal cytology			
Normal*	26 (50)	26 (50)	1.15
Inflammatory*	25 (48)	24 (46)	1.0
LSIL*	1 (2)	2 (4)	1.0
Vaginal candidiasis*	7 (14)	0 (0)	0.01
Gardnerella vaginallis vaginosis*	0 (0)	4 (8)	0.11
HPV infection*	1 (2)	2 (4)	1.0
HPV condilomata*	0 (0)	2 (4)	0.49

* Results expressed as n (%); ** median (maximal and minimal value);
*** or mean ± standard deviation; B = breasts; P = pubic hair;
LSIL = low squamous intraepithelial lesions; HPV = human papillomavirus.

in menstrual cycle. Besides, both groups did not differ significantly regarding the frequency of the different classes of cervicovaginal cytology: normal, inflammatory, dysplasia (LSIL), vaginal candidiasis, *Gardnerella vaginallis* vaginosis, and condilomata caused by HPV ($P > 0.05$) (Table 2).

Table 3 shows the activity, cumulative damage, and treatment of adolescents with JSLE with versus those without sexual dysfunction. Median SLEDAI [4(0-19) versus 6 (2-16), $P = 0.41$] and SLICC/ACR-DI [0 (0-1) versus 0 (0-1), $P = 0.8$] scores were similar in JSLE patients with and without sexual dysfunction, as well as the frequency of SLEDAI > 4 and SLICC/ACR-DI > 1 ($P > 0.05$). Use of prednisone, chloroquine, and immunosuppressants (cyclophosphamide, azathioprine, and methotrexate), as well as cumulative doses of prednisone and chloroquine, were also similar in both groups ($P > 0.05$) (Table 3).

DISCUSSION

This is the first study to evaluate sexual function and reproductive health of female adolescents with JSLE and to identify specific and global sexual dysfunction in adolescents with lupus when compared to a control group of the same pubertal stage, confirming delayed menarche in adolescents with lupus reported by other studies.

In the present study, female sexual function included clinical history characteristics regarding desire, excitation, vaginal lubrication, performance, orgasm, and satisfaction with one's sex life.[3,16] The few studies that evaluated sexual function of lupus patients did not have a control group and usually included adult patients of both genders.[3,6,8,17-20] Besides, none of those studies evaluated the menstrual cycle and cervicovaginal cytology concomitantly.

Stein *et al*.[17] observed that 4% of adult females and males with SLE had a history of sexual dysfunction. Folomeev & Alekberova[18] identified a high incidence of sexual/erectile dysfunction in 35% of males with SLE. Using structured interview with adult females, Curry *et al*.[19] observed a reduced incidence of sexual activity, vaginal lubrication, and sexual satisfaction in women with lupus *versus* the matched control group, similar to that observed in JSLE patients in the present study. Britto *et al*.[8] evaluated sexuality aspects of 178 adolescents with chronic rheumatologic disorders; however, only 15 of those patients had JSLE. Twenty-one percent of male and 69% of female adolescents were sexually active.

Sexual dysfunction in female adolescents with lupus is multifactorial and can be due to disease activity or drugs,

Table 2. Demographic and socio-economic-cultural data, pubertal landmarks, sexual function, menstrual cycle, and cervicovaginal cytology of adolescents with juvenile systemic lupus erythematosus (JSLE) with and without sexual dysfunction

Parameters	JSLE with sexual dysfunction (n = 7)	JSLE without sexual dysfunction (n = 5)	P
Demographic and socio-economic-cultural data			
Age of onset of JSLE, years**	12 (10-16)	15 (14-17)	0,18
Duration of JSLE, years**	3 (1-6)	4 (2-5)	0.084
Current age, years**	18 (15-19)	17 (15-18)	0.41
Number of school years**	11 (7-11)	11 (9-11)	0.66
Economic class C or D*	6 (86)	4 (80)	1.0
Professional activity*	1 (14)	0 (0)	1.0
Pubertal landmarks			
Age of menarche, years***	13.57±1.90	11.6±1.14	0.063
Tanner pubertal stage B4P4 or B5P5*	7 (100)	4 (80)	1.0
Sexual function			
Age of onset of sexual activities, years**	16 (14-17)	14 (13-18)	0.32
Sexual activity in the last month*	6 (86)	4 (80)	1.0
Number of sexual relationships in the last month**	4 (0-16)	2 (0-6)	0.32
Number of sex partners in the last month**	1 (1-5)	1	0.39
Use of condoms*	5 (71)	5 (100)	0.46
History of pregnancy*	1 (14)	0 (0)	1.0
Menstrual cycle			
Irregularities in duration and/or interval*	2 (29)	3 (60)	0.55
Amenorrhea*	0 (0)	0 (0)	1.0
Cervicovaginal cytology			
Normal*	3 (43)	0 (0)	0.20
Inflammatory*	3 (43)	5 (100)	0.08
LSIL*	1 (14)	0 (0)	1.0
Vaginal candidiasis*	1 (14)	1 (20)	1.0
Gardnerella vaginallis vaginosis*	0 (0)	0 (0)	1.0
HPV infection*	1 (14)	0 (0)	1.0
HPV condilomata*	0 (0)	0 (0)	1.0

*Results expressed as n (%); ** median (maximal and minimal value);
***or mean±standard deviation; B = breasts; P = pubic hair;
LSIL = low squamous intraepithelial lesion; HPV = human papillomavirus.

Table 3. Disease activity, cumulative damage, and treatment of female adolescents with juvenile lupus erythematosus (JSLE) with and without sexual dysfunction

Parameters	JSLE with sexual dysfunction (n = 7)	JSLE without Sexual dysfunction (n = 5)	P
JSLE activity and cumulative damage			
SLEDAI**	4 (0-19)	6 (2-16)	0.41
SLEDAI>4*	4 (57)	3 (60)	1.0
SLICC/ACR-DI**	0 (0-1)	0 (0-1)	0.8
SLICC/ACR-DI>1*	1 (14)	1 (20)	1.0
Treatment of JSLE			
Prednisone*	7 (100)	5 (100)	1.0
Cumulative dose, grams**	23 (10.55-36)	22.4 (2,34-24)	0.29
Chloroquine*	5 (71)	5 (100)	0.46
Cumulative dose, grams**	264 (45-428)	64,4 (9-274)	0.25
Cyclophosphamide*	2 (29)	0 (0)	0.46
Azathioprine*	2 (29)	0 (0)	0.46
Methotrexate*	1 (14)	0 (0)	1.0

* Results expressed as n (%); ** or median (maximal and minimal value);
SLEDAI = Systemic Lupus Erythematosus Disease Activity Index;
SLICC/ACR-DI = Systemic Lupus International Collaborating Clinics/ACR Damage Index.

such as corticosteroids and immunosuppressants.[3] In the present study, the association between sexual dysfunction and lupus activity, cumulative damaged caused by the disease, or medications was not observed. This can be explained by the small number of patients in each group, which can compromise statistical analysis, i.e., this could be a Beta error, when both groups have a real difference, but the size of the cohort was not enough to demonstrate this difference. However, sexual function is a complex parameter to be analyzed and young lupus patients may omit from parents and physicians that they are sexually active (fear, shame, et.). Besides, several other factors that were not investigated in this study could also have influenced sexual function, such as: factors characteristic of adolescence, reduced self-esteem, chronic disease-related stress, associated depression, and understanding of the sex partner.

The onset of sexual activity of JSLE patients was at the same age as healthy adolescents (median 16 years old), which is a relevant aspect observed in this study. This age was also similar to that observed in a study with a group of adolescents with epilepsy (median 15 years old) undertaken by the same

group of the present study, reinforcing that contraception to prevent sexually transmitted diseases, including acquired immunodeficiency syndrome (AIDS) and HPV,[3,6] should be an early concern in adolescents beginning sexual activities. Besides, unprotected sex has increased the number of undesired and non-planned pregnancies in those patients, as demonstrated by a recent national multicentric study of 12 Pediatric Rheumatology Departments.[22] Undesired pregnancies were also observed in 8% of sexually active lupus patients in the present study.

The use of condoms in al sexual activities and emergency contraception are crucial in adolescents with lupus treated with cyclophosphamide and methotrexate. In 2008, Kaufman suggested that emergency contraception (with 1.5 mg of levonorgestrel) should be used immediately in JSLE patients, especially in the first 72 hours after unprotected sex or in case of rupture of the condom during sex.[23] This or any other hormonal contraceptive method was not used by any of the patients in the present study.

Evaluation of reproductive health parameters was also a relevant aspect of this study. Despite a higher frequency of menstrual irregularities and amenorrhea in JSLE patients, statistically significant differences were not observed, which goes against a recent study undertaken by our group.[5] Premature ovarian failure was not observed in any of our patients, not even in those treated with immunosuppressants. Male adolescents with JSLE who use cyclophosphamide can also develop azoospermia and definitive dysfunction of testicular Sertoli cells.[20,24,25]

Similar to the results of another study,[6] vaginal candidiasis was more common in adolescents with lupus. This reinforces the importance of routine investigation for the presence of this infection, since fungal infection was one of the main causes of death in hospitalized patients with JSLE in our tertiary Pediatric Rheumatology Service.[26]

The present study included a wide evaluation of the sexual function and reproductive health that can be used in the daily practice of a pediatric rheumatologist. However, further studies with greater cohorts, more specific tools to evaluate sexual function,[16] and validated for the Brazilian population of adolescents with JSLE of both genders, besides global evaluation of the sexual function of their partners, are necessary.

This study identified sexual dysfunction in female adolescents with JSLE. Sexuality-related aspects need special attention of health care professionals who treat adolescents with lupus, providing better quality of life to patients and their partners.

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