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

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Abstract

Objectives: To assess the prevalence of combined hormonal contraceptives (CHC) in reproductive-aged women with systemic lupus erythematosus (SLE) with and without possible contraindications, and determine factors associated with their use in the presence of possible contraindications.

Methods: This observational cohort study included premenopausal women aged 18-45 enrolled in the Systemic Lupus International Collaborating Clinics (SLICC) Registry ≤15 months of SLE onset, with annual assessments spanning 2000–2017. World Health Organization Category 3 or 4 contraindications to CHC [e.g. hypertension, antiphospholipid antibodies (aPL)] were assessed at each study visit. High disease activity (Systemic Lupus Erythematosus Disease Activity Index >12 or use of >0.5 mg/kg/day of prednisone) was considered a relative contraindication.

Results: 927 SLE women contributed 6315 visits, of which 3811 (60%) occurred in the presence of ≥1 possible contraindication to CHC. Women used CHC during 512 (8%) visits, of which 281 (55%) took place in the setting of ≥1 possible contraindications. The most frequently observed contraindications were aPL (52%), hypertension (34%), and migraine with aura (22%). Women with ≥1 contraindication were slightly less likely to be taking CHC (7% of visits, 95% CI 7-8) than women with no contraindications (9%, 95% CI 8-10).

Conclusion: CHC use was low compared to general population estimates (>35%), and over 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.

Keywords

Systemic lupus erythematosus; antiphospholipid syndrome; contraception; epidemiology

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 antiphospholipid antibodies, hypertension, and migraine with aura

Introduction

Systemic lupus erythematosus (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 (CHC) are contraindicated in certain medical conditions, due to the excess risk of thromboembolic events associated with estrogen exposure [3]. The World Health Organization (WHO) [4, 5] and the United States Center 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 CHC, and despite this, 39% of this group were taking CHC [7]. Women with SLE may have a higher prevalence of medical contraindications to CHC compared to unaffected women, due to an increased prevalence of hypertension and thrombotic risk factors, including antiphospholipid antibodies (aPL) (i.e. lupus anticoagulant [LAC], anticardiolipin antibody [aCL], and anti-beta2 glycoprotein-1 antibodies [anti-$ß_2$-GPI]) [8-10].

Two randomized controlled trials (RCTs) established that CHC use in SLE did not increase flares [11] or global disease activity [12] at one year. However, the Safety of Estrogens in Lupus National Assessment (SELENA) trial excluded patients with high disease activity (Systemic Lupus Erythematosus Disease Activity Index >12 or use of >0.5 mg/kg/day of prednisone) and medical contraindications to estrogen, as well as those without stable or improving disease activity over the last 3 months [11]. Sanchez-Guerrero *et al.*'s RCT included women with positive aCL and anti-$ß_2$-GPI [12]. Although this trial was not powered to detect a difference in adverse events in the subgroup of aPL-positive subjects who received CHC, all 4 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 CHC [4,6], and recent European League Against Rheumatism (EULAR) recommendations state that CHC be used in those with stable or inactive SLE and negative aPL [13].

The prevalence of possible contraindications to CHC 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 CHC as well as the proportion of CHC users with and without concurrent possible contraindications to CHC. 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 Systemic Lupus International Collaborating Clinics (SLICC) cohort is a multi-national inception cohort for the study of SLE outcomes [14-17]. Patients meeting ≥4 American College of Rheumatology (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 2000-2017 according to a standardized protocol [15]. Local institutional review board approval was obtained at each of the 33 participating sites across 11 countries in North America, Europe, and Asia. This study complies with the declaration of Helskinki, and was approved by the institutional review boards of the McGill University Research Ethics Boards, as well as of all SLICC participating sites, and a data use agreement was in place. Patient consent was obtained when patient enrolled in the SLICC cohort.

The current study identified premenopausal women aged 18-45 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 Systemic Lupus Erythematosus Disease Activity Index 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 CHC [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 aged ≥35, 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 ischemic attack or ischemic stroke), ischemic heart disease (current or past myocardial infarction, angina, angioplasty, or coronary artery bypass grafting), peripheral vascular disease (current or past claudication), diabetes ≥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 LAC, aCL IgG, or anti-$ß_2$-GPI IgM or IgG), defined as a single titer above the laboratory cutoff value. aPL were measured at a central laboratory at the Oklahoma Medical Research Foundation, United States, 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 SLEDAI-2K score >12 or use of prednisone equivalent of >0.5 mg/kg per day, was also evaluated as a relative contraindication to CHC, as these were exclusion criteria in the SELENA trial [11], and the EULAR guidelines recommend using CHC only in stable or inactive disease [13].

Statistical analysis

Characteristics were summarized in the form of means and standard deviations (SDs) for continuous variables and proportions for categorical variables. We calculated the proportion of women having ≥1 possible contraindication during the study period, as well as the proportion of visits where ≥1 possible contraindication was present. The proportion of visits where CHC was

used with and without ≥1 possible contraindication was compared by calculating the 95% confidence intervals (CI) for the difference in proportion for two independent samples. Among study visits where CHC was used in the presence of ≥1 possible contraindications, 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 (GEE) approach, with each subject serving as a cluster. The outcome was a visit in which the patient was taking CHC in the presence of ≥1 possible medical contraindications. These contraindications included venous thromboembolism, migraine with aura, cerebrovascular disease, ischemic 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, high disease activity (SLEDAI-2K >12 or >0.5mg/kg/d 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, 2017, College Station TX).

Results

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

742 (80%) subjects possessed ≥1 possible contraindication to CHC at some point during the study, while 3811 (60%) visits took place when a subject had ≥1 possible contraindication to

CHC. Excluding high disease activity as a contraindication, 706 (76%) women possessed ≥1 possible contraindication to CHC at some point, representing 3675 (58%) visits with ≥ 1 WHO Category 3- or Category 4- contraindications to CHC.

Eighty-two (9%) women were on CHC 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 ≥1 possible contraindication to CHC compared to 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)] nor Black subjects [599/973 (62%, 95% CI 58-65)].

Among the 82 (9%) subjects on CHC at study entry, 45 (55%) possessed ≥ 1 possible contraindication to CHC, whereas among the 77 (8%) women who started CHC after their enrolment visit, 58 (75%) possessed ≥1 possible contraindication at some point after this visit. CHC was used at 512 (8%) visits overall, of which 281 (55%) took place in the presence of ≥1 possible contraindication. Women with ≥1 possible contraindication were slightly less likely to be taking CHC [281/3811 visits (7%, 95% CI 7-8)] compared to 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 CHC was taken in the presence of ≥1 possible contraindication to CHC, 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, CHC was used in the presence of 2 possible contraindications at 70 visits, and ≥3 simultaneous contraindications at 20 visits.

In the multivariate analysis including all CHC-user visits (n=512), subjects from Europe were more likely to use CHC in the presence ≥1 possible contraindication [OR 2.8 (1.3 to 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 CHC in the presence of ≥1 possible contraindications at any visit, 24 (23%) were observed to stop the CHC by the following visit and 56 (54%) continued on CHC despite having a possible contraindication, while 23 (22%) stopped having the contraindication or did not have a further visit. Thirteen women had 3 visits and 17 had ≥ 4 consecutive visits while taking CHC with a contraindication.

Discussion

In this large international inception cohort, over half of SLE women possessed ≥1 possible contraindications to CHC, which is much greater than prevalence estimates in general population samples (3% -18%) [7, 22, 23]. The high prevalence of possible contraindications to estrogen among SLE women reflects the fact that many are frequent co-morbidities and complications of SLE [9, 24, 25].

Over half of CHC users had ≥1 possible contraindications to estrogen, with the most common being aPL and hypertension. Women who presented ≥1 possible contraindication were almost as likely to be taking CHC as those who did not have any contraindications. Lauring *et al* observed that, among a general population sample, women with contraindications and those without also took CHC with approximate equal frequency (39% vs 47%) [7]. In our study, 11% of SLE women took CHC in the presence of ≥1 possible contraindication at some point, which might suggest room for improvement in prescribing practices. However, the finding that very few subjects took CHC in the presence of 2 or 3 simultaneous contraindications, and that nearly a quarter of subjects taking CHC with a contraindication had stopped the CHC by the following year, is reassuring. The benefits of reliable contraception offered by CHC, 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 to 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 similar prevalence to our study (6%) [30]. This may be due in part to an increased awareness of the potential for contraindications to CHC among providers and/or patients. Of note, progesterone-only con-

traception and intra-uterine devices can serve as safer alternatives for patients unable to take CHC [4], and we observed a low frequency of 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 request less contraception.

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

This study is the largest and only multi-centre 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 CHC in SLE based on internationally established criteria [4]. A cross-sectional study of 206 SLE women noted that 4/15 subjects taking CHC 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 benefit of 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 have not been involved in the decision-making process, stressing the need for more data on this issue. Although hypertension, thrombosis, ischemic 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 CHC, although thrombogenic conditions were considered contraindications as early as 2004 [35]. 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. Though 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 cutoff for aPL or the need for confirmatory testing and thus, all positive aPL (or unknown aPL status in an SLE patient) is considered a Category 4 contraindication [4, 6]. However, the risk of thrombosis among the different aPL is not uniform, the highest being with LAC [9], and varies according to aPL titres, with titers of > 40 U/mL aCL and anti-$ß_2$-GPI required for the classification of antiphospholipid syndrome [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 CHC. 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 CHC would have been even greater. No data was available on the type of CHC used, and while estrogen 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 CHC 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 CHC should not be withheld from SLE women, but that specific risk factors should be reviewed for each patient. Patients also should be educated regarding potential contraindications and risks/benefits of CHC. 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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Figure legend

Figure 1: Flow diagram of study inclusion

CHC: Combined Hormonal Contraceptive; SLICC: Systemic Lupus International Collaborating Clinics; aPL: antiphospholipid antibodies

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Table 1. Baseline characteristics, overall and among CHC users with and without ≥1 possible contraindications to estrogen

Characteristics	**Total population (n=927)**	**Combined Hormonal Contraceptive users (n=82)**	
		Without contraindication (n=37)	**With 1 or more contraindications (n=45)**
Age, mean (SD)	30.1 (7.6)	27.9 (6.8)	26.3 (5.7)
Education			
Years of post-secondary education, mean (SD)	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)
United States	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 (SD)	0.71 (0.74)	0.76 (0.86)	0.59 (0.72)
BMI, kg/m^2, mean (SD)	24.5 (5.6)	23.8 (3.5)	24.6 (4.9)

Table 2. Contraindications to CHC among SLE women using CHC with ≥1 possible contraindications

Contraindications to CHC	**Visits where CHC used with ≥1 contraindication (n= 281 visits)**
Antiphospholipid antibodies, n (%)* LAC, n(%) aCL, n(%) anti-B2-GPI n(%)	146 (52) 85 (30) 42 (15) 58 (21)
Hypertension, n (%)†	96 (34)
Migraine with aura, n (%) *	62 (22)
History of venous thromboembolism, n (%)†	21 (7)
SLEDAI score >12, n (%)	21 (7)
Prednisone use ≥0.5 mg/kg/d, n (%)	17 (6)
Ischemic stroke, n (%)*	13 (5)
Smoker aged ≥35, n (%)†	10 (4)
Valvular heart disease with pulmonary hypertension, n (%)*	5 (2)
Ischemic heart disease, n (%)*	4 (1)
Diabetes ≥ 20 years, n (%)†	3 (1)
History of breast cancer, n (%)*	1 (0)
Peripheral vascular disease, n (%)*	1 (0)

* WHO Grade 4 (unacceptable health risk, method not to be used) [4]† 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] CHC: Combined Hormonal Contraceptive; LAC: lupus anticoagulant; aCL: anticardiolipin antibody

Table 3. Univariate and multivariate logistic regression: factors associated with using CHC in the presence of ≥1 contraindications (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)		
United States	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)

CHC: Combined Hormonal Contraceptive; OR: Odds ratio.

Table 4. Factors associated with CHC use in the presence of ≥1 contraindications: 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)			
United States	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)	

CHC: Combined Hormonal Contraceptive; OR: Odds ratio.