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Original article

Use of combined hormonal contraceptives among women with systemic lupus erythematosus with and without medical contraindications to oestrogen

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Abstract

Objectives. To assess the prevalence of combined hormonal contraceptives (CHCs) in reproductive-age women with SLE with and without possible contraindications and to determine factors associated with their use in the presence of possible contraindications.

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CLINICAL SCIENCE

Methods. This observational cohort study included premenopausal women ages 18–45 years enrolled in the SLICC Registry ⩽15 months after SLE onset, with annual assessments spanning 2000–2017. World Health Organization Category 3 or 4 contraindications to CHCs (e.g. hypertension, aPL) were assessed at each study visit. High disease activity (SLEDAI score >12 or use of >0.5 mg/kg/day of prednisone) was considered a relative contraindication.
Results. A total of 927 SLE women contributed 6315 visits, of which 3811 (60%) occurred in the presence of one or more possible contraindication to CHCs. Women used CHCs during 512 (8%) visits, of which 281 (55%) took place in the setting of one or more possible contraindication. The most frequently observed contraindications were aPL (52%), hypertension (34%) and migraine with aura (22%). Women with one or more contraindication were slightly less likely to be taking CHCs [7% of visits (95% CI 7, 8)] than women with no contraindications [9% (95% CI 8, 10)].
Conclusion. CHC use was low compared with general population estimates (>35%) and more than half of CHC users had at least one possible contraindication. Many yet unmeasured factors, including patient preferences, may have contributed to these observations. Further work should also aim to clarify outcomes associated with this exposure.

Key words: systemic lupus erythematosus, anti-phospholipid syndrome, contraception, epidemiology

Rheumatology key messages

- Women with SLE have frequent contraindications to combined hormonal contraceptives.
- Half of SLE women took combined hormonal contraceptives in the presence of at least one possible contraindication.
- Most common contraindications to combined hormonal contraceptives included aPL, hypertension and migraine with aura.

Introduction

SLE is a chronic autoimmune rheumatic disease affecting predominantly women of reproductive age. Appropriate contraceptive counselling and use have been identified as quality indicators in SLE [1, 2]. Combined hormonal contraceptives (CHCs) are contraindicated in certain medical conditions, due to the excess risk of thromboembolic events associated with oestrogen exposure [3]. The World Health Organization (WHO) [4, 5] and the US Centers for Disease Control and Prevention (CDC) [6] have published evidence-based medical eligibility criteria for CHC use. A medical condition is assigned Category 3 when 'theoretical or proven risks usually outweigh advantages of use' (e.g. controlled hypertension, diabetes for ⩾20 years) and assigned Category 4 when there is an 'unacceptable health risk if used' (e.g. stroke, migraine with aura) [4–6].

A recent population-based study found that 13% of reproductive-age women possessed WHO/CDC Category 3 or 4 contraindications to CHCs; despite this, 39% of this group were taking CHCs [7]. Women with SLE may have a greater prevalence of medical contraindications to CHCs compared with unaffected women, due to an increased prevalence of hypertension and thrombotic risk factors, including aPL (i.e. lupus anticoagulant [LA], aCL, and anti-β_2 glycoprotein 1 (anti-β_2-GPI) antibodies [8–10]).

Two randomized controlled trials (RCTs) established that CHC use in SLE did not increase flares [11] or global disease activity [12] at 1 year. However, the Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA) trial excluded patients with high disease activity (SLEDAI >12 or use of >0.5 mg/kg/day of prednisone) and medical contraindications to oestrogen as well as those without stable or improving disease activity over the last 3 months [11]. Sanchez-Guerrero *et al.*'s RCT [12] included women with positive aCL and anti-β_2-GPI. Although this trial was not powered to detect a difference in adverse events in the subgroup of aPL-positive subjects who received CHCs, all four subjects who developed thrombosis had positive aPL and had received hormonal contraception [12]. Based on the available data, a diagnosis of SLE with positive aPL or SLE with an unknown aPL status is a Category 4 contraindication to CHCs [4, 6], and recent EULAR recommendations state that CHCs should be used in those with stable or inactive SLE and negative aPL [13].

The prevalence of possible contraindications to CHCs among SLE women of reproductive age is not known. Our objective was to characterize CHC use in a prospective cohort of women with incident SLE, determining the overall prevalence of possible contraindications to CHCs as well as the proportion of CHC users with and without concurrent possible contraindications to CHCs. We hypothesized that women with possible medical contraindications would be less likely to receive this form of contraception compared to those without contraindications.

Methods

Study design and participants

The SLICC cohort is a multinational inception cohort for the study of SLE outcomes [14–17]. Patients meeting four or more ACR classification criteria for SLE [18] were enrolled within 15 months of diagnosis. Disease activity, damage, serologic and other laboratory data, medication use and other clinical outcomes were assessed prospectively at yearly intervals from 2000 to 2017 according to a standardized protocol [15]. This study complies with the Declaration of Helsinki and was approved by the McGill University Research Ethics Board as well as the

institutional review boards of all SLICC participating sites, and a data use agreement was in place. Patient consent was obtained when the patient enrolled in the SLICC cohort.

The current study identified premenopausal women ages 18–45 years from the SLICC cohort who could potentially be eligible to receive a contraceptive medication. Visits during which a subject was pregnant and visits after which a subject had undergone menopause, hysterectomy and/or oophorectomy were excluded.

We also excluded subjects who did not have any data on aPL status from the central laboratory at any visit. The first cohort visit with available aPL data was considered the first study visit (i.e. baseline) and all visits thereafter were included in the analyses.

Data sources and measurement

Country of origin and race/ethnicity were evaluated at baseline and the following variables were assessed in all subjects at baseline and each follow-up visit: age, education, disease duration, corticosteroid use and dosage, reproductive data including pregnancies and menopausal status, disease activity as measured by the SLEDAI 2000 (SLEDAI-2K) [19] and disease damage as measured by the SLICC/ACR Damage Index (SDI) [20]. Current hormonal contraceptive use and type was assessed at baseline and each follow-up visit by study investigators using the standardized data collection form. The presence of the following Category 3 and Category 4 WHO medical contraindications to CHCs [4] was determined at baseline and each follow-up visit: hypertension (defined as the use of antihypertensive therapy not prescribed for renal disease), current smoker $\geqslant$35 years of age, history of venous thromboembolism (anticoagulant use and/or presence of the 'venous thrombosis' item on the SDI), migraine with aura, cerebrovascular disease (current or past transient ischaemic attack or ischaemic stroke), ischaemic heart disease (current or past myocardial infarction, angina, angioplasty or coronary artery bypass graft), peripheral vascular disease (current or past claudication), diabetes $\geqslant$20 years duration, history of breast cancer, valvular heart disease with pulmonary hypertension (defined by the presence of these SDI items) and the presence of positive aPL (either lupus anticoagulant [LA], aCL IgG or anti-β_2-GPI IgM or IgG), defined as a single titre above the laboratory cut-off value. aPL was measured at a central laboratory at the Oklahoma Medical Research Foundation (Oklahoma City, OK, USA) as previously described [21]. Migraine with aura was determined at each study visit from the linked registry of neuropsychiatric events within the SLICC inception cohort, ascertained through a detailed checklist [14]. High disease activity, defined as a SLEDAI-2K score $>$12 or use of prednisone equivalent of $>$0.5 mg/kg/day, was also evaluated as a relative contraindication to CHCs, as these were exclusion criteria in the SELENA trial [11], and the EULAR guidelines recommend using CHCs only in stable or inactive disease [13].

Statistical analysis

Characteristics were summarized in the form of means and S.D.s for continuous variables and proportions for categorical variables. We calculated the proportion of women having one or more possible contraindication during the study period, as well as the proportion of visits where one or more possible contraindication was present. The proportion of visits where a CHC was used with and without one or more possible contraindication was compared by calculating the 95% CIs for the difference in proportion for two independent samples. Among study visits where CHCs were used in the presence of one or more possible contraindication, the frequency of each medical contraindication was determined.

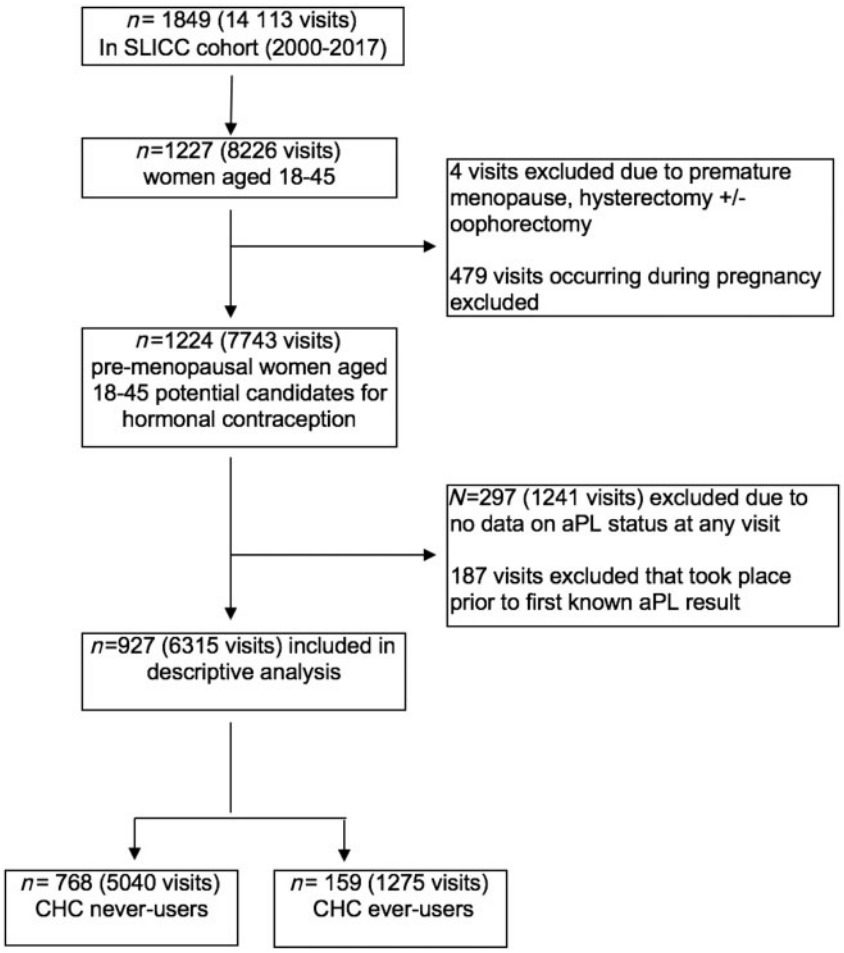
To assess potential predictors of possibly contraindicated CHC use, we performed a multivariate analysis using a generalized estimating equation approach, with each subject serving as a cluster. The outcome was a visit in which the patient was taking a CHC in the presence of one or more possible medical contraindication. These contraindications included venous thromboembolism, migraine with aura, cerebrovascular disease, ischaemic heart disease, peripheral vascular disease, diabetes $>$20 years, valvular heart disease with pulmonary hypertension or history of breast cancer. In a given patient, once one of these contraindications was identified, they were considered to have this possible contraindication from that point forward. Additional possible contraindications, assessed in a time-dependent manner, included smoking and age $>$35 years, high disease activity (SLEDAI-2K score $>$12 or $>$0.5 mg/kg/day prednisone dose), hypertension and positive aPL. These items were allowed to change from one visit to the next. The baseline visit for the current study was considered the first visit at which an aPL value was measured. Missing aPL values at later visits were assigned the same value as the most recent preceding visit where a result was available. We included in our model education, race/ethnicity and geographic region as potential predictors. All analyses were performed using STATA version 15 (StataCorp, College Station, TX, USA).

Results

A total of 1224 SLE women contributing 7743 visits from 2000 to 2017 met inclusion criteria for the study, but 297 subjects (1241 visits) were excluded due to a lack of any data on aPL status from the central laboratory and a further 187 visits were excluded since they took place prior to the first known aPL result. Thus 927 women were enrolled in the current study, contributing 6315 eligible visits (Fig. 1). The clinical and demographic characteristics of CHC users at baseline with and without one or more possible contraindication are listed in Table 1. The mean age was 30.1 years (S.D. 7.6) at study entry, 39% of subjects were Caucasian and 65% had some post-secondary education.

A total of 742 (80%) subjects possessed one or more possible contraindication to CHCs at some point during

Fig. 1 Flow diagram of study inclusion



the study, while 3811 (60%) visits took place when a subject had one or more possible contraindication to CHCs. Excluding high disease activity as a contraindication, 706 (76%) women possessed one or more possible contraindication to CHCs at some point, representing 3675 (58%) visits with one or more WHO Category 3 or Category 4 contraindication to CHCs.

Eighty-two (9%) women were on CHCs at baseline, while 17 (2%) were on progesterone-only contraception. Across all study visits, Caucasians had the greatest CHC use [332/2335 (14%; 95% CI 13, 16)], with lower use among Hispanics [45/1209 (4%; 95% CI 3, 5)], Asians [64/1248 (5%; 95% CI 4, 7)] and Blacks [25/973 (3%; 95% CI 2, 4)]. Although Hispanic subjects had more visits with one or more possible contraindication to CHCs compared with Caucasians [827/1209 (68%; 95% CI 66, 71) *vs* 1395/2335 (60%; 95% CI 58, 62)], this was not observed for Asian subjects [689/1248 (55%; 95% CI 52, 58)] or Black subjects [599/973 (62%; 95% CI 58, 65)].

Among the 82 (9%) subjects on CHCs at study entry, 45 (55%) possessed one or more possible contraindication to CHCs, whereas among the 77 (8%) women who started CHCs after their enrolment visit, 58 (75%) possessed one or more possible contraindication at some point after this visit. CHCs were used at 512 (8%) visits overall, of which 281 (55%) took place in the presence of one or more possible contraindication. Women with one or more possible contraindication were slightly less likely to be taking CHCs [281/3811 visits (7%; 95% CI 7, 8)] compared with women with no contraindications to CHC [231/2504 visits (9%; 95% CI 8, 10); difference of proportion 2% (95% CI 0, 3)].

Among the 281 visits during which CHCs were taken in the presence of one or more possible contraindication to CHCs, 146 visits (52%) were in the presence of positive aPL. Other frequently observed potential contraindications were hypertension (34%) and migraine with aura (22%) (Table 2). Across all study visits, CHCs were used in the presence of two possible contraindications at 70 visits and three or more simultaneous contraindications at 20 visits.

In the multivariate analysis including all CHC-user visits ($n = 512$), subjects from Europe were more likely

TABLE 1 Baseline characteristics overall and among CHC users with and without one or more possible contraindications to oestrogen

Characteristics	Total population ($n = 927$)	CHC users ($n = 82$)	
		Without contraindication ($n = 37$)	With one or more contraindication ($n = 45$)
Age, years, mean (S.D.)	30.1 (7.6)	27.9 (6.8)	26.3 (5.7)
Education			
Post-secondary education, years, mean (S.D.)	3.5 (2.1)	4.1 (2.4)	3.2 (1.7)
Any post-secondary education, *n* (%)	607 (65)	28 (76)	29 (64)
Ethnicity, *n* (%)			
Asian	190 (20)	5 (14)	2 (4)
Black	157 (17)	3 (8)	3 (7)
Caucasian	357 (39)	22 (59)	33 (73)
Hispanic	140 (15)	2 (5)	5 (11)
Indian subcontinent	38 (4)	3 (8)	0 (0)
Other	45 (5)	2 (5)	2 (4)
Country/continent, *n* (%)			
Canada	231 (25)	15 (41)	17 (38)
USA	222 (24)	8 (22)	12 (27)
Mexico	111 (12)	2 (5)	4 (9)
Europe	239 (26)	11 (30)	12 (27)
Asia	124 (13)	1 (3)	0 (0)
Disease duration, years, mean (S.D.)	0.71 (0.74)	0.76 (0.86)	0.59 (0.72)
BMI, kg/m^2, mean (S.D.)	24.5 (5.6)	23.8 (3.5)	24.6 (4.9)

TABLE 2 Contraindications to CHCs among SLE women using CHCs with one or more possible contraindications

Contraindications to CHCs	Visits where CHCs used with one or more contraindication ($n = 281$ visits)
Anti-phospholipid antibodies, *n* (%)[a]	146 (52)
Lupus anticoagulant	85 (30)
aCL	42 (15)
Anti-β_2-GPI	58 (21)
Hypertension, *n* (%)[b]	96 (34)
Migraine with aura, *n* (%)[a]	62 (22)
History of venous thromboembolism, *n* (%)[b]	21 (7)
SLEDAI score >12, *n* (%)	21 (7)
Prednisone use $\geqslant$0.5 mg/kg/day, *n* (%)	17 (6)
Ischaemic stroke, *n* (%)[a]	13 (5)
Smoker $\geqslant$35 years of age, *n* (%)[b]	10 (4)
Valvular heart disease with pulmonary hypertension, *n* (%)[a]	5 (2)
Ischaemic heart disease, *n* (%)[a]	4 (1)
Diabetes $\geqslant$20 years, *n* (%)[b]	3 (1)
History of breast cancer, *n* (%)[a]	1 (0)
Peripheral vascular disease, *n* (%)[a]	1 (0)

[a]WHO Grade 4 (unacceptable health risk, method not to be used) [4]. [b]WHO Grade 3 (theoretical or proven risks usually outweigh the advantages) or Grade 4 (unacceptable health risk, method not to be used) depending on clinical circumstances [4].

to use CHCs in the presence of one or more possible contraindication [odds ratio (OR) 2.8 (95% CI 1.3, 6.2)], while effect estimates for other variables were inconclusive (Table 3). We performed sensitivity analyses to ensure that this effect estimate was not driven by potential collinearity between country of origin and race/ethnicity (Table 4). The first model excluded race/ethnicity entirely and the second excluded all Asian and Hispanic subjects (including but not limited to all subjects at the South Korean and Mexican study centres). In both cases, the effect estimate for Europe was maintained.

Of the 103 (11%) women who took CHCs in the presence of one or more possible contraindication at any visit, 24 (23%) were observed to stop the CHC by the following visit and 56 (54%) continued on CHCs despite having a possible contraindication, while 23 (22%) stopped having the contraindication or did not have a further visit. Thirteen women had three visits and 17 had four or more consecutive visits while taking CHCs with a contraindication.

Discussion

In this large international inception cohort, more than half of SLE women possessed one or more possible contraindication to CHCs, which is much greater than prevalence estimates in general population samples (3–18%) [7, 22, 23]. The high prevalence of possible contraindications to oestrogen among SLE women reflects the fact that many are frequent co-morbidities and complications of SLE [9, 24, 25].

More than half of CHC users had one or more possible contraindication to oestrogen, with the most common being aPL and hypertension. Women who presented one or more possible contraindication were almost as likely to be taking CHCs as those who did not have any contraindications. Lauring *et al.* [7] observed that, among a general population sample, women with contraindications and those without also took CHCs with approximately equal frequency (39% *vs* 47%). In our study, 11% of SLE women took CHCs in the presence of one or more possible contraindication at some point, which might suggest room for improvement in prescribing practices. However, the finding that very few subjects took CHCs in the presence of two or three simultaneous contraindications and that nearly a quarter of subjects taking CHCs with a contraindication had stopped the CHC by the following year is reassuring. The benefits of reliable contraception offered by CHCs in some patients (with or without intolerance to other contraceptive types) may outweigh the risk associated with the possible contraindication. For example, adverse pregnancy outcomes are increased among patients with active SLE [26] and nephritis [27], while teratogenic medications mandate the use of reliable contraception.

We found a low prevalence of any hormonal contraceptive use in SLE women (11% at baseline) compared with general population estimates (28–46%) [7, 28] and other cohort studies of SLE women (18–24%) [2, 28, 29], although one earlier Finnish study found a prevalence similar to our study (6%) [30]. This may be due in part to an increased awareness of the potential for contraindications to CHCs among providers and/or patients. Of note, progesterone-only contraception and intrauterine devices can serve as safer alternatives for patients unable to take CHCs [4], and we observed a low frequency of

Table 3 Univariate and multivariate logistic regression: factors associated with using CHCs in the presence of one or more contraindication ($n = 512$)

Variable	Univariate, OR (95% CI)	Multivariate, OR (95% CI)
Post-secondary education	0.69 (0.42, 1.15)	0.74 (0.44, 1.25)
Race (*vs* Caucasian)		
Asian	0.89 (0.36, 2.2)	0.96 (0.33, 2.75)
Black	1.10 (0.38, 3.23)	0.98 (0.32, 2.99)
Hispanic	2.24 (0.76, 6.61)	1.87 (0.12, 29.73)
Indian subcontinent	0.58 (0.12, 2.8)	0.37 (0.07, 1.97)
Other	0.96 (0.29, 3.19)	0.76 (0.22, 2.66)
Region (*vs* Canada)		
USA	1.30 (0.61, 2.79)	1.33 (0.61, 2.89)
Mexico	3.37 (1.02, 11.18)	1.62 (0.08, 32.08)
Europe	2.38 (1.12, 5.05)	2.80 (1.26, 6.23)
Asia	1.13 (0.19, 6.59)	1.25 (0.17, 9.10)

Table 4 Factors associated with CHC use in the presence of one or more contraindication: sensitivity analyses

Variable	Model 1: original ($n = 512$ visits), OR (95% CI)	Model 2: exclusion of race/ethnicity ($n = 512$ visits), OR (95% CI)	Model 3: exclusion of potential collinear variables (Asia, South Korea, Hispanic, Mexico) ($n = 403$ visits), OR (95% CI)
Post-secondary education	0.74 (0.44, 1.25)	0.73 (0.44, 1.23)	0.81 (0.48, 1.39)
Race (*vs* Caucasian)			
Asian	0.96 (0.33, 2.75)		
Black	0.98 (0.32, 2.99)		0.89 (0.28, 2.83)
Hispanic	1.87 (0.12, 29.73)		
Indian subcontinent	0.37 (0.07, 1.97)		0.29 (0.05, 1.67)
Other	0.76 (0.22, 2.66)		0.68 (0.18, 2.53)
Region (*vs* Canada)			
USA	1.33 (0.61, 2.89)	1.34 (0.62, 2.87)	1.67 (0.71, 3.92)
Mexico	1.62 (0.08, 32.08)	3.1 (0.93, 10.39)	
Europe	2.8 (1.26, 6.23)	2.45 (1.15, 5.21)	4.39 (1.77, 10.86)
Asia	1.25 (0.17, 9.1)	1.22 (0.21, 7.15)	

progesterone-only contraceptive use (2%). Previous research has suggested a deficiency of contraceptive counselling in SLE women [2, 29, 31], and interdisciplinary collaboration may be helpful for counselling SLE women on contraceptive options. SLE women may be less sexually active than the general population due to a variety of psychosocial and chronic disease factors [32] and thus request less contraception.

The SLICC cohort provides a broad representation of SLE patients from varying sociodemographic backgrounds and health care settings. The prevalence of CHC use across different regions and ethnicities was variable, with ethnic minorities (Black, Asian, Hispanic) having a lower frequency of CHC use than Caucasians, despite having a similar prevalence of possible contraindications to CHCs. Although European subjects were more likely to take CHCs in the presence of a possible contraindication in the multivariate analysis, heterogeneity in CHC use among individual European countries and the low numbers of subjects in several centres makes generalization within this region difficult. These results should serve to highlight the need for centre-specific evaluation and optimization of contraceptive use among SLE patients.

This study is the largest and only multicentre assessment to date of CHC use in SLE women from the time of SLE onset. Furthermore, it is the first to systematically assess the prevalence of contraindications to CHCs in SLE based on internationally established criteria [4]. A cross-sectional study of 206 SLE women noted that 4 of 15 subjects taking CHCs had aPL or a history of thrombosis, but other possible medical contraindications were not assessed [2]. Our research has identified a potential unmet need in this population, since 55% of CHC users possessed a possible medical contraindication.

Our study has limitations. A Category 3 designation acknowledges that although the risks outweigh the benefits of a CHC, it could be used if an alternative method was not available. Therefore some providers might have made an appropriate treatment decision, given the well-established risks of pregnancy in some clinical situations [33, 34]. No information was available on contraceptive prescribers (specialty, clinic setting) or the patients' role in the contraceptive choice. The treating rheumatologist may not have been involved in the decision-making process, stressing the need for more data on this issue. Although hypertension, thrombosis, ischaemic heart disease, stroke and migraine with aura were included as contraindications in the first edition of the WHO medical eligibility criteria for contraceptive use in 1996 [5], the presence of a positive aPL in SLE was added as a contraindication in the fourth edition (2009) [35], after cohort inception (2000). This may partly explain why aPL was a frequently observed contraindication among women taking CHCs, although thrombogenic conditions were considered contraindications as early as 2004 [36]. We used aPL values generated in the central lab of one of the study investigators (JM), and these results were not fed back to the clinical centres. Although each centre presumably had done aPL testing of their patients for clinical reasons, the results could have been divergent (i.e. a test could have been negative at the local test centre and positive at the central lab). Rightly or wrongly, the WHO/CDC recommendations do not specify a titre cut-off for aPL or the need for confirmatory testing and thus all positive aPL tests (or unknown aPL status in an SLE patient) are considered a Category 4 contraindication [4, 6]. However, the risk of thrombosis among the different aPLs is not uniform, the highest being with lupus anticoagulant [9], and varies according to aPL titres, with titres >40 U/mL aCL and anti-β_2-GPI required for the classification of APS [37]. Although there could be a reduced thrombotic risk after an initially positive aPL becomes negative [38, 39], the WHO [4], CDC [6] and EULAR recommendations [13] do not address this scenario in the management of CHCs. If aPL had been considered a time-independent variable (always a contraindication even if future testing is negative), the prevalence of subjects with contraindications to CHCs would have been even greater. No data were available on the type of CHC used, and while oestrogen type may influence the cardiovascular safety of these medications [40], current CHC recommendations are uniform regardless of CHC type [4, 6].

Altogether, this study highlights the challenge of ensuring safe contraceptive use in SLE women of reproductive age. Medical contraindications to CHCs are common. Even in the absence of apparent contraindications, hormonal contraception use is low. Health professionals (primary care physicians, gynaecologists, rheumatologists) should be aware that CHCs should not be withheld from SLE women, but specific risk factors should be reviewed for each patient. Also, patients should be educated regarding potential contraindications and risks/benefits of CHCs. Physicians' and patients' perspectives should be sought in order to optimize contraceptive counselling and appropriate contraceptive use in this population. Finally, adverse outcomes associated with CHC exposure in SLE women with possible contraindications is an important area of future research.

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