# Oral contraceptives did not increase risk for flare in women with systemic lupus erythematosus

Petri M, Kim MY, Kalunian KC, et al. **Combined oral contraceptives in women with systemic lupus erythematosus.** N Engl J Med. 2005;353:2550-8.

**Clinical impact ratings:** GIM/FP/GP ★★★★★☆☆ Hematol/Thrombo ★★★★★★☆ Rheumatology ★★★★★★☆

## QUESTION

In young women with stable systemic lupus erythematosus (SLE), do combined oral contraceptives (OCs) increase risk for lupus flare?

## METHODS

**Design:** Randomized, placebo-controlled, noninferiority trial (OC study of the Safety of Estrogens in Lupus Erythematosus National Assessment [OC-SELENA] trial).
**Allocation:** {Concealed}†.*
**Blinding:** Blinded {clinicians, patients, data collectors, outcome assessors, data analysts, and data safety and monitoring committee}†.*
**Follow-up period:** 12 months.
**Setting:** 15 centers in the United States.
**Patients:** 183 women 18 to 39 years of age (< 36 y if a smoker) (mean 30 y) with inactive (76%) or stable active (24%) SLE. Exclusion criteria included use of OCs for > 1 month since SLE diagnosis, hypertension, uncontrolled diabetes, presence of anticardiolipin antibodies or lupus anticoagulant, and history of thrombosis or gynecologic or breast cancer.
**Intervention:** Triphasic ethinyl estradiol (35 µg) plus norethindrone (0.5, 0.75, and 1.0 mg) OC ($n$ = 91) or placebo ($n$ = 92).
**Outcomes:** Severe flare (> 12 out of 105 on the SELENA revision of the SLE Disease Activity Index [SLEDAI], new or worsening disease activity, increase in prednisone to > 0.5 mg/kg per d or new immunosuppressive drug for SLE, hospitalization for SLE, or Physician's Global Assessment score > 2.5 out of 3), mild or moderate flare, and change from baseline in SELENA-SLEDAI score, assessed at 1, 2, 3, 6, 9, and 12 months.
**Patient follow-up:** 83% (100% included in intention-to-treat analysis).

## MAIN RESULTS

OC did not differ from placebo for proportions of women having a severe lupus flare (7.7% vs 7.6%) or a mild-to-moderate flare (69% vs 60%) at 12 months, or for mean change in SELENA-SLEDAI score at any time point (Table). Groups did not differ for type or frequency of adverse events, including thrombosis.

## CONCLUSION

In young women with stable systemic lupus erythematosus, combined oral contraceptives did not increase risk for severe or mild-to-moderate lupus flare.

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*See Glossary.
†Information provided by author.

**Risk for lupus flare with oral contraceptives (OC) vs placebo in young women with systemic lupus erythematosus at 12 months‡**

| Outcomes | OC | Placebo | Difference (1-sided upper 95% CI) |
|---|---|---|---|
| Severe flare§ | 0.084 | 0.087 | –0.003 (0.069‖) |
| Mild or moderate flare§ | 1.40 | 1.44 | –0.04 |
| | | | Difference in mean change (CI) |
| Mean change in SELENA-SLEDAI | 0.12 | –0.11 | 0.23 (–0.67 to 1.13) |

‡SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment–Systemic Lupus Erythematosus Disease Activity Index. CI defined in Glossary.
§Rate per person-year, estimated using the Kaplan-Meier method.
‖Criteria for noninferiority were met because the upper limit of the CI is < 0.09.

## COMMENTARY

A decade ago, patients with SLE were commonly advised not to take combined OCs, based on anecdotal clinical reports and experiments in murine models, both of which may be misleading with such a heterogeneous disorder as lupus. Earlier observers pressed the need for proper trials before leaping to conclusions (1). Subject to a satisfactory resolution of some caveats, the study by Petri and colleagues provides evidence that OCs can safely be prescribed for patients with SLE. This form of contraception did not adversely affect disease course, judged by the carefully scored and analyzed clinical and laboratory measurements adopted for this important study.

The outcome fulfils the first author's earlier predictions (2) and is supported by a similar recent study (3). However, the results do not mean that combined OCs can now be prescribed to patients with SLE with complete equanimity and without need for further monitoring. The study patients had either inactive or stable active disease; however, SLE does not run a predictable course and new disease features may appear at a later stage. Even during the brief period of the study, 7 patients in each group had flares of disease activity. 12 months is a short period of observation in this disease, the number of patients was small, and over a third of each group was nonadherent.

Further reassurance on many points is needed from larger, longer-term studies. The trial patients had inactive or stable active disease defined by exact and well-validated criteria. However, one cannot assume that OCs would be equally well tolerated during periods of greater disease activity. Scoring systems have improved, but there is still the risk that the dangers of a major disease feature could be overlooked. For example, 37% of patients had "renal disorder" of unspecified severity. Ironically, "nephritis" was a feature in the disease flares of 4 of the 7 patients who received placebo but only in 1 of the 7 who received OCs.

It would be foolish to conclude from these limited data that OCs never exacerbate lupus nephritis. The overall conclusion must be that OCs can be safely prescribed to selected SLE patients, but it would be as premature to relax our guard completely now as it was to make false deductions in an earlier era.

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***References***

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2. **Petri M, Robinson C.** Arthritis Rheum. 1997;40:797-803.
3. **Sánchez-Guerrero J, Uribe AG, Jiménez-Santana L, et al.** N Engl J Med. 2005;353:2539-49.