Archives of Gynecology and Obstetrics (2019) 299:1597–1605
https://doi.org/10.1007/s00404-019-05131-x

GENERAL GYNECOLOGY

Disease activity and thromboembolic events in women with systemic lupus erythematosus with and without anti-phospholipid syndrome: users of the 52-mg levonorgestrel-releasing intrauterine system

Rafaella C. Rebelo[1] · Estephania Pignaton[2] · M. Valeria Bahamondes[1] · Lilian T. L. Costallat[2] · Simone Appenzeller[2] · Luis Bahamondes[1] · Arlete Fernandes[1]

Received: 26 October 2018 / Accepted: 25 March 2019 / Published online: 2 April 2019

Abstract

Purpose The disease status and thromboembolic events in women with systemic lupus erythematosus (SLE), with and without anti-phospholipid syndrome (APS), were evaluated before and after placement of the 52-mg levonorgestrel-releasing intrauterine system (LNG-IUS).

Methods A retrospective cohort study, with review of medical records of SLE women, who received an LNG-IUS placement between January 2007 and December 2016, carried out at the University of Campinas Medical School, Brazil. The outcomes included the disease activity (SLEDAI-2K) and damage index scores (SLICC/ACR-DI) presented for each year of device use, as well as venous/arterial thrombotic events, insertion up to a median of 5 years. The author's used χ^2, Fisher's exact and the Mann–Whitney tests for analysis and generalized estimating equations for score comparison.

Results The study evaluated 46 women with SLE, 18 with and 28 without APS; the mean age (± standard deviation [SD]) was 31.8 (SD ± 8.3) years old. The length of follow-up after LNG-IUS placement was 5.6 (SD ± 2.7) and 4.1 (SD ± 2.3) years for the groups with and without APS, respectively. Comparison of the groups found that the SLEDAI and SLICC mean scores were low for both at baseline, without variations through the follow-up. After LNG-IUS placement, two women presented three thrombotic arterial events, and one of them died from causes unrelated to LNG-IUS use.

Conclusions Our results, although restricted, provide information to policymakers and health professionals that the use of a 52 mg LNG-IUS over a 5-year median did not increase disease activity or damage index scores among women with SLE, with and without APS.

Keywords Systemic lupus erythematosus · Antiphospholipid syndrome · Levonorgestrel-releasing intrauterine system · Arterial and venous thrombotic events

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune chronic inflammatory disease more prevalent among women at reproductive age [1]. Due to the period of disease exacerbation, clinical control is achieved with the use of antimalarials, glucocorticosteroids and immunosuppressants, some of which have teratogenic effects if administered during pregnancy [2–4]. It is recommended that pregnancy occur during the disease remission periods, and it is important that women with SLE at the reproductive age receive counselling about the use of highly effective contraception.

The association between SLE and anti-phospholipid syndrome (APS) has been described, ranging between 6.5 and 19% among different populations [5–8]. The criteria for APS

✉ Arlete Fernandes
arlete@fcm.unicamp.br

[1] Family Planning Clinic, Department of Obstetrics and Gynaecology, School of Medical Sciences, University of Campinas (UNICAMP), Caixa Postal 6181, Campinas, SP 13083-970, Brazil

[2] Rheumatology Division, Department of Clinical Medicine, School of Medical Sciences, University of Campinas (UNICAMP), Rua Alexander Fleming, 101, Cidade Universitária, Campinas, SP 13083-881, Brazil

diagnosis are clinical—including history of thrombosis (arterial, venous or microvascular) or pregnancy complications (miscarriage, prematurity, eclampsia or placental insufficiency)—and found through laboratorial exams—including positivity for lupus anticoagulant and positive tests for anti-cardiolipine (aCL) and anti-β2 glicoprotein-I (anti-β2GPI) antibodies twice within at least 12 weeks [9, 10]. One characteristic of APS is the risk of venous or arterial thrombosis, and women with SLE and APS are prone to present the severe clinical impairments of arthralgia, arthritis, autoimmune hemolytic anemia, livedo reticularis, epilepsy, glomerular thrombosis and myocardial infarction [11].

Women with SLE, with and without APS, experience periods of disease activation triggered by the formation of immune complexes in the microvasculature, activation of the complement system and inflammation [12], all of which determine different degrees of activity and permanent damage caused by the disease itself, by the therapeutic drugs and/or by associated co-morbidities. Some tools have been used in clinical practice to evaluate the activation/severity periods of the disease and to measure permanent damage. Among these tools are the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) and, to determine disease damage, the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index for Systemic Lupus Erythematosus (SLICC/ACR-DI) [12]. Two clinical trials have evaluated the use of hormonal contraceptives, compared to non-hormonal methods or placebo, for women with SLE without APS and found no change in disease activity and/or severity in the 12-month follow-up period [13, 14].

However, among women with SLE and APS, the use of combined contraceptive methods is contraindicated, and even progestin-only contraceptives were restricted [15]. Although it was considered that progestin-only compounds are safe for women with risk factors for thrombosis [16–18], the evidence is scarce and suggested an increase in the risk of venous thromboembolism (VTE) among users of progestin-only contraceptives with other medical conditions [19, 20].

Due to the lack of studies regarding the use of progestin-only contraceptives among women with SLE with APS, our objective was to compare the disease activity, disease damage and thromboembolic events between women with SLE with APS and women with SLE only, who were further assessed by qualified rheumatologists, after placement of the 52-mg levonorgestrel-releasing intrauterine system (LNG-IUS).

Methods

This retrospective cohort study was conducted at the Family Planning Clinic of the Department of Obstetrics and Gynaecology and at the Rheumatology Division of the Department of Clinical Medicine, School of Medical Sciences, University of Campinas (UNICAMP), Campinas, SP, Brazil, from July through December 2017. The project was approved by the Research Ethics Committee of the University and the research was carried out according to the Declaration of Helsinki.

We reviewed the medical records to identify women with an International Classification of Disease (ICD-10) code for SLE (M32) who received a 52 mg LNG-IUS (Mirena®, Bayer Oy, Turku, Finland) placement from January 2007 to December 2016. Afterwards, we conducted an active search of the medical records of the same women at the Rheumatology Division, and only those who were followed at our teaching medical complex were included.

The studied variables were age at SLE diagnosis, sociodemographic variables, obstetric history, duration of SLE before LNG-IUS placement, body mass index (BMI; kg/m^2), use of tobacco, age at LNG-IUS placement, length of contraceptive use and information about positive antibodies for lupus anticoagulant, aCL and anti-β2GPI.

Due to the fact that women with SLE are high risk patients, they are routinely asked for symptoms at their annual follow-up and/or whenever symptoms are grounds for complaints, and imaging examinations are requested. Venous or arterial thrombotic events were assessed through computer tomography (CT) scan, magnetic resonance imaging (MRI), vascular Doppler, ultrasound and angiogram/venogram by MRI. At each clinical follow-up, the disease activity was assessed through the SLEDAI-2K, and the disease damage was assessed through the SLICC/ACR-DI [12, 21, 22].

The SLEDAI-2K is the scale used as a standard pattern for assessing disease activity with a maximum score of 105 points, including both clinical and laboratory parameters [21] and assessing the disease activity on the last 10 days prior to the clinical visit. Scores > 8 indicate active disease; variations of three points between two visits indicate disease activation; and variations greater than 12 points indicate severe disease activity. The SLICC/ACR assesses 12 organs/systems and has a maximum score of 46 points. This score has prognostic value and defines the permanent damage provoked by SLE, by therapies or by co-morbidities occurring during the last 6 months before the consultation [22].

Our evaluation of the SLEDAI-2K and SLICC/ACR scores are those scored by the specialist with information obtained within the last 15 days prior to insertion of the IUS and, afterwards, every 12 months in routine visits. Women consulted with the rheumatologist at regular intervals (twice a year); however, in cases of disease activity, returns were more frequent. For women who were more often evaluated, the highest score was taken into account. Loss of follow-up was defined as the absence of the woman in the consultations in both clinics for 12 months.

Two women were diagnosed with SLE with APS after IUS placement, one during the first year of use the other in the second year of use. The first was excluded from the analysis 'at baseline' scores, and the second woman was excluded from the analysis 'at baseline' and 'year 1' scores. One woman was diagnosed with only SLE after 2 years of IUS use and was excluded from the analysis 'at baseline', 'year 1' and 'year 2' scores.

Statistical analysis

For analysis, we constructed two groups: women with SLE and APS and women with only SLE. We used the $\chi 2$, Fisher's exact and the Mann–Whitney tests to compare variables between the groups. We also used generalized estimating equations for longitudinal comparison of the SLEDAI-2K and SLICC/ACR scores. The estimates were calculated by maximum likelihood for the treatment of losses over time. The data were transformed into ranks due to the absence of normal distribution. The level of significance was established at $p < 0.05$. SAS software, version 9.3 (Institute Inc., 2002-2008, Cary, NC, USA) was used for the analyses.

Results

We evaluated 46 patients, 18 with SLE and APS and 28 with only SLE. At the end of this study (December 2017), the follow-up time of the 46 women for disease score evaluation and the length of IUS use ranged from 1 to 10 years, with a median of 5 years. Loss of follow-up occurred in two women among those with APS and five women among those without APS, and one woman of the APS group died (Fig. 1). At the end of the survey period, 27 out of 46 women were still using the device—12 among those with APS and 15 among those without APS. The remaining 11 women discontinued the contraceptive: three because they were not satisfied, three because they reached menopause, two because they wished to become pregnant, one because she was submitted to tubal ligation, one because she was submitted to hysterectomy due to leiomyoma, and there was one expulsion (Fig. 1).

Tables 1 and 2 show the characteristics of the groups at baseline. Both groups were similar regarding most of the studied variables. The length of use of the LNG-IUS was 5.6 years (SD ± 2.6) among the women with APS and 4.1 years (SD ± 2.2) years among those without APS, without significance (Table 1).

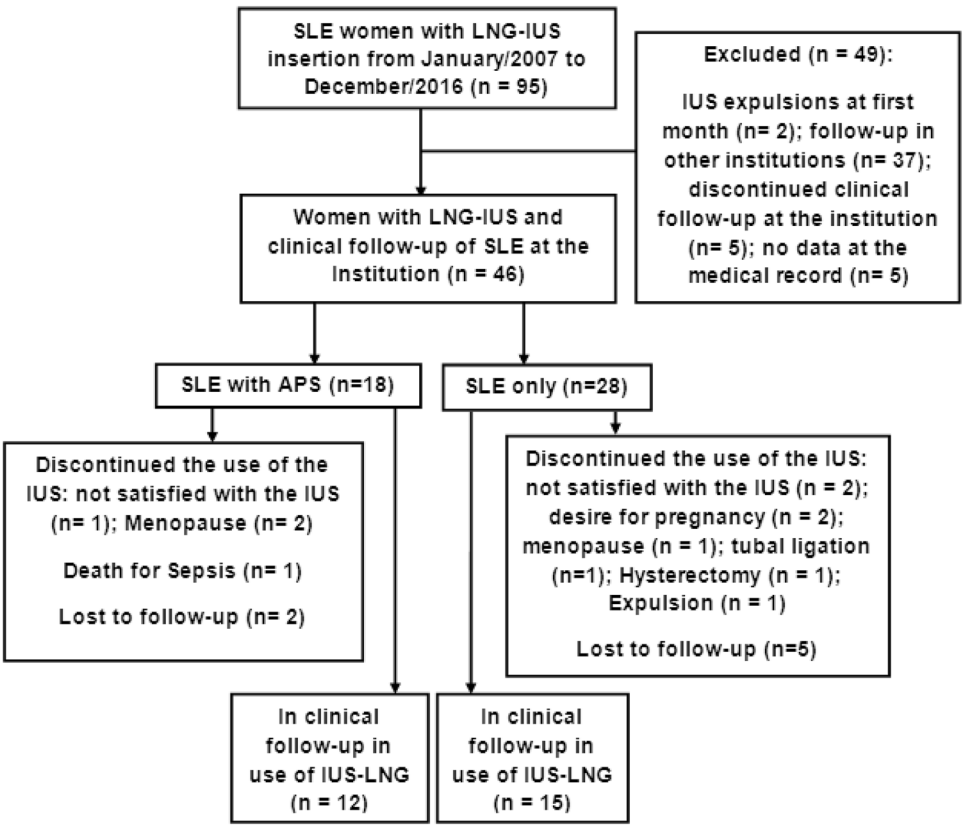

Fig. 1 Flowchart of women with SLE included in the study. *SLE* systemic lupus erythematous, *APS* antiphospholipid syndrome

Table 1 Characteristics of the women with SLE at the time of 52-mg LNG-IUS placement (baseline)

Characteristics	SLE with APS $n=18$	SLE only $n=28$	p value
Age at SLE diagnosis mean ± SD	26.0 ± 6.2	24.0 ± 9.0	0.315[a]
Age at LNG-IUS placement, mean ± SD	31.7 (8.4)	31.9 (8.4)	0.928[a]
Years of schooling, *n* (%)			1.000[b]
≤ 8	4 (26.6)	8 (30.7)	
> 8	11 (73.3)	18 (69.2)	
Missing value	3	2	
Marital status, *n* (%)			0.109[c]
Without a partner	8 (50.0)	20 (74.0)	
With a partner	8 (50.0)	7 (25.9)	
Missing value	2	1	
Smoking habits, *n* (%)			0.635[b]
Yes	1 (5.8)	3 (12.0)	
No	16 (94.1)	22 (88.0)	
Missing value	1	3	
Number of pregnancies, mean ± SD	1.6 ± 1.4	1.4 ± 1.0	0.840[a]
Missing value	1	1	
Number of deliveries, mean ± SD	1.0 ± 1.1	1.3 ± 0.9	0.196[a]
Missing value	1	1	
Number of premature deliveries, mean ± SD	0.1 ± 0.3	0.3 ± 0.5	0.099[a]
Missing value	2	4	
Number of live children, mean ± SD	0.9 ± 0.9	1.3 ± 0.9	0.183[a]
Missing value	1	1	
Number of abortions, mean ± SD	0.7 ± 1.2	0.2 ± 0.4	0.083[a]
Missing value	1	1	
BMI (kg/m^2) at LNG-IUS placement, mean ± SD	29.7 ± 6.1	25.7 ± 3.9	0.044[a]

SLE systemic lupus erythematosus, *APS* antiphospholipid syndrome, *LNG-IUS* levonorgestrel-releasing intrauterine system, *BMI* body mass index, *VTE/ATE* venous thromboembolism/arterial thrombosis event, *SD* standard deviation

[a]Mann–Whitney test

[b]Fisher's exact test

[c]Chi-square test

At the time of LNG-IUS placement, more than two-thirds of the women had been diagnosed with SLE for up to 15 years (Table 2). In addition, VTE events were more frequent before device placement; among women with APS, 12 (66%) had a history of VTE; seven (39%) had pulmonary thromboembolism (PTE); and six (33%) had a history of stroke and other arterial thrombosis. At the time of device insertion 15 women of the group with SLE and APS had histories of 37 venous and/or arterial thrombotic events; however, two women with SLE only had a history of three events (Table 2).

The SLEDAI-2K and SLICC/ACR mean scores were low for both groups of women at the time of device placement, and there were no variations among the mean scores through the follow-up (Table 3). The disease activity and the damage index were not significantly different over the follow-up period between the groups with and without APS, or with the group-time interaction (Table 3).

Through the follow-up, two women presented three thrombotic arterial events. One 37-year-old woman, who had been diagnosed with SLE with cutaneous and renal compromise when she was 17 years old and with APS 10 years later, was overweight and nulligravid, presented photosensitivity and was FAN positive. At baseline, she presented severe arterial thrombotic microangiopathy and was gangrenous in one toe. One year later, she had a stroke with left hemiparesis. Two years later, she chose LNG-IUS (SLEDAI-2K = 0; SLICC/ACR = 2) and presented two episodes of ischemic stroke at three and 5 years after LNG-IUS placement. The first episodes occurred after 10 days of warfarin interruption and the second during warfarin use. She was using the second LNG-IUS (49 months) with SLEDAI-2K = 0 and SLICC/ACR = 4 at a later consultation. She is still on follow-up.

The second woman—also nulligravid and overweight—was diagnosed with SLE with cutaneous and renal compromise at

Table 2 Characteristics of clinical history of women with SLE and venous and arterial thrombotic events at time of the 52-mg LNG-IUS placement (baseline)

Characteristics	SLE with APS $n=18$	SLE only $n=28$	p value
Time between SLE diagnosis and IUS placement; n (%)			0.663[b]
< 5 years	8 (44.4)	10 (35.7)	
5–15 years	6 (33.3)	13 (46.4)	
> 15 years	2 (11.1)	4 (14.3)	
SLE diagnosis post IUS placement	2 (11.1)	1 (3.5)	
With antibodies test	18 (100.0)	25 (89.3)	0.269[b]
Missing value		3	
Positive anticardiolipin antibody	13 (72.2)	3 (12.0)	< 0.000[c]
Missing value		3	
Positive lupic antibody	13 (72.2)	5 (20.0)	0.000[c]
Missing value		3	
Positive antibody beta 2	9 (50.0)	5 (20.0)	0.038[c]
Missing value		3	
Women with events pre IUS placement			
VTE	12 (66.6)	1 (3.5)	< 0.000[b]
PTE	7 (38.9)	0	0.000[b]
Stroke	6 (33.3)	1 (3.5)	0.010[b]
Arterial thrombosis	1 (5.5)	0	–
Number of VTE/ATE events, mean ± SD	2.1 ± 1.6	0.1 ± 0.4	< 0.000[a]
Women with at least one event pre IUS placement	15	2	
Total events pre IUS placement	37	3	

SLE systemic lupus erythematosus, *APS* antiphospholipid syndrome, *VTE* venous thromboembolism, *PTE* pulmonary thromboembolism

[a]Mann–Whitney test

[b]Fisher's exact test

[c]Chi-square test

26 years old. She also presented photosensitivity, was FAN positive (1/640) and was positive for anti-DNA and arthritis. At the time of SLE diagnosis, she presented two positive tests for aCL with strong IgG and anti-β2GPI; however, she had no previous thrombotic events. The first LNG-IUS was placed when she was 28 years old (SLEDAI-2K = 10; SLICC/ACR = 1), and it was used for 78 months. At 34 years old, she received a second device (SLEDAI-2K = 12; SLICC/ACR = 1) for 28 months. Six months after the first LNG-IUS insertion, she was diagnosed with obstructive arterial disease at the right leg. She presented exacerbation of the disease with arthritis and lupic nephritis. She had several orthopaedic surgeries with impairment of motility and several renal infections. At 37 years old, she presented sepsis after sinusitis, bronchopneumonia, abdominal cellulitis and subcutaneous abscess, renal insufficiency, and, from these, she died.

Discussion

In our sample, the disease activity and the damage index were similar at baseline and through the follow-ups after LNG-IUS placement, over a period of median 5 years, with no significant differences between women with and without APS. Two of 18 women presented three thrombotic arterial events after LNG-IUS placement; however, no events were recorded among women without APS. In addition, no VTE events were recorded during a median of 5 years of follow-up after LNG-IUS placement.

The stability in the scores of disease activity found in this study agrees with previous studies that evaluate the use of hormonal contraceptives in women with SLE without APS [13, 14]. A clinical trial, which evaluated

Table 3 Comparison between women with SLE with and without APS regarding the disease activity (Sledai-2K) and damage risk (Slicc ACR-DI) scores trough the time of use of the 52-mg LNG-IUS

Scores	SLE with APS		SLE only		*p* value[b]	*p* value[c]	*p* value[d]
Sledai-2K	*n*[e]	Mean ± SD	*n*[e]	Mean ± SD			
Before IUS placement (Baseline)	16	1.5 ± 2.6	27	1.9 ± 3.1	0.2389	0.4975	0.5296
Excluded[a]	2		1				
Year 1	17	2.0 ± 2.6	27	1.9 ± 4.1			
Excluded[a]	1		1				
Year 2	16	2.0 ± 2.5	23	1.5 ± 2.9			
Excluded[a]			1				
Discontinued	1		1				
Loss follow-up	1		1				
Not completed 1 year (in follow-up)			2				
Year 3	12	0.7 ± 0.9	21	1.6 ± 3.3			
Discontinued			2				
Loss follow-up			1				
Lacked annual return	2						
Not completed 1 year (in follow-up)	2						
Year 4	14	2.5 ± 3.9	14	1.3 ± 3.2			
Discontinued			1				
Loss follow-up			1				
Not completed 1 year (in follow-up)			5				
Year 5	12	2.0 ± 3.2	12	1.5 ± 2.9			
Loss follow-up	1		2				
Not completed 1 year (in follow-up)	1		2				
Year 6	10	3.6 ± 4.4	8	1.6 ± 2.0			
Discontinued	1		2				
Not completed 1 year (in follow-up)	1		1				
Year 7	8	2.6 ± 3.5	5	1.4 ± 1.6			
Discontinued	1		2				
Slicc/ACR-DI							
Before IUS placement (Baseline)	16	0.7 ± 0.9	27	0.3 ± 0.8	0.0674	0.3553	0.5279
Year 1	17	0.6 ± 1.0	27	0.4 ± 0.9			
Year 2	16	0.5 ± 0.9	23	0.5 ± 1.0			
Year 3	12	0.6 ± 1.2	21	0.6 ± 1.1			
Year 4	14	0.9 ± 1.2	14	0.7 ± 1.2			
Year 5	12	1.3 ± 1.5	12	0.6 ± 1.2			
Year 6	10	1.5 ± 1.6	8	0.3 ± 0.7			
Year 7	8	1.7 ± 1.7	5	0.2 ± 0.4			

Sledai-2K Systemic Lupus Erythematosus Disease Activity Index 2000, *Slicc/ACR-DI* Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus

[a]Two women had diagnosis of SLE with APS after IUS placement, one during the first year of use and another in the second year of use of the method; the first one was excluded from the analysis "before placement" scores, and the second woman was excluded from the analysis "before placement" and "year 1" scores. One woman had the diagnosis of only SLE after 2 years of IUS use and was excluded from the analysis "before placement, year 1 and year 2" scores

Mann–Whitney test for comparison between groups at baseline: for Sledai scores $p = 0.9552$ and for Slicc scores $p = 0.0866$. Generalized estimating equations: [b]Factor group; [c]Factor time; [d]Interaction group-time

[e]Number of women evaluated

disease activity in women with SLE without APS in the first year of combined oral contraceptive (COC) (30 µg ethinylestradiol [EE] and 150 mg LNG), progestin-only pills (30 µg LNG) and TCu380A intrauterine devices, with 54 women randomised to each group, found no differences in global disease activity at any of the follow-up points in

any of the groups, including a separate analysis of patients with active disease at baseline [13]. Another multicentre, double-blind, placebo-controlled study allocated 183 women with SLE, without APS or APL-antibodies, either treated with a 35 μg EE triphasic COC or placebo, also found no differences between groups in disease severity over 12 months of follow-up [14]. Although neither trial included women with APS, the results indicated that the use of COC or progestin-only pills did not induce severe exacerbation or other measures of disease severity over the 12-month period.

We believe that the thrombotic arterial events observed in our study were consequences of the SLE disease, which is more severe among women with APS, and not related to the use of the LNG-IUS because both groups of women were similar regarding age at SLE diagnosis, duration of the disease and previous obstetric history. In addition, the group of women with APS had already shown previous thrombotic events before device insertion. The lack of VTE events post device placement agrees with previous reports in a general population, which did not show VTE events among users of progestin-only contraceptives [19, 23–25]. Additionally, a recent review of 26 publications concerning women with medical conditions for VTE did not show increments on the risk of VTE, stroke or myocardial infarction among users of progestin-only contraceptives [19].

Arterial events are associated with higher mortality and more serious consequences for survivors than VTE [26], and, in patients with SLE, these events were associated with increased mortality risk [7]. One study [27] of patients with SLE and 5 years of follow-up reported 16% arterial events, with a proportion of three VTEs for each arterial event—most of them occurring during the first year of follow-up. The authors also identified other risk factors, such as higher age, smoking, arterial hypertension, diabetes, dyslipidemia, nephrotic syndrome, chronic damage and cumulative use of prednisone. Other described risk factors for arterial events were positive antibody aCL, livedo reticularis, lupus nephritis, Raynaud's phenomenon, ethnicity and genetic factors [10, 28–31]. It is recommended by the European Union that healthcare professionals working in family planning develop a stratification of vascular risk factors for women with SLE and APS to reduce future damage [15].

Progestins could exert vascular effects, such as reduction of blood flow, including increased distensibility in veins and arterial vasoconstriction [32]. Additionally, it is possible that the lower serum concentrations of the LNG-IUS users exert less influence on the vessels. A study with women who used LNG-IUS and LNG pills evaluated the concentrations of LNG in different tissues and found that plasma concentrations were many-fold lower in the endometrium of the IUS group when compared to the orally treated group [33]. Regarding the arterial thrombotic events occurring in the two women from this study's sample, it is well know that, since the second year of LNG-IUS use, the device released lower amounts of LNG than at placement [34], and, if there is any LNG dose-relationship to the arterial thrombotic events, it was expected that the events would have occurred during the first year of use, which is contrary to the situations observed in our cohort.

The greatest limitation of our study was the low number of women. Though, in our service, the number of LNG-IUS insertions among women with SLE was higher than reported here, we only considered those women with follow-ups at our hospital. Another problem was the lack of some information among the women with loss of follow-up, which could impair our results. However, the study's main strength was the long time of follow-up after device placement and the inclusion of patients with APS.

Contraceptive choice in patients with SLE with APS is important. As there are no studies on the use of progestogen-only contraceptives in women with SLE and APS, we believe that these results may be useful in considering the choice of contraceptive method for women under these conditions, when there are no other acceptable methods. Counselling on contraception must be offered as soon as possible to women diagnosed with SLE to avoid complications; however, this practice is uncommon [35]. Most of the women with SLE could become pregnant, and it is possible to have a safe pregnancy and delivery with low risks [15]. The World Health Organization (WHO) Medical Eligibility Criteria for the use of contraceptives established that a 52-mg LNG-IUS is considered Category 2 for women with SLE, if the woman does not present other risk factors [20]. However, the risk is higher if the SLE is associated with APS, and, in such a case, the use of progestin-only contraceptives is considered Category 3 [10, 20].

We conclude that the 52-mg LNG-IUS should be maintained as a contraceptive option for use by women with SLE, with and without APS. As the major limitation of the study is the small number of women, the results should be interpreted with caution. However, new studies with larger numbers of women, and with a comparison, control group of non-users, are necessary to assure the safety of the method for these women.

Author contributions RCR protocol/project development and data collection. EP protocol/project development and data collection. MVB protocol/project development and data collection. LTLC protocol/project development and Manuscript writing/editing. SA protocol/project development. LB manuscript writing/editing and revision. AF protocol/project development and manuscript writing/editing and revision.

Funding The original study was funded by the Brazilian National Research Council (CNPq) and the São Paulo Foundation for the Support of Research (*Fundação de Amparo a Pesquisa do Estado de São Paulo*—FAPESP). The sponsors played no role in the study design, in

the collection, analysis or interpretation of data, in writing the report or in the decision to submit the article for publication. The authors claim they do not have a financial relationship with the organizations that sponsored the research. They claim that they have had full control of all primary data and agree to allow the Journal to review their data if requested.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest. The authors alone are responsible for the content and writing of the paper. LB received honorarium to be a member of an advisory board and has been an invited speaker at scientific meetings for Bayer Healthcare Pharmaceuticals. He is a member of the ICA Foundation without remuneration. The LNG-IUS were donated by the International Contraceptive Access (ICA) Foundation, Turku, Finland, under an unrestricted grant.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Since it was a retrospective study with a review of medical records, the waiver of signature in the consent form was requested and approved in the evaluation of the project.

References

1. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF et al (1982) The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 25:1271–1277
2. Williamson RA, Karp LE (1981) Azathioprine teratogenicity: review of the literature and case report. Obstet Gynecol 58:247–250
3. Ossandon A, Cassarà EA, Priori R, Valesini G (2002) Thalidomide: focus on its employment in rheumatologic diseases. Clin Exp Rheumatol 20:709–718
4. Rengasamy P (2017) Congenital malformations attributed to prenatal exposure to cyclophosphamide. Anticancer Agents Med Chem 17:1211–1227
5. Vianna JL, Haga HJ, Tripathi P, Cervera R, Khamashta MA, Hughes GR (1992) Reassessing the status of antiphospholipid syndrome in systemic lupus erythematosus. Ann Rheum Dis 51:160–161
6. Gould T, Tikly M, Asherson R, Loizou S, Singh S (2006) Prevalence and clinical correlates of anti-phospholipid antibodies in South Africans with systemic lupus erythematosus. Scand J Rheumatol 35:29–34
7. Mok CC, Chan PT, Ho LY, Yu KL, To CH (2013) Prevalence of the antiphospholipid syndrome and its effect on survival in 679 Chinese patients with systemic lupus erythematosus: a cohort study. Medicine (Baltim) 92:217–222
8. Franco JS, Molano-González N, Rodríguez-Jiménez M, Acosta-Ampudia Y, Mantilla RD, Amaya-Amaya J et al (2014) The coexistence of antiphospholipid syndrome and systemic lupus erythematosus in Colombians. PLoS One 24(9):e110242
9. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R et al (2006) International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 4:295–306
10. Garcia D, Erkan D (2018) Diagnosis and management of the antiphospholipid syndrome. N Engl J Med 378:2010–2021
11. Pons-Estel GJ, Andreoli L, Scanzi F, Cervera R, Tincani A (2017) The antiphospholipid syndrome in patients with systemic lupus erythematosus. J Autoimmun 76:10–20
12. Griffiths B, Mosca M, Gordon C (2005) Assessment of patients with systemic lupus erythematosus and the use of lupus disease activity indices. Best Pract Res Clin Rheumatol 19:685–708
13. Sánchez-Guerrero J, Uribe AG, Jiménez-Santana L, Mestanza-Peralta M, Lara-Reyes P, Seuc AH et al (2005) A trial of contraceptive methods in women with systemic lupus erythematosus. N Engl J Med 353:2539–2549
14. Petri M, Kim MY, Kalunian KC, Grossman J, Hahn BH, Sammaritano LR et al (2005) Combined oral contraceptives in women with systemic lupus erythematosus. N Engl J Med 353:2550–2558
15. Andreoli L, Bertsias GK, Agmon-Levin N, Brown S, Cervera R, Costedoat-Chalumeau N et al (2017) EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. Ann Rheum Dis 76:476–485
16. Conard J, Plu-Bureau G, Bahi N, Horellou MH, Pelissier C, Thalabard JC (2004) Progestogen-only contraception in women at high risk of venous thromboembolism. Contraception 70:437–441
17. Blanco-Molina MA, Lozano M, Cano A, Cristobal I, Pallardo LP, Lete I (2012) Progestin-only contraception and venous thromboembolism. Thromb Res 129:e257–e262
18. Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C (2009) Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ 339:b2890
19. Tepper NK, Whiteman MK, Marchbanks PA, James AH, Curtis KM (2016) Progestin only contraception and thromboembolism: a systematic review. Contraception 94:678–700
20. World Health Organization (2015) Medical eligibility criteria for contraceptive use—5th ed. Switzerland. http://apps.who.int/iris/bitstream/10665/181468/1/9789241549158_eng.pdf?ua=1. Accessed 01 June 2018
21. Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH (1992) Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on Prognosis Studies in SLE. Arthritis Rheum 35:630–640
22. Romero-Diaz J, Isenberg D, Ramsey-Goldman R (2011) Measures of adult systemic lupus erythematosus: updated version of British Isles Lupus Assessment Group (BILAG 2004), European Consensus Lupus Activity Measurements (ECLAM), Systemic Lupus Activity Measure, Revised (SLAM-R), Systemic Lupus Activity Questionnaire for Population Studies (SLAQ), Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). Arthritis Care Res (Hoboken) 63(Suppl 11):S37–S46
23. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception (1998) Cardiovascular disease and use of oral and injectable progestogen-only contraceptives and combined injectable contraceptives. Results of an international, multicenter, case-control study. Contraception 57(5):315–324
24. van Hylckama Vlieg A, Helmerhorst FM, Rosendaal FR (2010) The risk of deep venous thrombosis associated with injectable depot-medroxyprogesterone acetate contraceptives or a levonorgestrel intrauterine device. Arterioscler Thromb Vasc Biol 30:2297–2300
25. Mantha S, Karp R, Raghavan V, Terrin N, Bauer KA, Zwicker JI (2012) Assessing the risk of venous thromboembolic events in women taking progestin only contraception: a meta-analysis. BMJ 345:e4944

26. Lidegaard Ø, Løkkegaard E, Jensen A, Skovlund CW, Keiding N (2012) Thrombotic stroke and myocardial infarction with hormonal contraception. N Engl J Med 366:2257–2266
27. Hinojosa-Azaola A, Romero-Diaz J, Vargas-Ruiz AG, Nuñez-Alvarez CA, Cicero-Casarrubias A, Ocampo-Torres MC et al (2016) Venous and arterial thrombotic events in systemic lupus erythematosus. J Rheumatol 43:576–586
28. Choojitarom K, Verasertniyom O, Totemchokchyakarn K, Nantiruj K, Sumethkul V, Janwityanujit S (2008) Lupus nephritis and Raynaud's phenomenon are significant risk factors for vascular thrombosis in SLE patients with positive antiphospholipid antibodies. Clin Rheumatol 27:345–351
29. Urbanus R, Siegerink B, Roest M, Rosendaal F, de Groot P, Algra A (2009) Antiphospholipid antibodies and risk of myocardial infarction and ischaemic stroke in young women in the RATIO study: a case-control study. Lancet Neurol 8:998–1005
30. Matyja-Bednarczyk A, Swadźba J, Iwaniec T, Sanak M, Dziedzina S, Ćmiel A et al (2014) Risk factors for arterial thrombosis in antiphospholipid syndrome. Thromb Res 133:173–176
31. Kaiser R, Tang LF, Taylor KE, Sterba K, Nititham J, Brown EE et al (2014) A polymorphism in TLR2 is associated with arterial thrombosis in a multiethnic population of patients with systemic lupus erythematosus. Arthritis Rheumatol 66:1882–1887
32. Kuhl H (1996) Effects of progestogens on haemostasis. Maturitas 24:1–19
33. Nilsson CG, Haukkamaa M, Vierola H, Luukkainen T (1982) Tissue concentrations of levonorgestrel in women using a levonorgestrel-releasing IUD. Clin Endocrinol (Oxf) 17(6):529–536
34. Seeber B, Ziehr SC, Gschließer A, Moser C, Mattle V, Seger C et al (2012) Quantitative levonorgestrel plasma level measurements in patients with regular and prolonged use of the levonorgestrel-releasing intrauterine system. Contraception 86:345–349
35. Brito MB, Casqueiro JS, Alves FSS, Lopes JB, Alves RDMS, Santiago M (2018) Low prevalence of contraceptive use among Brazilian women of reproductive age with systemic lupus erythematosus. J Obstet Gynaecol 19:1–4