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Copper intrauterine device is an appropriate method of contraception for a patient with a history of systemic lupus erythematosus

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Copper intrauterine device is an appropriate method of contraception for a patient with a history of systemic lupus erythematosus

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ABSTRACT A clinical decision report using:

Sánchez-Guerrero J, Uribe AG, Jiménez-Santana L, et al. A Trial of Contraceptive Methods in Women with Systemic Lupus Erythematosus. *N Engl J Med*. 2005;353(24):2539-2588. https:/doi.org/10.1056/nejmoa050817

for a patient with systemic lupus erythematosus choosing a method of contraception.

Keywords: *Systemic lupus erythematous, SLE, contraception, contraceptive, LARC*

Clinical-Social Context

Emily Jones (pseudonym), a 25-year-old G0P0 Hispanic woman with a history of systemic lupus erythematous (SLE), presented to an outpatient obstetrics/gynecology (OBGYN) clinic for her annual gynecologic exam and contraceptive counseling. She is sexually active and expressed no desire for pregnancy at that time. Ms. Jones was diagnosed with SLE three years ago and follows closely with her rheumatologist. Of note, she was found to be negative for antiphospholipid antibodies at the time of diagnosis. Her disease is stable with daily hydroxychloroquine. Her most recent flare was six months ago, which resolved after a short course of low-dose prednisone. Gynecologic exam was unremarkable and urine pregnancy test was negative. Vaginal swabs were obtained and cultures sent to rule out infection per routine protocols. Review of systems was negative. Her menstrual cycles occur regularly at 28-30 day intervals, usually lasting 4 days with subjectively light flow. Ms. Jones always uses condoms during intercourse but desired a more reliable method of contraception. She works full time, denied current financial hardships, and has good health insurance through her employer. She denied any tobacco or recreational drug use and endorsed rare alcohol use. Ms. Jones mentioned that she had some friends that had good experiences with intrauterine devices, however she was hesitant about an invasive method due to mistrust in the medical system after an initial misdiagnosis of her SLE. After much discussion, she remained open to all contraception options but expressed that she wanted something that would not affect her SLE, was highly effective for pregnancy prevention, and integrated well into her busy lifestyle.

Clinical Question

Which contraceptive therapy is most appropriate for a young Hispanic woman with a history of stable systemic lupus erythematous concerned about disease activity?

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Research Article

Sánchez-Guerrero J, Uribe AG, Jiménez-Santana L, et al. A Trial of Contraceptive Methods in Women with Systemic Lupus Erythematosus. *N Engl J Med*. 2005;353(24):2539-2588. https:/doi.org/10.1056/nejmoa050817 [1]

Description of Related Literature

Initial research began with an UpToDate search for "contraception" to understand available treatment options for women with SLE. We identified several non-permanent options for contraception such as long-acting reversible contraceptives (LARCs), including intrauterine devices (IUDs) and contraceptive implants; hormonal contraception, with combined estrogen-progestin and progestin-only options; followed by barrier protection and pericoital methods.[2] A systematic review was referenced in the UpToDate article with recommendations for efficacy and safety of contraceptive in patients with SLE, suggesting LARCs may be appropriate in this population.[3]

Research for relevant studies began with a PubMed search using the terms "systemic lupus erythematosus" AND "contraception." SLE and contraception are well-researched topics yielding 382 results, therefore only primary research was included through the use of filters for "clinical trials" and "randomized controlled trial". Abstracts of the resulting studies were reviewed and included in this review if they were relevant to the clinical question.

Of the eleven articles found in the initial query, six were rejected because they were not relevant the clinical question. The remaining five articles were thoroughly reviewed. One study examined combined oral contraceptives (COC), two articles discussed progesterone only methods, and the remaining two studied COC, progestin-only pill (POP), and the copper IUD.

Petri et al. conducted a double-blind, randomized, prospective clinical trial to assess the effect of COC on disease activity in 183 women with inactive or stable active SLE across 15 sites in the United States.[4] Incidence of severe lupus flare was infrequent in both the treatment group and the placebo-control group. There was no significant difference between the groups for rates of mild or moderate flares or mean change in disease activity as determined by the Safety of Estrogen in Lupus Erythematosus National Assessment - Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI)[5] scores.

The data supports the use of COC for SLE patients with stable, moderate disease at low risk of thrombosis, however it is limited for use in my patient because it does not compare other methods of contraception.

Mintz et al. is a prospective clinical trial that examined the efficacy and tolerance of POP (0.03 mg/day levonorgestrel, n=15) or 200 mg intramuscular norethisterone enanthate (n=10) when compared to a placebo-control group (n=18).[6] The study concluded that progestogens may be an acceptable method of contraception in SLE patients based on rates of active disease compared to the control group. However, a small sample size of n=43 make this article of low clinical utility.

Chabbert-Buffet et al. is a prospective cohort study that identified the efficacy and tolerance of two different oral pregnane progestin contraceptives in 187 women with SLE.[7] There were no pregnancies, disease activity was lower than at the start of the study, and incidence of venous thromboembolism (1.39/year x 1000 women) and macroarterial disease (2.79/year x 1000 women) was low. While the study shows that pregnane progestins are safe and effective for patients with SLE, the study is longitudinal and nonrandomized, and is of low utility as it does not assess other methods of contraception.

Cravioto et. al is a clinical trial comparing non-disease related side effects and acceptability of contraception in 162 women with SLE randomly assigned to receive COC (n=54), POP (n=54), or a copper IUD (n=54).[8] All treatment groups demonstrated mild weight gain, while there were no significant changes in blood pressure. The POP group had the highest rate of discontinuation for any reason (55%) compared to the COC (35%) and IUD (29%) groups, suggesting lower acceptability of POP use. While this study provided important information relevant to Ms. Jones, it did not address her concerns about contraception effect on disease activity.

Ultimately, the study by Sánchez-Guerrero et. al was chosen for critical appraisal.[1] The authors recruited patients with active SLE from their hospital's outpatient rheumatology clinic in Mexico City, randomly assigned the patients (n=162) to one of three contraception groups (COC, POP, & copper IUD), and monitered the patients' disease activity for 12 months. They concluded that not one tested contraceptive that was superior to another in regard to their metrics of disease. This study was most appropriate for

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clinical review based on the large sample size, Hispanic population, randomized assignment, greater variety of contraception options, adequate follow-up period, and emphasis on my patient's priorities of safety and disease activity of effective contraception. As a non-controlled randomized clinical trial, this meets Level 2 SORT criteria. The Grade of Recommendation is B, based on small consistent trials.[9]

Critical Appraisal

This study is a prospective, single-blinded, randomized clinical trial assessing disease activity as determined by SLEDAI in patients with SLE assigned to a COC (30 µg ethinyl estradiol plus 150 µg levonorgestrel), POP (30 µg levonorgestrel), or copper IUD (Ortho Pharmaceutical TCu 380A copper device) for contraception.

Women with SLE from the hospital's outpatient rheumatology clinic who wished to receive contraception were assessed for eligibility. Inclusion criteria included women 40 years of age or younger who were not lactating or pregnant. Exclusion criteria consisted of (1) patients with severe SLE at baseline (SLEDAI >30), (2) undiagnosed cause of vaginal bleeding, (3) liver or cardiovascular disease, (4) platelet count <50,000/mm^3, (5) history of cancer or thrombosis, (6) recent pelvic inflammatory disease, (7) use of rifampicin or anticonvulsant drugs, and (8) heavy smoking (≥15 cigarettes/day) in women 35 years or older. The mean age of patients in the COC group was 27.4 years, 26.6 years in the POP group, and 27.4 years in the IUD group. My patient meets inclusion criteria and is only 1-2 years younger than the mean age of each group, therefore data should be applicable.

Subjects were assigned to each treatment group by computer randomization. Ultimately, 162 women received treatment, with 54 patients in each treatment group. Two rheumatologists, who underwent training and calibration sessions for the SLEDAI, and one gynecologist managed treatment and assessment of all participants to minimize variation. The SLEDAI is a 24-item weighted scoring system for disease activity. Group assignment was revealed to the gynecologist to manage administration of contraception; however, the rheumatologists were blinded to assignment, did not provide any gynecological care, and patients were instructed not to discuss their assignment with the rheumatologists.

In the beginning of the trial, information on sociodemographic and clinical factors was collected, including a thorough appraisal of SLE history and current disease state, with reassessment occurring at 1, 2, 3, 6, 9, and 12 months. Demographics and disease manifestations were similar among all three treatment groups. Active disease was quantified as SLEDAI score ≥1. Rate and doses of SLE treatment with steroids, immunosuppressants, chloroquine, and nonsteroidal anti-inflammatory drugs were similar among groups.

Baseline disease activity was demonstrated by a mean SLEDAI of 6.1 in the COC group, 6.4 in the POP group, and 5.0 in the IUD group. SLEDAI scores remained mild and stable throughout the duration of the study in all groups. Analysis of the incidence of flares was based on incidence-density rates, with number of flares as the numerator and patient-years of follow-up as the denominator. Relative risk and 95 percent confidence intervals were used as measures of association. Number of flares and incidence-density rate were comparable, with 36 flares occurring in the COC group (0.86 incidence-density rate), 40 flares in the POP group (1.14), and 40 flares in the IUD group (0.91). Rates of severe flares, as defined by increase in SLEDAI of 12 or more points, among groups were also similar. All three groups showed equal median times to flare of three months.

Four subjects receiving hormonal contraception developed thromboses. However, the Petri et al. study demonstrated thromboses in their control group, and unlike Ms. Jones, all patients were positive for antiphospholipid antibodies.[4] There were no differences between treatment groups with respect to adverse events (thrombosis, infection, hospitalization) or pregnancy.

Limitations of the study include a single-blind design and a lack of control group, although the authors maintain that assessment of outcomes is unlikely to have been affected by single-blinding and results are consistent with other double-blinded, placebo-controlled studies. Although the sample size allowed for an 80% chance of detecting a difference in the SLEDAI value of 3.25 or more, smaller differences may not be detected. While the study is largely supported by nonpartisan organizations, Dr. Sánchez-Guerrero receives funding from pharmaceutical companies, Wyeth, whom provided COCs for the study, and Genelabs, potentially creating a bias based on interest in contraceptive success. Finally, a selection bias is present in that patients were selected from one clinical site in Mexico, but authors report consistency of results with the Petri et. al multicenter, multinational study.[4]

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Metrics of disease activity and adverse events suggest that no one method of contraception is superior to another for women with SLE, allowing all three treatments to be contraceptive options for my patient.

Clinical Application

Ms. Jones inquired which contraceptive therapy was best suited for her, given her priorities of efficacy, safety with respect to her SLE, and integration into her lifestyle. There were a number of safe and highly effective options appropriate for this patient, including COC, POP, and IUD, as demonstrated by Sánchez-Guerrero et. al. Despite her previous skepticism of more invasive options, Ms. Jones felt reassured after we discussed the outcomes of the studies above. Ultimately, she decided to move forward with a copper IUD, which she chose because it will not interfere with her daily routine once inserted, has very high efficacy for pregnancy prevention, and does not have significant impact on her underlying disease activity. Although the copper IUD can increase menstrual bleeding, she found this to be an acceptable side effect based on her history of light menstrual flow.[2] She returned to the clinic a month later for IUD insertion, which was uncomplicated, and was scheduled for a follow-up appointment two months later. Ms. Jones was counseled to continue use of barrier protection to prevent sexually transmitted infections and to follow-up immediately if she believes she has become pregnant.

New Knowledge Related to Clinical Decision Science

There is a vast range of contraceptives on the market today and choosing a method of contraception is a deeply personal choice for patients. Shared decision making between patients and physicians should be based on clinical evidence and patient preference, with consideration for effectiveness, safety, and lifestyle. There is increased risk of adverse effects in patients with comorbid conditions, such as SLE, which makes the role of patient education and evidence-based decision making even more essential. Providers must remain up to date on current safety data for various modes of contraception and guide their counseling to determine the best intersection of safety and patient preference. By staying humble and sharing clinical research information with patients, we can address concerns of patients arising from previous negative healthcare interactions.

Conflict Of Interest Statement

The author declares no conflicts of interest.

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