Oral contraceptives and risk of systemic lupus erythematosus

Systemic lupus erythematosus (SLE) predominantly affects women and its incidence is highest during child-bearing years. Therefore, endogenous sex hormones are thought to be an important causal factor in SLE etiology. Furthermore, exogenous hormonal factors, such as estrogen-containing oral contraceptives (OCs), have for many years been suspected in triggering SLE. Up to now, the etiologic role of OCs in SLE was a matter of debate, since studies had suggested conflicting results. Although several case reports showed an association between OC exposure and SLE onset, case–control studies did not confirm this. However, in recent years, data incriminating OCs as a potential trigger of SLE are now accumulating. The purpose of this paper is to present a systematic review of this literature.

KEYWORDS: disease risk ■ estrogen ■ observational studies ■ oral contraceptives ■ systemic lupus erythematosus

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Systemic lupus erythematosus (SLE) occurs predominantly in women, who represent approximately 90% of affected individuals. SLE incidence increases after puberty, peaking during the child-bearing period. Thus, endogenous and exogenous sex hormones are thought to play an important role in SLE etiology. Notably, estrogen in oral contraceptives (OCs) has been questioned, since estrogen can influence the immune system and may promote autoimmunity [1]. Some studies have reported alterations in SLE disease activity during pregnancy, with OC use, and even with menstrual cycles, further suggesting a role for estrogen [2–4].

Until recently, the etiologic role of OCs was debated because observational studies, hampered by methodological limitations, had produced conflicting results (Table 1) [5–10]. This year, a large nested case–control study was reported, which brought new evidence to the debate [11].

Formulations & types of OC

Studies assessing the risk of SLE following OC use can be limited by exposure definitions. Not all OCs contain estrogen. In addition, OCs have changed over time and different types and formulations now exist. It is therefore important to know which OCs were in use within the context of each specific study.

Oral contraceptives were initially marketed in the USA in 1960 [12]. The first marketed OCs contained 150 µg of the estrogen component, mestranol. Over the past 50 years, many other formulations have been introduced, with decreasing dosages of both the estrogen and progestin components. Since 1975, all formulations contain less than 50 µg of ethinyl estradiol [12].

The three common types of OC formulations are fixed-dose combination, phasic combination and daily progestin. The combined OCs are the most widely used and contain two or three different dosages of the same estrogen and progestin, which will vary during the cycle. Fixed-dose products consist of tablets containing both estrogen and progestin. Daily progestin features oral progestin pills without estrogen [12].

Formulations with 50 µg of estrogen (ethinyl estradiol or mestranol) or more have been termed first-generation OCs. Those with less than 50 µg of estrogen (usually 20–35 µg of ethinyl estradiol) are termed second-generation if they contain any progestin, excluding the newest levonorgestrel derivatives (i.e., desogestrel, norgestimate and gestodene). OCs containing one of the latter three progestins are referred to as third generation [12].

Effects of estrogen on the immune system

Sex hormones, including estrogen, have been shown to influence immune system regulation and disease activity in patients with SLE [4,13–17]. Women with SLE may experience an increase in disease activity during pregnancy or with their menses [2–4]. Furthermore, polymorphisms of the estrogen receptor gene have been associated with SLE [18].

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Table 1. Characteristics of the different observational studies of oral contraceptives and systemic lupus erythematosus onset.

Authors	Study type	Number of SLE cases	Exposure assessment	OC type or formulation	Effect estimate for ever use (95%CI)	Effect estimate for current use (95%CI)	Ref.
Grimes *et al.* (1985)	Case–control	109	Interview and chart review	Not assessed	–	0.50 (0.11–2.3)	[5]
Strom *et al.* (1994)	Case–control	195	Interview and chart review	Not assessed	0.9 (0.5–1.5)	–	[6]
Cooper *et al.* (2002)	Case–control	240	Interview	Not assessed	1.30 (0.9–2.1)	1.5 (0.8–2.5)	[7]
Bengtsson *et al.* (2002)	Case–control	85	Mailed questionnaire	Not assessed	–	–	[8]
Sanchez-Guerrero *et al.* (1997)	Cohort	99	Mailed questionnaire	Not assessed	1.4 (0.9–2.1)	–	[9]
Costenbader *et al.* (2007)	Cohort	262	Mailed questionnaire	Assessed	1.5 (1.1–2.1)	–	[10]
Bernier *et al.* (2009)	Nested case–control	786	Administrative database	Assessed	1.19 (0.98–1.45)	1.54 (1.15–2.07)	[11]

OC: Oral contraceptive; SLE: Systemic lupus erythematosus.

Estrogen has pleiotropic effects on the immune system. It plays an important role in B-cell maturation, selection and activation, and potentially participates in the breakdown of immune tolerance in SLE [19,20]. For example, estrogen upregulates Bcl-2, blocking tolerance induction of naive B cells [21]. An increase in estrogen levels can break tolerance of high-affinity DNA-reactive B cells [1]. Moreover, estradiol upregulates CD-154 expression on T cells in women with SLE, but not in controls [22], and increases signal transduction pathways in activated SLE T cells that control T-cell function [23].

Estrogen prevents apoptosis of peripheral blood mononuclear cells and activates dendritic cells [24]. In addition, phytoestrogens have been shown to produce a threefold increase in anti-Ro levels in human keratinocytes, and estrogen-containing OCs have been associated with antinuclear antibody production [1,25].

Furthermore, estrogen metabolism may be different in women with SLE, promoting more biologically active estrogenic metabolites [26]. A meta-analysis of case–control studies of hormonal levels showed significantly higher levels of estradiol in women with existing SLE compared with controls [27]. However, studies assessing estrogen levels and the risk of SLE have not been conducted.

Evidence from randomized controlled trials on OCs & risk of SLE flare

In the past, many have postulated that OC use exacerbated SLE activity, but this was controversial. Recently, two randomized controlled trials (RCTs) addressed this debate and provided similar results. The first RCT was single-blinded, and included 162 women with SLE who were randomly assigned to a combined OC (containing 30 µg ethinyl estradiol), a non-eluting intrauterine device, or a progestin-only pill for 12 months [28]. There was no difference in the flare rate between these groups.

The second RCT was double-blinded, and evaluated a combined OC (containing 35 µg ethinyl estradiol) versus placebo for 12 months [29]. It included 183 women with SLE who had, at baseline, inactive or stable active disease, and showed no difference in the severe flare rate, with flares being very uncommon in both groups. Of note, since both RCTs excluded SLE patients with unstable active disease, the results may not be applicable to all women with SLE.

Furthermore, data from a trial examining hormone replacement therapy (HRT) further cloud the issue [30]. In this RCT, 351 menopausal SLE patients were randomized to HRT (containing 0.625 mg of conjugated estrogen plus progesterone) or placebo for 12 months. Although there was no difference in the severe flare rate, mild-to-moderate flares were increased in the hormone therapy group (relative risk [RR]: 1.34; 95% CI: 1.07–1.66). These results have led some to question the effects of exogenous estrogen on the risk of SLE flare, particularly in postmenopausal women and in patients with high disease activity.

Observational studies of OCs & risk of developing SLE

The first case–control study assessing the association of OC exposure and risk of SLE was performed in 1985 [5]. This hospital-based

case–control study included 109 incident cases of SLE, who were initially identified from hospital records, and confirmed according to the American Rheumatism Association (ARA) diagnostic criteria. An equal number of controls were randomly selected from all women discharged from the hospital during the same period. Women admitted for obstetric or gynecologic conditions or complications were excluded from being controls. Data were collected through chart review and interviews.

In this study, OC use was not associated with SLE onset. However, the authors did not precisely define OC exposures. Furthermore, the only reported odds ratio (OR) for OC use was for current use, which was associated with an OR of 0.50, with a 95% CI of 0.11–2.3. The authors stated that current OC use was infrequent, albeit without mentioning the frequency; this evidently limited the precision of the results [5].

In 1994, Strom *et al.* undertook a population-based case–control study to explore many potential determinants of SLE etiology [6]. A total of 195 cases of SLE diagnosed between 1985 and 1987 were compared with 143 controls, friends of the cases matched for age and sex. Cases were defined as outpatients with a recent-onset clinical diagnosis of SLE (i.e., within the 3 years prior to study initiation), meeting four or more of the revised ARA criteria for the definition of SLE. Through personal interviews and chart reviews, data were collected on a multitude of different exposures, including reproductive factors and medication. No information was provided on formulations and types of OC.

No association was found between SLE onset and any of the following:

- OC use in the 3 years before the year of diagnosis (OR: 0.6; 95% Cl: 0.2–1.4);
- Any OC use (OR: 0.9; 95% CI: 0.5–1.5);
- Any OC use prior to the diagnosis (OR: 0.8; 95% CI: 0.5–1.4);
- OC use during the 4–6 years prior to the diagnosis (OR: 0.8; 95% CI: 0.4–1.6).

The authors concluded that if the development of SLE was affected by OC use, this effect was extremely modest [6]. However, this study had an important limitation: the use of friend controls. As friend controls may be overmatched to cases on many factors, potentially including OC use; this could bias the results toward the null hypothesis for these variables. That is, if friends tend to have the same contraceptive practices, the study design could have masked a true association between OCs and SLE.

In 2002, the Carolina Lupus Study assessed the link between different hormonal factors and SLE development [7]. This population-based case–control study included 240 female SLE patients from outpatient clinics, diagnosed between 1995 and 1999, and meeting the American College of Rheumatology (ACR) classification criteria. Female controls (n = 321) were selected from driver's license records. Data were collected by interviews, and formulations or types of OCs were not specified.

Although the study was unable to demonstrate a definite association between SLE and OC use, there were trends for an association with past use (OR: 1.3; 95% CI: 0.8–2.0), current use (OR: 1.5; 95% CI: 0.8–2.7) or ever use (OR: 1.3; 95% CI: 0.9–2.1) of OCs. In this case–control study, data collection involved an extensive interview, encompassing a vast reproductive history. Poor recall may have been an issue, leading to nondifferential misclassification of the exposure, which could have biased the results toward the null hypothesis.

In 2002, a Swedish group of investigators reported a population-based case–control study investigating potential risk factors for the development of SLE [8].

The recruitment area comprised a population of 92,962 females from a southern region in Sweden. A total of 85 SLE cases were identified from records of the only hospital in the area, between 1981 and 1999. Case definition included the presence of a multisystemic disorder with an autoimmune serology or low complement levels, in the absence of any better alternative diagnosis. For each case, two age-matched female controls were randomly selected from the same area. Mailed questionnaires were used to collect information, which included whether the subject had ever used estrogen-containing OCs. Exposure to OCs was not further defined.

In total, 85 cases out of 91 (93%) and 205 controls out of 383 (53%) agreed to participate. A relatively high proportion of cases (48%) had used estrogen-containing OCs, but the proportion was similar in controls (53%). Although the authors concluded that OC use was not associated with SLE onset, they did not provide any type of adjusted analyses [8].

Data from the Nurses' Health Study (NHS) have been used in two cohort studies on the risk of developing SLE after OC exposure. The first was reported in 1997 and prospectively followed

121,645 women every 2 years between 1976 and 1990 [9]. Women were classified as never users or past users of OCs, based on self-report. OC types or formulations were not assessed. Using medical chart review after a mailed screening questionnaire, SLE incidence was defined by the presence of four or more ACR criteria, with a second stricter definition also requiring clinical confirmation by a rheumatologist.

Current users accrued 22,873 person-years without any case of SLE occurring in this group. Therefore, the investigators analyzed the whole population based only on past use of OCs. The RR for the incidence of SLE in women with four or more ACR criteria (n = 99) was 1.4 (95% CI: 0.9–2.1) for past users compared with never users of OCs. Using the stricter case definition (ACR criteria plus clinical diagnosis; n = 58), the RR for past users compared with never users was 1.9 (95% CI: 1.1–33). No association was demonstrated between SLE risk and OC use duration or time since first use.

This study, the first to demonstrate an increased risk of SLE with OC use, was subject to possible exposure misclassification, since OC use was collected by self-report. However, the authors stated that this misclassification was probably minimal, since self-report has been shown to be highly accurate in this cohort of registered nurses [9]. Furthermore, the misclassification was probably nondifferential because exposure information was collected prospectively before diagnosis, preventing recall bias. Thus, if anything, the results should be conservative, tending toward the null hypothesis.

A second study was performed 10 years later to reassess these associations among women of the NHS and NHS-II cohorts [10]. A larger cohort of 238,308 women was therefore prospectively examined.

After using a mailed screening questionnaire, incident cases of SLE diagnosed between 1976 and 2003 were confirmed by medical record review, requiring three or more ACR criteria and reviewers' consensus. All exposure information was self-reported on the mailed questionnaires, administered every 2 years since 1976 in the NHS, and every 2 years since 1989 in the NHS-II. Information on OC use was categorized as never use, past use (defined as use that ceased at least 1 month before questionnaire return) or current use (defined as use within 1 month of questionnaire return).

Detailed data concerning type and formulation of OCs were obtained from the NHS-II participants. At cohort entry in 1989, these women were asked to note the number of months they had taken specific OC types, identified from a booklet with pictures of all OC brands. Information on OC exposure was updated every 2 years, in the same manner.

A total of 262 incident cases of SLE were confirmed among both cohorts. Ever use of OCs was shown to confer an increased risk of developing SLE, with a pooled RR of 1.5 (95% CI: 1.1–2.1). The risk of SLE was the highest among women with a short exposure (<2 years) to OCs (RR: 1.9; 95% CI: 1.3–2.8). OC use appeared to have a long-lasting effect; in those reporting 10 years or more since last OC use, the RR was 1.7 (95% CI: 1.2–2.4). The type or the potency of OCs was not associated with the risk of developing SLE.

This study was strengthened by the large number of incident SLE cases observed in these combined cohorts and the long duration of follow-up. In both NHS cohorts, participants were mainly educated Caucasian women, which may limit the generalizability of these data. Furthermore, the second study found that a remote exposure to OC 10 years or more ago was associated with the risk of SLE. Since estrogen is thought to exert mainly short-term effects on SLE activity [2–4], this long-term risk is difficult to explain.

More recently, Bernier *et al.* conducted a population-based nested case–control study to assess whether combined OC (COC) use increased the risk of incident SLE [11]. This study was nested in a population of 1,723,781 women aged 18–45 years, using the UK's General Practice Research Database (GPRD). They identified all incident cases of SLE, using the GPRD medical codes, from 1994 to 2004 (n = 786), and matched with up to ten controls (n = 7817) free of SLE at the time of the case's diagnosis. They also matched on calendar year to control for trends over time in OC use.

An OC exposure was characterized as COC if the drug prescribed contained both estrogen and progestin. They also classified OCs according to their generation (i.e., first, second or third). Current use of COCs was defined as one or more prescription in the 3 months prior to SLE diagnosis, and past use as the last prescription filled 3 months or more prior to diagnosis.

The RR of developing SLE associated with any use of COCs compared with non-use was 1.19 (95% CI: 0.98–1.45). While current use of COCs was associated with an increased rate of SLE (RR: 1.54; 95% CI: 1.15–2.07), this was not clearly observed with past use (RR: 1.06;

95% CI: 0.85–1.33). Furthermore, there was a trend for higher SLE risk with newly started, short-term current use of COCs (i.e., current use with no other prescriptions in the 3 years prior to the index date; RR: 2.52; 95% CI: 1.14–5.57) relative to longer term current use (i.e., current use preceding the 3 months prior to the index date; RR: 1.45; 95% CI: 1.06–1.99).

First- or second-generation OCs were also associated with a higher rate of SLE (RR: 1.65; 95% CI: 1.20–2.26), while this association was not clearly observed for third-generation OCs (RR: 1.12; 95% CI: 0.57–2.19). In addition, there was a trend for higher SLE risk with increasing dose of ethinyl estradiol (RR: 1.42, 1.63 and 2.92 for <30, 31–49 and 50 µg, respectively).

In this study, Bernier *et al.* showed that the use of COCs was associated with an increased risk of incident SLE, which appeared to be most prominent in the first 3 months of use, especially with first- and second-generation OCs containing higher doses of ethinyl estradiol [11]. This suggests that OCs have an acute effect on the risk of SLE, with a dose–response relationship that further supports causality.

This study had several strengths. Use of a nested case–control study design reduced selection bias since cases and controls came from the same base population. Furthermore, use of prospectively recorded data to assess exposure before first SLE diagnosis precluded recall bias and limited other types of differential exposure misclassification. In addition, matching on calendar time controlled for time-dependent variations in the outcome and exposure, which was particularly important for variations in OC formulations over time. While the NHS studies have been criticized for their lack of generalizability, the GPRD study had the advantage of using a population-based database, with a more varied multiethnic representation [11].

Conclusion

Recent observational studies, using large samples of subjects with prospectively collected data, have brought new evidence indicating that OCs appear to confer an increased risk of SLE [9–11]. This association finds a biologic plausibility in experimental studies showing that estrogen influences the immune system and promotes autoimmunity [13–17], as well as in clinical studies showing that SLE activity may increase with pregnancy, menstrual cycle or even HRT (Figure 1) [2–4]. Causality is further suggested by the dose–response effect presented in one study [11].

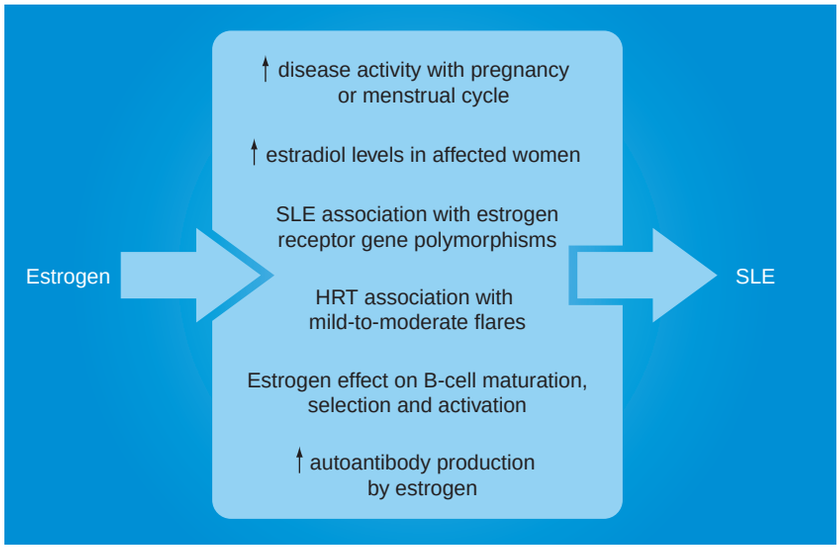

Figure 1. Theoretical links between estrogen and systemic lupus erythematosus.
HRT: Hormone replacement therapy; SLE: Systemic lupus erythematosus.

Earlier case–control studies did not clearly show this association [5–8]. In some of the studies, this may have been due to poor precision or potential flaws in study design and patient selection. Most importantly, in many of the earlier studies, exposure measurement was retrospective (which may lead to inaccurate recall and potential bias), and often did not provide information on OC types or formulations.

Obviously, OCs or estrogen are not the only causal factors in SLE, and the absolute risk of SLE following OC exposure is small. Since SLE occurs in children, in postmenopausal women or even in males, other etiologic factors are clearly involved in its pathogenesis. Still, the association of OCs (and estrogen) with SLE risk provides at least some insight as to why this disease affects women so predominantly. At the present time, given the lack of data to confirm OCs as a trigger for flares in confirmed SLE, there are no formal recommendations to avoid OC use in women with inactive or stable active SLE, unless other contraindications apply (e.g., hypercoagulable states).

Future perspective

In the next few years, it is expected that other studies will try to confirm the recently demonstrated association between OC use and SLE risk across diverse populations. Further characterization of risk according to demographics (e.g., age and ethnicity) will be of particular interest. Finally, ongoing assessments of women exposed long term to the newest OC formulations will provide updated information.

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Executive summary

Formulations & types of oral contraceptives

- The three common types of oral contraceptives (OCs) are fixed-dose combination, phasic combination and daily progestin.
- Formulations with 50 µg or more of estrogen are termed first generation. Second- and third-generation OCs contain less than 50 µg of estrogen (usually 20–35 µg of ethinyl estradiol).

Effects of estrogen on the immune system

- Estrogen plays an important role in B-cell maturation, selection and activation.
- Estrogen metabolism may be different in women with systemic lupus erythematosus (SLE), promoting more estrogenic metabolites.

Evidence from randomized controlled trials on OCs & risk of SLE flare

- Two randomized controlled trials showed no increase in flares with OC use in women with SLE.
- A randomized controlled trial reported an increase in mild-to-moderate SLE flares with hormone replacement therapy, although there was no difference in the severe flare rate.

Observational studies of OCs & risk of developing SLE

- Case–control studies did not demonstrate an association between OC use and the risk of developing SLE.
- These studies were limited by potential flaws in design and patient selection.
- Two cohort studies and a large nested case–control study showed a positive association between the use of OC and SLE onset.
- These studies were strengthened by their prospective exposure measurement.

Conclusion

- The association of OCs with SLE risk provides some insight as to why this disease affects women so predominantly.

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