

# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

DECEMBER 15, 2005

VOL. 353 NO. 24

## A Trial of Contraceptive Methods in Women with Systemic Lupus Erythematosus

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### ABSTRACT

#### BACKGROUND

The effects of estrogen-containing contraceptives on disease activity in women with systemic lupus erythematosus have not been determined.

#### METHODS

We conducted a single-blind clinical trial involving 162 women with systemic lupus erythematosus who were randomly assigned to combined oral contraceptives, a progestin-only pill, or a copper intrauterine device (IUD). Disease activity was assessed at 0, 1, 2, 3, 6, 9, and 12 months according to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). The primary outcome was global disease activity, which we estimated by measuring the area under the SLEDAI curve. Secondary outcomes included the maximum SLEDAI score, change in SLEDAI score, incidence of lupus flares, median time to first flare, systemic lupus erythematosus treatment, and adverse events. The results were analyzed by the intention-to-treat method.

#### RESULTS

At baseline, all demographic features and disease characteristics were similar in the three groups. The mean ( $\pm$ SD) SLEDAI score was  $6.1\pm 5.6$  in the group assigned to combined oral contraceptives,  $6.4\pm 4.6$  in the group assigned to the progestin-only pill, and  $5.0\pm 5.3$  in the group assigned to the IUD (54 patients in each group) ( $P=0.36$ ). Disease activity remained mild and stable in all groups throughout the trial. There were no significant differences among the groups during the trial in global or maximum disease activity, incidence or probability of flares, or medication use. The median time to the first flare was three months in all groups. Thromboses occurred in four patients (two in each of the two groups receiving hormones), and severe infections were more frequent in the IUD group. One patient receiving combined oral contraceptives died from amoxicillin-related severe neutropenia.

#### CONCLUSIONS

Global disease activity, maximum SLEDAI score, incidence of flares, time to first flare, and incidence of adverse events were similar among women with systemic lupus erythematosus, irrespective of the type of contraceptive they were using.

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N Engl J Med 2005;353:2539-49.

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**S**YSTEMIC LUPUS ERYTHEMATOSUS IS AN autoimmune disease primarily affecting young women.<sup>1,2</sup> Several studies have demonstrated the involvement of sex hormones in systemic lupus erythematosus.<sup>3-13</sup> Overall, the data suggest that estrogens favor the development or exacerbation of the disease, whereas androgens seem to be protective. Because disease activity during pregnancy is generally high in women who conceived when they had active lupus, and the outcome for the fetuses of these women is worse, pregnancy should be planned to begin during a period of disease quiescence.<sup>14,15</sup>

Recommending a contraceptive method to women with systemic lupus erythematosus is difficult. Because barrier- or behavior-based methods have a high failure rate, use of these methods alone is not recommended.<sup>16</sup> Intrauterine devices (IUDs) and combined oral contraceptives are highly effective but are associated with the development of local infections<sup>17</sup> and thromboembolism,<sup>18</sup> respectively. There is concern that the use of combined oral contraceptives may exacerbate systemic lupus erythematosus. Progestin-only contraceptives are not widely used, because of their effects on the endometrial bleeding pattern.<sup>19</sup>

The scant information available to date on the effects of contraceptives on systemic lupus erythematosus is based on isolated reports.<sup>20-25</sup> The World Health Organization Medical Eligibility Criteria for Contraceptive Use do not include information about systemic lupus erythematosus.<sup>16</sup> Therefore, it is important to determine the effects on disease activity and the safety profile of commonly used methods.

Our study investigated whether there were clinically significant differences in systemic lupus erythematosus activity, as measured by the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI),<sup>26</sup> in women taking combined oral contraceptives in comparison with those using a progestin-only pill or an IUD.

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#### METHODS

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We conducted a randomized, single-blind, 12-month clinical trial in women with systemic lupus erythematosus attending the outpatient clinic at our hospital. The study was approved by our hospital's institutional review board, and all patients provided written informed consent.

#### PATIENTS

From January 1996 through December 2002, 1981 women with systemic lupus erythematosus, as defined by the 1982 criteria of the American College of Rheumatology,<sup>27</sup> were assessed for eligibility. Eligible women were 40 years old or younger and were neither pregnant nor lactating. The exclusion criteria were severe lupus activity at baseline (SLEDAI score, more than 30), vaginal bleeding of undiagnosed cause, liver or cardiovascular disease, a platelet count of less than 50,000 per cubic millimeter, a history of cancer or thrombosis, recent pelvic inflammatory disease, use of rifampicin or anticonvulsant agents, and (for women 35 years old or older) heavy smoking, defined as smoking 15 cigarettes or more per day.

#### PROTOCOL

A computer-generated randomization list was used to assign the women to one of three regimens. The combined oral contraceptive regimen consisted of 30 µg of ethinyl estradiol plus 150 µg of levonorgestrel (Nordet, Laboratorios Wyeth). The progestin-only pill contained 30 µg of levonorgestrel (Microlut, Schering Mexicana). The IUD was the TCu 380A copper device (Ortho Pharmaceutical). The study coordinator assigned the next available number to each patient on her entry into the trial and revealed the code to the gynecologist, who dispensed the assigned contraceptive. Women who declined to use the contraceptive method to which they were assigned were removed from further study, although some information about them, for comparison purposes, appears in the Results section. Each time a woman declined to participate, one of the next three random numbers, including the number that had been declined by the patient who had withdrawn, was assigned to the next woman who agreed to participate in the study. To maintain blinding, the rheumatologists were instructed not to provide gynecologic care or perform pelvic examinations, and the women were asked not to reveal their contraceptive method to the rheumatologists and to avoid discussing any related issues with them. Thus, the contraceptive regimens were concealed from the rheumatologists who assessed disease activity. The randomization code was broken at the end of the study.

#### CLINICAL ASSESSMENTS

At baseline, data on sociodemographic and clinical characteristics were collected by the investigators.

Information about the course of systemic lupus erythematosus, such as the date of diagnosis (i.e., the date on which 4 of the 11 criteria were met), duration of disease, number of criteria met, and damage accrual according to the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR-DI),<sup>28</sup> was extracted from each patient's medical chart.

Systemic lupus erythematosus activity was assessed at baseline and at 1, 2, 3, 6, 9, and 12 months. Two rheumatologists performed all assessments. To reduce the variability in these evaluations, a training session and a calibration exercise in the application of the SLEDAI were held before the study began. Treatment of the disease was administered according to the judgment of each participating provider and was recorded at each evaluation. An independent examination at each study visit was performed by the study gynecologist. Adherence to oral contraceptive agents was assessed by self-reported medication intake. Study treatment was discontinued in women who became pregnant during the study or who had severe lupus activity, thrombosis, uncontrolled hypertension, or any other severe complication.

#### OUTCOME MEASURES

The primary outcome was global disease activity throughout the follow-up period, estimated as the area under the SLEDAI curve (SLEDAI-AUC). The secondary outcomes were the incidence of lupus flares, the time to the first flare, changes in SLEDAI values from baseline at each follow-up visit, and maximum disease activity. Lupus flares and severe flares were defined as increases in the SLEDAI of 3 or more or 12 or more points, respectively, from the previous visit.<sup>29</sup>

The data were also analyzed with the use of a new version of the SLEDAI (SLEDAI-2K)<sup>30</sup> and a modified SLEDAI (SLEDAIm) that excludes microhematuria and pyuria because they may be associated with contraception. We also recorded systemic lupus erythematosus treatment, hospitalizations, thromboses, severe infections, pregnancies, and deaths.

#### STATISTICAL ANALYSIS

One-way analysis of variance was used for between-group comparisons of lupus activity as measured by the SLEDAI-AUC, maximum SLEDAI, and change in SLEDAI score from baseline at each follow-up visit. Within-group comparisons were made with use of the Wilcoxon signed-rank test.

Analysis of the incidence of flares was based on incidence-density rates, with patient-years of follow-up as the denominator and with relative risk and 95 percent confidence intervals as the measure of association. For each patient, we calculated the time from baseline until the first flare, withdrawal from the study, end of follow-up, or death, whichever came first. The probability of flares throughout the study was calculated with use of life-table analyses and the log-rank test. All reported P values are two-sided. All analyses were conducted by the intention-to-treat method with SPSS software, version 11.5.

On the assumption of a mean ( $\pm$ SD) baseline SLEDAI value of  $5.43 \pm 5.04$ ,<sup>29</sup> we estimated that the planned sample size would provide an 80 percent chance of detecting a difference in SLEDAI of 3 points or more (on a scale of 0 to 105, with higher scores indicating greater severity) at a significance level of 0.05. With allowance for a 20 percent loss to follow-up, the planned sample size was 54 patients per group.

The IUDs were purchased by the investigators with grant funds; the combined oral contraceptives and the progestin-only pills were provided by Wyeth Mexico and Schering Mexicana, respectively; neither company participated in trial design, gathering and analysis of the data, or writing of the manuscript.

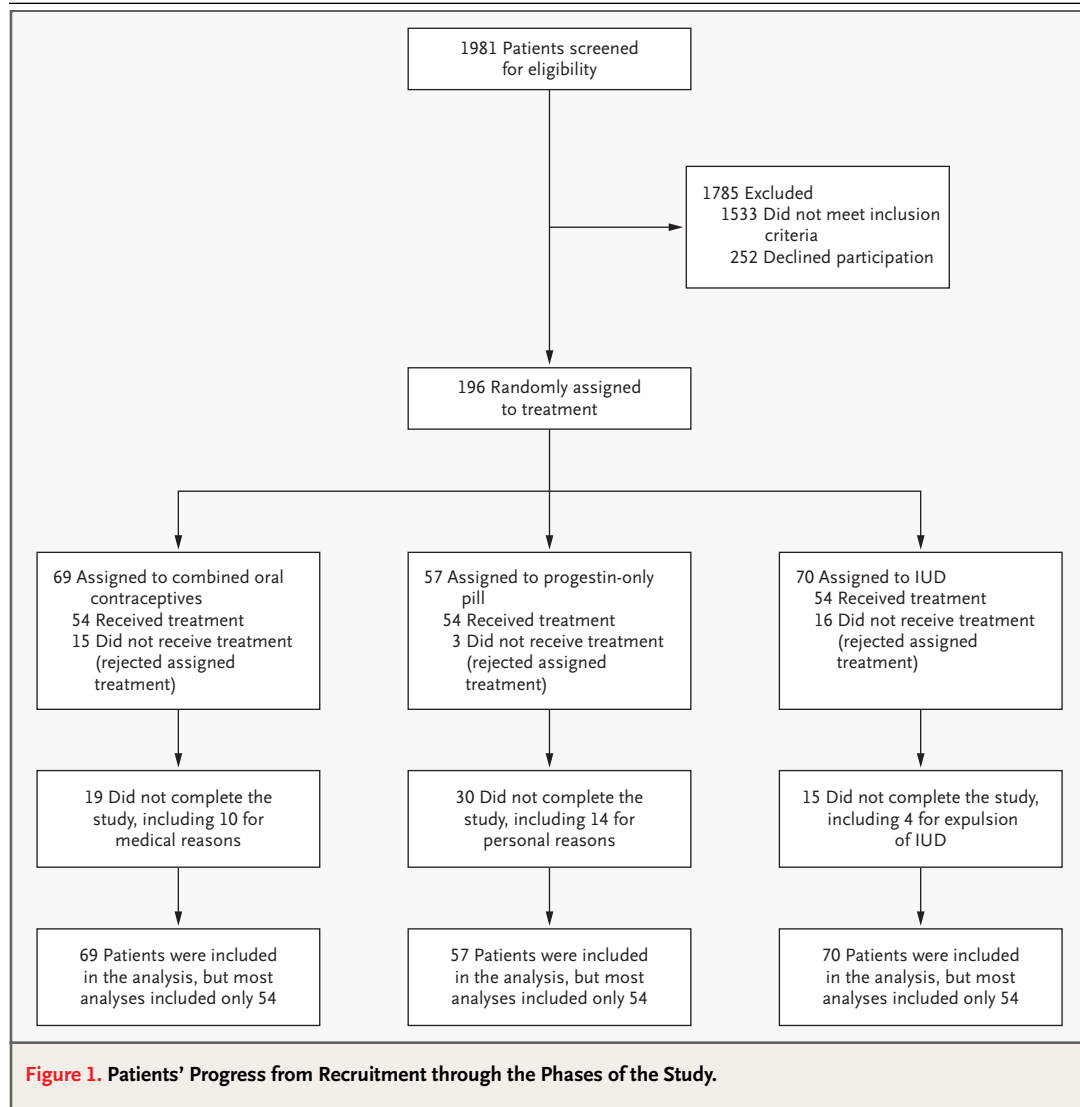
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## RESULTS

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Of the 1981 patients who underwent screening, 1785 were excluded because they did not meet the inclusion criteria (1533 patients) or declined to participate (252 patients), leaving 196 patients to be randomly assigned to treatment. After undergoing randomization, 34 women declined the assigned contraceptives; the remaining 162 received treatment with combined oral contraceptives, the progestin-only pill, or the IUD (54 patients in each group) (Fig. 1). The eligibility, enrollment, and recruitment fractions were 23 percent, 36 percent, and 8 percent, respectively; and the number of women who had to be screened in order to identify 1 patient to be enrolled in the study was 12.2.

Women who declined to participate in the study before undergoing randomization and those who underwent randomization had similar demographic characteristics, except that those who underwent randomization were younger ( $27.3 \pm 5.7$  vs.  $30.4 \pm 5.2$  years,  $P < 0.001$ ), and the features of their disease



were similar. Among women who both underwent randomization and accepted treatment with the assigned contraceptive, the duration of disease was shorter, but not significantly so ( $3.7 \pm 4.2$  vs.  $5.2 \pm 5.7$  years,  $P=0.08$ ), the SLEDAI scores were higher ( $5.6 \pm 5.1$  vs.  $3.4 \pm 3.4$ ,  $P=0.02$ ), and the percentage of patients with anti- $\beta_2$ -glycoprotein I antibodies was higher, but not significantly so (7.4 percent vs. 0 percent,  $P=0.06$ ), than among women who underwent randomization but then did not agree to the assigned contraceptive treatment. In the latter group, there were no differences in demographic characteristics or manifestations of systemic lupus erythematosus among those who were assigned to the combined contraceptive, the progestin-only pill, or the IUD before withdrawing from the study. The wom-

en who accepted the IUD and those who accepted the combined oral contraceptives were more likely to have previously used contraceptives ( $P<0.001$ ) and were also older at menarche ( $P=0.009$ ) than those who underwent randomization but did not accept treatment with the assigned contraceptive.

The baseline demographic features and manifestations of systemic lupus erythematosus were similar among the three groups of women who underwent randomization and accepted treatment (Table 1). There were 1435 patient-months of follow-up (74 percent of the possible 1944 total months of follow-up — 489 patient-months in the group receiving combined oral contraceptives, 421 in the group receiving the progestin-only pill, and 525 in the IUD group).

**Table 1. Selected Baseline Demographic Features and Disease Characteristics of the 162 Women, According to the Assigned Method of Contraception.\***

Variable	Combined Oral Contraceptives (N=54)	Progestin-Only Pill (N=54)	Intrauterine Device (N=54)	P Value
<b>Demographic features</b>				
Age — yr	27.4±5.3	26.6±5.3	27.4±5.0	0.65
Education — yr	12.5±3.7	11.6±3.9	12.8±3.4	0.26
Body-mass index†	24.1±3.7	24.7±4.0	25.4±4.4	0.25
No. of previous pregnancies	0.9±1.0	1.2±1.3	1.2±1.3	0.26
Current smoker — no. (%)	10 (18.5)	12 (22.2)	17 (31.5)	0.26
<b>Disease characteristics</b>				
Duration — yr	3.4±4.2	3.7±4.2	4.0±4.2	0.77
No. of SLE criteria met	5.7±1.4	5.9±1.7	5.6±1.3	0.45
SLICC Damage Index score	0.4±0.8	0.4±0.8	0.3±0.7	0.73
<b>SLEDAI score</b>				
Mean ±SD	6.1±5.6	6.4±4.6	5.0±5.3	0.36
Range	0–22	0–20	0–26	
SLEDAI score distribution — no. (%)				0.14
0	7 (13.0)	9 (16.7)	12 (22.2)	
1–5	25 (46.3)	13 (24.1)	20 (37.0)	
6–10	13 (24.1)	24 (44.4)	17 (31.5)	
≥11	9 (16.7)	8 (14.8)	5 (9.3)	
<b>Positive test for antiphospholipid antibodies — no. (%)</b>				
IgM anticardiolipin antibodies	9 (16.7)	12 (22.2)	10 (18.5)	0.78
IgG anticardiolipin antibodies	11 (20.4)	10 (18.5)	11 (20.4)	0.95
Any anticardiolipin antibody	14 (25.9)	18 (33.3)	17 (31.5)	0.72
IgM anti-β <sub>2</sub> GPI antibodies	3 (5.6)	6 (11.1)	2 (3.7)	0.39
IgG anti-β <sub>2</sub> GPI antibodies	6 (11.1)	2 (3.7)	3 (5.6)	0.39
Any anti-β <sub>2</sub> GPI antibody	10 (18.5)	10 (18.5)	6 (11.1)	0.48
<b>Treatment at baseline — no. (%)</b>				
Prednisone	35 (64.8)	37 (68.5)	35 (64.8)	0.90
Immunosuppressive agents	24 (44.4)	29 (53.7)	23 (42.6)	0.46
Antimalarial drugs	31 (57.4)	24 (44.4)	25 (46.3)	0.35
NSAIDs	9 (16.7)	11 (20.4)	18 (33.3)	0.10
Low-dose aspirin	12 (22.2)	13 (24.1)	11 (20.4)	0.90

\* Plus–minus values are means ±SD. SLE denotes systemic lupus erythematosus, SLICC Systemic Lupus International Collaborating Clinics, SLEDAI Systemic Lupus Erythematosus Disease Activity Index, anti-β<sub>2</sub>GPI anti-β<sub>2</sub>-glycoprotein I, and NSAIDs nonsteroidal antiinflammatory drugs. SLEDAI scores range from 0 to 105, with higher scores indicating more severe disease.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

**DISEASE ACTIVITY**

At baseline, the mean SLEDAI score was 6.1±5.6 in the group receiving combined oral contraceptives, 6.4±4.6 in the group receiving the progestin-only pill, and 5.0±5.3 in the IUD group (P=0.36) (Table 1). There were no significant differences among the groups in the SLEDAI-AUC or in the maximum

SLEDAI score throughout the study period (Table 2). No patient was withdrawn from the study because of severe disease activity. SLEDAI scores remained mild and stable during the trial, and there were no significant differences among the groups (Fig. 2).

Changes in SLEDAI scores from baseline to

**Table 2. Disease Activity among the 162 Treated Women and the Subgroup of 134 Women Who Had Active Disease at Baseline.\***

Variable	Combined Oral Contraceptives	Progestin-Only Pill	Intrauterine Device	P Value
<b>All treated patients</b>				
No. of patients	54	54	54	
Mean SLEDAI-AUC				
1 Mo	5.4	5.9	5.1	0.63
2 Mo	9.7	11.8	10.0	0.39
3 Mo	14.6	17.4	14.6	0.41
6 Mo	31.0	32.5	27.9	0.60
9 Mo	45.3	50.8	39.7	0.30
12 Mo	60.3	52.2	53.3	0.61
Maximum SLEDAI score				
Mean $\pm$ SD	8.8 $\pm$ 4.9	9.0 $\pm$ 4.9	8.6 $\pm$ 4.9	0.94
Range	2–22	0–24	2–30	
<b>Treated patients with active disease at baseline</b>				
No. of patients	47	45	42	
Baseline SLEDAI score				
Mean $\pm$ SD	7.0 $\pm$ 5.5	7.7 $\pm$ 4.0	6.5 $\pm$ 5.2	0.51
Range	1–22	2–20	2–26	
Mean SLEDAI-AUC				
1 Mo	6.1	6.6	6.1	0.79
2 Mo	10.9	12.9	11.6	0.52
3 Mo	16.4	19.2	17.1	0.53
6 Mo	33.8	36.3	33.4	0.82
9 Mo	49.5	56.6	47.1	0.46
12 Mo	66.9	59.8	63.4	0.79
Maximum SLEDAI score				
Mean $\pm$ SD	10.3 $\pm$ 5.5	10.4 $\pm$ 4.4	9.7 $\pm$ 5.8	0.79
Range	3–22	4–24	2–30	

\* SLEDAI denotes Systemic Lupus Erythematosus Disease Activity Index, and SLEDAI-AUC the area under the SLEDAI curve. Active disease was defined as an SLEDAI score of at least 1.

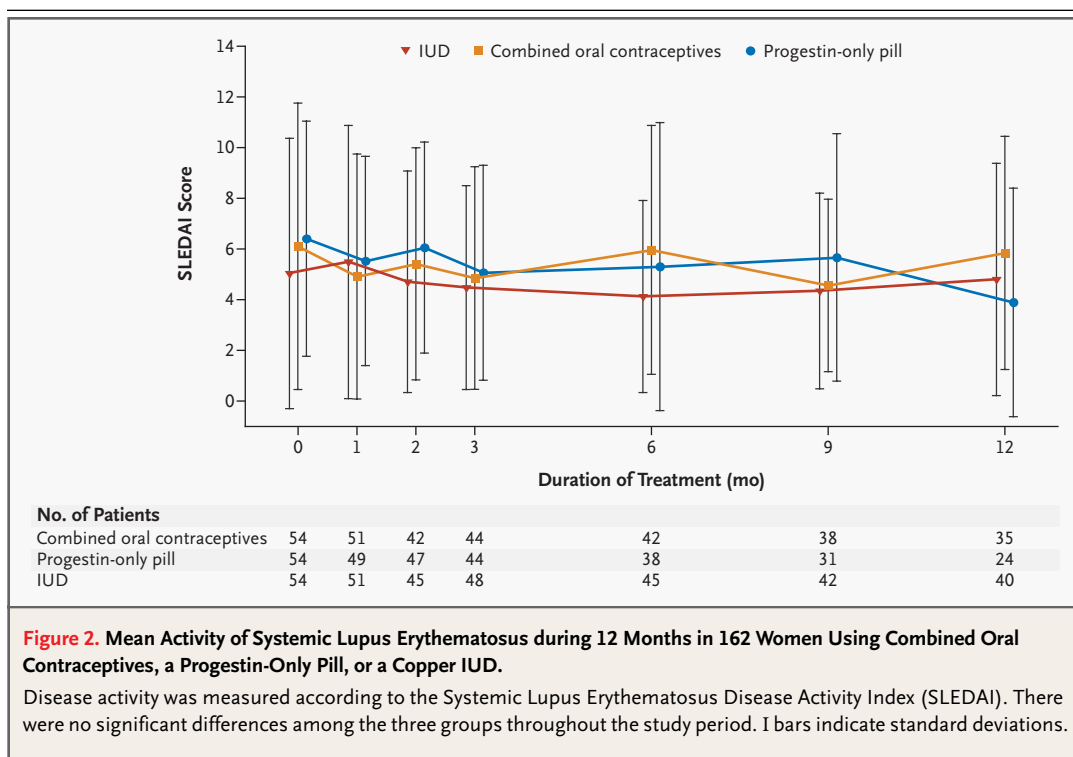
each follow-up visit were assessed in all groups. The mean change in SLEDAI ranged between  $-1.1$  ( $P=0.46$ ) and  $0.52$  ( $P=0.65$ ) in the group receiving combined oral contraceptives and between  $-0.3$  ( $P=0.69$ ) and  $-2.0$  ( $P=0.02$ ) in the group receiving the progestin-only pill. In the latter group, the mean changes in SLEDAI score at months 3 and 12 were  $-1.5$  ( $P=0.05$ ) and  $-2.0$  ( $P=0.02$ ), respectively. In the IUD group, the mean change ranged between  $-0.5$  ( $P=0.45$ ) and  $0.7$  ( $P=0.37$ ).

When the data on patients with active disease (SLEDAI of 1 or greater) at baseline were analyzed separately, the baseline SLEDAI scores and the SLEDAI-AUC and maximum SLEDAI scores during

follow-up did not differ among treatment groups (Table 2). The results obtained with the use of the SLEDAI-2K and SLEDAIm were similar to those of the primary analysis (data not shown).

#### FLARES

The number of flares and the incidence-density rate of flares per patient-year were similar in the three treatment groups: there were 36 flares, with an incidence-density rate of 0.86, in the group receiving combined oral contraceptives; 40 flares, with an incidence-density rate of 1.14, in the group receiving the progestin-only pill; and 40 flares, with an incidence-density rate of 0.91, in the IUD group. As



**Figure 2. Mean Activity of Systemic Lupus Erythematosus during 12 Months in 162 Women Using Combined Oral Contraceptives, a Progestin-Only Pill, or a Copper IUD.**

Disease activity was measured according to the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). There were no significant differences among the three groups throughout the study period. I bars indicate standard deviations.

compared with the IUD group, the group receiving combined oral contraceptives had a relative risk of flares of 0.94 (95 percent confidence interval, 0.58 to 1.52;  $P=0.79$ ) and the group receiving the progestin-only pill had a relative risk of 1.25 (95 percent confidence interval, 0.78 to 1.98;  $P=0.33$ ).

The number and incidence-density rate of severe flares per patient-year were also similar among the three treatment groups: there were two severe flares, with an incidence-density rate of 0.049, in the group receiving combined oral contraceptives; four severe flares, with an incidence-density rate of 0.114, in the group receiving the progestin-only pill; and two severe flares, with an incidence-density rate of 0.046, in the IUD group. The relative risk of severe flares was 1.07 for the group receiving combined oral contraceptives (95 percent confidence interval, 0.08 to 14.8;  $P=0.95$ ) and 2.49 for the group receiving the progestin-only pill (95 percent confidence interval, 0.36 to 27.6;  $P=0.31$ ), as compared with the IUD group.

The median time to the first flare was three months in all groups. The probability of flare in the group receiving combined oral contraceptives, the group receiving the progestin-only pill, and the IUD group during the trial was 0.91, 0.93, and 0.88, re-

spectively ( $P=0.67$ ); the probability of severe flare was 0.05, 0.10, and 0.04, respectively ( $P=0.62$ ) (Table 3).

Among the patients with active disease at baseline, there were no differences according to treatment group in the probability of flares or of severe flares (Table 3). The numbers and incidence rates of flares and of severe flares were also similar among the treatment groups (data not shown).

**OTHER SECONDARY OUTCOMES**

The rate of use and the dose of prednisone, immunosuppressants, chloroquine, and nonsteroidal antiinflammatory drugs were similar among the groups during the study.

Lower-limb thromboses occurred in four patients, two in each group receiving hormones. There were two venous and two arterial thromboses, for an incidence-density rate of 4.75 per 100 patient-years in the group receiving combined oral contraceptives and 5.44 per 100 patient-years in the group receiving the progestin-only pill; all four patients had low titers of antiphospholipid antibodies. One thrombosis developed after one month of treatment, two after two months of treatment, and one after nine months of treatment. Severe infections

**Table 3. Cumulative Net Probabilities of Flares and Severe Flares at 3, 6, and 12 Months in the 162 Treated Women and in the Subgroup of 134 Women Who Had Active Disease at Baseline.\***

Variable	Combined Oral Contraceptives	Progestin-Only Pill	Intrauterine Device	P Value
<b>All treated patients</b>				
No. of patients	54	54	54	
	<i>probability (±SE)</i>			
Flares†				0.67
3 Mo	0.59±0.08	0.65±0.07	0.60±0.07	
6 Mo	0.72±0.07	0.74±0.07	0.65±0.07	
12 Mo	0.91±0.06	0.93±0.05	0.88±0.05	
Severe flares‡				0.62
3 Mo	0.02±0.02	0.07±0.04	0.04±0.03	
6 Mo	0.05±0.04	0.10±0.05	0.04±0.03	
12 Mo	0.05±0.04	0.10±0.05	0.04±0.03	
<b>Treated patients with active disease at baseline</b>				
No. of patients	47	45	42	
	<i>probability (±SE)</i>			
Flares				0.69
3 Mo	0.60±0.08	0.65±0.08	0.58±0.08	
6 Mo	0.71±0.08	0.77±0.07	0.58±0.08	
12 Mo	0.93±0.05	0.95±0.04	0.84±0.07	
Severe flares				0.72
3 Mo	0.03±0.03	0.06±0.04	0.03±0.03	
6 Mo	0.06±0.04	0.09±0.05	0.03±0.03	
12 Mo	0.06±0.04	0.09±0.05	0.03±0.03	

\* Active disease was defined by a score on the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) of at least 1.

† A flare was defined as an increase of 3 or more points in the SLEDAI score from the previous visit.

‡ A severe flare was defined as an increase of 12 or more points in the SLEDAI score from the previous visit.

developed in three patients in the group receiving combined oral contraceptives, two in the group receiving the progestin-only pill, and five (including two cases of meningitis) in the IUD group. Eleven patients in the group receiving combined oral contraceptives, seven in the group receiving the progestin-only pill, and nine in the IUD group were hospitalized. Five pregnancies occurred during the study: two in each group receiving hormones and one in the IUD group. All patients decided to continue their pregnancies, resulting in three live births (two at term and one at 31 weeks) and two stillbirths. One patient receiving combined oral contraceptives died during the trial; her death was ascribed to amoxicillin-related severe neutropenia.

## DISCUSSION

We evaluated the effects on disease activity of combined oral contraceptives, as compared with a progestin-only pill and an IUD, in women with systemic lupus erythematosus. Over 12 months of follow-up, disease activity remained stable, and no clinically significant differences were seen among any of the treatment groups.

Disease activity was assessed by a validated measure that was sensitive to change over time,<sup>26</sup> and the incidence of flares was estimated with the use of a validated definition.<sup>29</sup> We also analyzed disease activity according to the SLEDAI-2K and SLEDAIm and in the subgroup of patients with active disease

at entry. The results of these analyses were similar to those of the primary analyses. We believe that the assessments of disease activity were adequate and that the use of combined oral contraceptives does not increase lupus activity to a clinically significant degree. Thus, our results do not support concerns that the use of exogenous estrogens by women with systemic lupus erythematosus will lead to disease exacerbation.

Case reports have described the onset of systemic lupus erythematosus or lupus flares related to the use of combined oral contraceptives.<sup>21,22,31</sup> Jungers et al.<sup>20</sup> observed a high rate of flares in women taking combined oral contraceptives. In their study, contraceptives were nonrandomly assigned, the ethinyl estradiol dose was 30 µg or more, and disease activity was evaluated retrospectively according to an arbitrary definition of flare. Our results are consistent with a survey of contraceptive use in systemic lupus erythematosus,<sup>32</sup> with data on the use of hormone-replacement therapy in systemic lupus erythematosus,<sup>33</sup> and with a clinical trial<sup>34</sup> in which no increases in disease activity were observed.

Patients assigned to the progestin-only pill had a consistent decrease in SLEDAI scores, a result suggesting a decrease in disease activity. There are several possible explanations for this unexpected finding. Because synthetic progestins, such as levonorgestrel, have androgenic and progestational effects, they might share some antiinflammatory properties with the endogenous steroids that could help reduce the activity of systemic lupus erythematosus.<sup>35,36</sup> This hypothesis would be consistent with older observations that progestin-only contraceptives had fewer deleterious effects on systemic lupus erythematosus activity than estrogen-containing contraceptives.<sup>19,20,24</sup> However, the group receiving the progestin-only pill had the highest average SLEDAI score at entry, and thus regression to the mean is another possible explanation.<sup>37</sup> Finally, the result might be spurious, since this group had the shortest follow-up and, paradoxically, the highest incidence of flares, despite the decrease in SLEDAI scores. The high rate of discontinuation for various reasons, including menstrual disturbances in three patients, reduces our confidence in this result. A low rate of adherence to the progestin-only pill by women with systemic lupus erythematosus because of high rates of intolerance has been reported.<sup>19</sup> To the best of our knowledge, no data are

available on the effects of IUDs on systemic lupus erythematosus activity.

No differences were observed among the treatment groups with respect to adverse events or pregnancies; however, the study was not adequately powered to detect differences among the groups in the incidence rates of most adverse events. Thrombotic events occurred only in women receiving oral contraceptives. However, in another study, venous thromboses occurred in the placebo group.<sup>34</sup> Because patients with systemic lupus erythematosus have a substantial risk of thrombosis over time,<sup>38</sup> the use of combined oral contraceptives might constitute an independent risk factor for thrombosis.<sup>18</sup> However, although the risk associated with use of the progestin-only pill is undefined, a dose-response effect has been suggested<sup>39</sup>; thus, the effect of oral contraceptives on the risk of thrombosis in systemic lupus erythematosus remains unclear. Since all patients in whom thromboses developed were positive for antiphospholipid antibodies, caregivers might consider avoiding the use of oral contraceptives in women with systemic lupus erythematosus who are positive for antiphospholipid antibodies at any titer. Although no differences in the incidence of severe infections were observed among the treatment groups, the possibility of a higher risk with the use of an IUD should be considered, since infections are a common cause of morbidity and mortality in systemic lupus erythematosus. The number of unintended pregnancies observed during the study falls within the rates expected during the first year of typical use of the assigned contraceptives.<sup>16</sup>

Our study has several limitations. It was a single-blind clinical trial without a placebo group. Although a double-blind, placebo-controlled trial would have been optimal, we believe that the single-blind design was unlikely to have affected the assessment of study outcomes. The rheumatologists were effectively blinded, because the patients were instructed not to reveal what contraceptive method they were using and were unaware of the study hypothesis. The consistency of our results with those of another double-blind trial that compared the effects of combined oral contraceptives and placebo on the activity of systemic lupus erythematosus<sup>34</sup> would support this view. The treatment of systemic lupus erythematosus was administered at the discretion of the rheumatologist, and no differences among the patient groups in the therapy adminis-

tered were evident at entry or throughout the follow-up period. Adherence to oral regimens was self-reported, but the close surveillance and counseling provided by the study gynecologist arguably helped to enhance adherence.

Because this study was conducted in a single center with limited ethnic variation among the patients, one must be circumspect about extrapolating the results to all women with systemic lupus erythematosus. However, our results are consistent with those of a multicenter, multiethnic study.<sup>34</sup> Our study was a nonequivalence trial; although we were unable to reach the planned power, the sample size we achieved provided an 80 percent chance of detecting a difference in the SLEDAI value of 3.25 or more, instead of the originally planned 3.0. Thus, although we did not detect any clinically significant differences in disease activity among patients assigned to the three contraceptive regimens,<sup>40</sup> the study had limited power to detect a smaller difference.

The present trial evaluated the effect of three widely used contraceptive methods on the activity of systemic lupus erythematosus. The disease characteristics at baseline were similar to those reported in other cohorts.<sup>29,30</sup> We offered participation in the study to all women with systemic lupus erythematosus who requested contraception in our center, including those with variable disease activity and those who were positive for antiphospholipid

antibodies, provided they had no history of thrombosis. Our patients were all Mexican women, and we think the results can be generalized to most Hispanic women with systemic lupus erythematosus. Whether these contraceptive methods have different effects on disease activity or adverse events in women of other ethnic groups remains to be determined.

In conclusion, although estrogen-containing oral-contraceptive regimens do not appear to increase the risk of disease exacerbation in women with systemic lupus erythematosus, one should still be cautious about the possibility of an increased risk of thrombosis with hormonal methods of contraception. At present, both patients and physicians must consider the manifestations of the disease, the potential risks and benefits, and patient preference when selecting a contraceptive method for women with systemic lupus erythematosus.

Supported by grants from the Department of Reproductive Health and Research of the World Health Organization (97135) and the Consejo Nacional de Ciencia y Tecnología de México (CONACYT) (3367P-M). The combined oral contraceptives and the progestin-only pills were provided by Wyeth Mexico and Schering Mexicana, respectively.

Presented in part at the 68th Annual Scientific Meeting of the American College of Rheumatology, San Antonio, Texas, October 17–20, 2004.

Dr. Sánchez-Guerrero reports having received grant support from Genelabs and Wyeth.

This article is dedicated to the memory of Dr. Donato Alarcón-Segovia.

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