Therapy Insight: guidelines for selection of contraception in women with rheumatic diseases

Lisa R Sammaritano

SUMMARY

Use of contraceptives by women with rheumatic diseases, especially those with systemic lupus erythematosus, has long been thought to carry risks, such as disease exacerbation, thrombosis and other adverse effects. The use of effective contraception has, therefore, been avoided, despite many affected women being of reproductive age. Knowledge of risks and benefits of contraceptive methods in the general population has improved, as have the safety and effectiveness of hormonal contraceptives. Methods of administration have evolved and now include transdermal and intravaginal routes, a progesterone-releasing intrauterine device, and an extended-cycle oral contraceptive. Birth control pills are not all alike; the risk of adverse effects varies depending on the amount of estrogen and type of progestin used. Data show that patients with stable systemic lupus erythematosus are not at increased risk of disease flare while taking standard oral contraceptives. Despite a lack of randomized studies, evidence strongly suggests that the elevated risk of thrombosis makes estrogen-containing contraceptives unsuitable for patients with antiphospholipid antibody. Other important issues include potential interactions between hormonal contraceptives and other medications and possible risk of infection if an intrauterine device is used. Rheumatologists are increasingly working with gynecologists and patients to make choices about which contraceptive methods to use. Decisions should be individualized according to the patient's medical status, personal preference, and stage of reproductive life.

KEYWORDS antiphospholipid antibody, contraception, rheumatic disease, rheumatoid arthritis, systemic lupus erythematosus

REVIEW CRITERIA

The data for this Review were obtained by searching the MEDLINE database from 1 January 1966 to 1 July 2006. Search terms used were "contraception", "oral contraceptives", "intrauterine devices", and "DMPA", alone or in combination with "update", "thrombosis", "autoimmune disease", "systemic lupus erythematosus", "rheumatoid arthritis", "systemic sclerosis", "Raynaud's syndrome", "Sjogren's syndrome", and "vasculitis". Gynecology textbooks were also reviewed to provide basic background information.

CME

LR Sammaritano is an Associate Professor of Clinical Medicine at the Weill Medical College of Cornell University, Hospital for Special Surgery in New York, NY, USA.

Correspondence
Department of Medicine, Hospital for Special Surgery, 535 East 70th Street, New York, NY 10021, USA
sammaritan@hss.edu

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Learning objectives

Upon completion of this activity, participants should be able to:

1 Identify forms of contraception potentially suitable for women with rheumatic diseases.
2 Describe newer and currently available preparations of oral contraceptives.
3 List risk factors for venous thromboembolism for women considering using oral contraceptives.
4 List contraindications for using estrogen-containing oral contraceptives in women with systemic lupus erythematosus.
5 Summarize the pros and cons of using different types of intrauterine devices.

INTRODUCTION

The risks of adverse events, such as disease flare and thrombosis, associated with hormonal methods of contraception have long been a concern for women with rheumatic diseases, especially those with systemic lupus erythematosus (SLE). As a result, the use of effective forms of contraception has been avoided for many years in patients with SLE, despite the fact that a large proportion of affected women are of reproductive age. More than four decades after the development of oral contraceptives, studies have demonstrated that use of this form of contraception does not increase risk of flare in patients with stable SLE. Progesterone-only contraceptives are increasingly being offered to patients in whom estrogen is contraindicated, such as those with antiphospholipid antibody, particularly those who require anticoagulation and who benefit from the marked decrease in menstrual bleeding. In addition to a growing appreciation of

Table 1 Methods and effectiveness of contraception.[3,56 a]

Method	Effectiveness with typical use	Effectiveness with perfect use
No method	85%	85%
Sterilization		
Male	0.15%	0.1%
Female	0.5%	0.5%
Natural methods		
Withdrawal	27%	4%
Natural family planning	25%	1–9%
Barrier methods		
Male condom	15%	2%
Female condom	21%	5%
Diaphragm	16%	6%
Cervical cap	20–40%	9–26%
Spermicide	29%	18%
Intrauterine devices		
Copper T	0.8%	0.6%
Levonorgestral-releasing	0.1%	0.1%
Hormonal		
Combined OC	8%	0.3%
Transdermal patch	8%	0.3%
Vaginal ring	8%	0.3%
Progestin-only pill	8%	0.5%
Medroxyprogesterone acetate injection	3%	0.3%

[a]Expressed as the percentage of women experiencing unintended pregnancy during the first year of use. Abbreviation: OC, oral contraceptive.

the need for effective contraception for patients with rheumatic diseases, over the past 5 years several novel forms of contraception have been approved in the US. This Review describes the current contraceptive options, their general risks and benefits, and specific safety issues relevant to patients with rheumatic diseases. General guidelines to aid in the choice of contraceptive method are suggested.

CURRENT CONTRACEPTIVE METHODS

Contraceptive methods currently include periodic abstinence, barrier methods, intrauterine devices (IUDs), and hormonal contraception. The effectiveness of each contraceptive method is expressed as perfect use (risk of conception with correct use of the contraceptive) versus typical use (risk of conception with correct and incorrect use; Table 1).[1–3]

Intrauterine devices

Currently available IUDs have a low risk of infection and nulliparity is no longer an absolute contraindication for use.[3] The copper-containing IUD (Paragard®, Gynopharma Inc., Somerville, NJ) is effective for 10 years but menstrual bleeding and dysmenorrhea are notably increased with use. By contrast, the newer levonorgestrel-releasing intrauterine system Mirena® (Leiras Oy, Turku, Finland), which requires replacement every 5 years, is associated with a 75% decrease in menstrual bleeding—a potential advantage beyond its contraceptive benefit. Complications related to IUD use include the risk of pelvic inflammatory disease within the first month of insertion and expulsion of the device at any time. The Mirena® IUD can cause irregular vaginal bleeding during the first 3 months of use; by 1 year, however, up to 20% percent of users develop amenorrhea. The effects of levonorgestrel are primarily local.[4] Contraindications to IUD use include pregnancy, history of ectopic pregnancy, current pelvic inflammatory disease, undiagnosed vaginal bleeding, and uterine or cervical malignancy; multiple sexual partners and diagnosis of severe immunodeficiency disorders or aggressive immunosuppressive therapy represent relative contraindications that need to be assessed on a case by case basis.[1–3] Although concerns regarding immunosuppressive therapy are based on a theoretical increase in infection risk with IUD use, no available data indicate when this risk becomes substantial enough to disallow this convenient and effective contraceptive.

Hormonal contraception

The range of available hormonal contraceptives has evolved considerably since the first birth-control pill was approved for use in the US in 1960.[5] Hormonal contraceptives consist of a combination of estrogen and progesterone, or progesterone alone. Routes of administration include oral, intramuscular, transdermal, and intravaginal. Current combination oral contraceptives (OCs) differ in the amount of estrogen (ranging from 20–50 μg), type of progesterone, and dose throughout the menstrual cycle. The effects on menstruation can vary; for example, an approved extended-regimen OC limits the number of menstrual periods to just four per year (Seasonale®, Medical College of Hampton Roads, Norfolk, Virginia).[6]

In combination OCs, the synthetic estrogen is ethinylestradiol (20–50 μg) and the progestin is one of the multiple 17-α ethinyl analogs of 19-nortestosterone. The specific progestin used determines the potential side effects; both components contribute to the contraceptive action. Second-generation OCs contain less than 50 μg ethinylestradiol and any progestin except desogestrel, norgestimate, and gestodene,[1] which are newer and contained only in third-generation agents. These three progestins were developed

to decrease androgenic effects such as acne, nausea, and lipid changes seen with the second-generation OCs. A novel OC (Yasmin®, Schering AG, Berlin, Germany) contains drospirenone, an analog of spironolactone that exhibits anti-androgenic activity. The transdermal combination patch (Ortho Evra®, Johnson & Johnson, New Brunswick, NJ) delivers 20 μg ethinylestradiol and 150 μg norelgestromin daily; the patch is changed weekly for 3 weeks and followed by a week during which no patch is used. Adherence to the regimen is greater than with OCs[6] and the patch presents an appealing alternative for adolescents and women who wish to avoid a daily oral regimen. Although the efficacy of the transdermal combination patch is similar to that of OCs, the FDA warns of exposure to 60% more estrogen with the patch than with a standard OC containing 35 μg ethinylestradiol.[7] Whether this increased exposure to estrogen also translates to a greater risk of adverse events is, however, unclear. The contraceptive vaginal ring (NuvaRing®, NV Organon, Oss, The Netherlands) releases 15 μg ethinylestradiol and 120 μg etonogestrel daily and is used for 3 weeks continuously, followed by removal for 1 week.[5]

Oral progestin-only contraceptives contain either norethindrone or norgestrel and are used less frequently than combined contraceptives because of related irregular vaginal bleeding. They do, however, represent a viable option for patients in whom estrogen is contraindicated.[1,2] The progesterone-only contraceptive medroxyprogesterone acetate is administered as an intramuscular injection every 12 weeks, making it a convenient option that requires little effort on behalf of the patient in relation to administration and adherence, and has superior efficacy to progestin-only OCs.[8] Negative side effects of medroxyprogesterone acetate include irregular vaginal bleeding, weight gain, reversible bone loss due to reduced ovarian estrogen secretion and a prolonged delay in return to fertility after discontinuation.[9] Finally, emergency OC regimens are effective if used within 72 h of unprotected intercourse.[5]

Noncontraceptive benefits of OCs have occasionally been the principal reason for their use. Benefits include the regulation of menstrual dysfunction and the decrease in functional ovarian cysts. Combination OCs can also lower risk of acute pelvic inflammatory disease and of ovarian, endometrial and possibly colorectal cancer. Numerous studies suggest a positive effect on bone mass, even in women with normal estrogen levels.[10]

Mild side effects associated with the use of combination OCs include nausea, edema, and breast tenderness. Progestin-only medications often cause irregular menstrual bleeding, acne, and weight gain, leading to a high rate of discontinuation.[1,2] Hormonal contraceptives (combination and progestin-only) might contribute to impaired glucose tolerance and risk of hypertension. Estrogen increases levels of HDL cholesterol and decreases those of LDL cholesterol, and progestins exert an opposite effect. In low-dose combination OCs, therefore, changes in the lipid profile are not generally clinically significant. The more androgenic the progestin, however, the greater the negative effect; thus, the third-generation progestin pills are least harmful with regard to lipid changes. Medroxyprogesterone acetate does not impair glucose tolerance, increase blood pressure, or affect cholesterol levels.[1,10]

Serious complications related to use of combination OCs are unusual, but can include venous thromboembolism, stroke and myocardial infarction. The risk of developing cervical cancer is increased in patients with concurrent human papilloma virus infection,[11] and a slightly raised risk of developing breast cancer has been reported in current but not past users.[12] Effects of oral contraceptives on the coagulation system include increased levels of clotting factors, decreased levels of antithrombin III, and the downregulation of fibrinolysis;[13] the net effect is prothrombotic. Annual worldwide incidence of venous thromboembolism in young, healthy women is 1 in 10,000; this rate is increased by a factor of 3–5 in women on current OC preparations.[13] Both estrogen and progestin contribute to the increased risk of venous thrombosis,[14] and third-generation OCs confer almost two-times greater risk than do second-generation formulations[15] because of a related rise in resistance to activated protein C.[16] Thromboembolic risk is also influenced by duration of OC use: risk is highest in the first year of use and decreases by more than 50% after the first year.[17] Nonoral preparations are likely to have similar thrombotic risks.[18] The presence of certain additional risk factors leads to a cumulative rise in risk in women taking OCs: genetic or acquired thrombophilia, smoking (>10 cigarettes/day), age (>35 years), and obesity (BMI ≥25 kg/m^2).[3] Obesity is a strong risk factor for thromboembolism in patients taking OCs, increasing risk by a factor of 10.[19]

Risk of ischemic stroke and myocardial infarction is increased twofold in all users of

OCs,[20,21] but can be raised depending on presence of concomitant risk factors. The risk of stroke decreases with decreasing OC estrogen dose (with 50 μg the relative risk is 2.65; with 20 μg the relative risk is 1.59).[22] Unlike the risk of venous thrombosis, risk of stroke in women using third-generation OCs is no greater than that in those using second-generation drugs, and might even be lower.[22] Risk of ischemic stroke is raised in women taking OCs who are older than 35 years, who smoke, or who have hypertension or migraine;[20] however, in healthy, normotensive, nonsmoking women who are younger than 35 years and who are using low-dose OCs, no increased risk of hemorrhagic or ischemic stroke is seen.[23] As expected, the risk of myocardial infarction in OC users is increased if other cardiovascular risk factors are present,[24] as is that for peripheral arterial disease.[25] Absolute contraindications to use of combination OCs include a history of thrombosis, cerebrovascular or coronary artery disease, uncontrolled hypertension, diabetes with vascular complications, age older than 35 years in cigarette smokers, pregnancy, and the presence of estrogen-dependent neoplasia, breast cancer, active liver disease or malignancy, complicated migraines, and known thrombogenic mutations. Relative contraindications include hyperlipidemia, migraines, and long-term immobilization.[1–3]

USE OF CONTRACEPTIVES IN PATIENTS WITH AUTOIMMUNE DISEASE

Antiphospholipid-antibody-positive patients

Although antiphospholipid syndrome is a well-characterized, prothrombotic condition, clinicians' ability to predict the risk of thrombosis for a given asymptomatic antibody-positive individual is still limited. Current theories suggest that thrombosis is more likely to develop with a 'second hit'—that is, the presence of two or more risk factors. Well-recognized genetic factors associated with increased thrombotic risk include factor V Leiden, prothrombin mutation G20210A, hyperhomocysteinemia due to mutations in the *MTHFR* gene, and deficiencies of proteins C, S, and antithrombin III. Lifestyle risk factors include cigarette smoking and use of combination OCs. Medical risk factors might include severe illness, surgery, other long-term immobilization, presence of malignant disease, or pregnancy.

Factor V Leiden accounts for up to 20% of first-time venous thromboembolism; the prothrombin mutation confers a twofold to fourfold risk of this complication.[13] As expected, use of oral contraceptives exerts a marked additive effect on the risk of thrombosis in these patients, many of whom might not be aware of their genetic phenotype.[26] Despite the increase in risk, routine screening of patients without a personal or family history of thrombosis before starting OCs is not recommended because of poor cost-effectiveness.[3]

The combination of antiphospholipid antibody and genetic prothrombotic risk factors clearly increases risk of thrombosis.[27,28] Patients who have experienced thrombosis or fetal loss associated with antiphospholipid syndrome are more likely to also have heritable risk factors than asymptomatic individuals with antiphospholipid antibody.[27] In a cohort study of patients with SLE, factor V Leiden and prothrombin mutation were found to contribute to risk of venous thromboembolism, and to raise risk when combined with lupus anticoagulant or antibodies to cardiolipin.[28] No well-designed studies have examined whether risk of thrombosis is increased in patients positive for antiphospholipid antibodies who are taking OCs; multiple reports, however, describe an association between OC use and the occurrence of thrombosis.[29] Other risk factors for arterial complications, such as complicated migraines, atherosclerosis or hyperlipidemia, might be increased in SLE patients positive for antiphospholipid antibodies, and could further increase risk of stroke or myocardial infarction. As a result, substantial concern has been expressed regarding the prescription of OCs to such women. The Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA) study was designed to assess the risk of flare in SLE patients taking OCs. Patients who had moderate to high titers of antiphospholipid antibodies or lupus anticoagulant were excluded, even with no history of thrombosis. No increase in thrombotic complications was observed in the OC group; two patients in the OC group and three in the placebo group had thromboses.[30] In another randomized SLE trial, treatment with either combined or progestin-only OCs resulted in the same rate of thrombosis (2 of 54 patients in each group), but all 4 patients with thromboses had low titers of antiphospholipid antibodies.[31]

Avoiding the use of OCs in all patients with moderate or high titers antiphospholipid antibodies (≥40 GPL or MPL units) seems reasonable; whether use by such patients who are taking

Table 2 Studies on the risk of disease flare in patients with systemic lupus erythematosus using oral contraceptives.

Author (year)	Type of study	Number of patients with SLE	Contraceptive therapy	Outcome
Jungers *et al*. (1982)[40]	Retrospective	20 11	30–50 μg EE Progestin-only	43% flare (19% renal) No flares
Mintz *et al.* (1984)[41]	Prospective	10 15	Intramuscular norethisterone every 3 months 30 μg levonorgestrel daily	Same as controls Same as controls
Julkunen (1991)[39]	Retrospective interview	31	30–50 μg EE	13% flare Same as controls
Buyon *et al.* (1995)[42]	Retrospective questionnaire	55	Not specified	13% self-reported flare rate
Petri *et al.* (2005)[30]	Prospective (double-blind, randomized, placebo-controlled)	91 92	Triphasic 35 μg EE Placebo	7.7% flare (1 year) 7.6% flare (1 year) (NS)
Sanchez-Guerrero *et al.* (2005)[31]	Prospective (single-blind, randomized)	54 54 54	30 μg EE/levonorgestrel 150 μg/day Levonorgestrel 0.3 mg/day Copper IUD	0.92 risk of flare at 1 year 0.90 risk of flare at 1 year 0.87 risk of flare at 1 year (NS)

Abbreviations: EE, ethinylestradiol; NS, not significant.

warfarin has notable associated risks remains an unanswered question but it is not advised. Decisions regarding use of OCs in patients with low titers of antiphospholipid antibodies are less clear-cut than for those with higher titers. The presence of two or more risk factors might, however, increase risk substantially; screening for heritable prothrombotic risk factors could, therefore, prove helpful for these patients. Progestin-only contraception is a good alternative to OCs for antiphospholipid-antibody-positive patients, as they are not associated with increased thrombosis risk. The progestin-only pill must be taken at the same time daily to maintain effectiveness and, therefore, quarterly intramuscular administration of medroxyprogesterone acetate could be a more useful option if compliance is poor. Medroxyprogesterone acetate has no associated prothrombotic risk, but it can cause reversible osteoporosis and return of fertility might be delayed after discontinuation. A notable decrease in menstrual blood flow is seen with medroxyprogesterone acetate and the Mirena® IUD,[32] which might be particularly beneficial in patients receiving treatment with warfarin. An additional benefit of progestin-only contraception is decreased risk of ovarian cyst rupture.

Systemic lupus erythematosus

Multiple observations have suggested that estrogen influences SLE disease activity,[33,34] and that estrogen has an immunostimulatory effect.[35] A slightly increased risk of developing SLE associated with past use of OCs was demonstrated in the Nurses' Health Study;[36] however, later population-based case–control studies of SLE patients did not identify an association with OC use.[37,38] Although early reports suggested increased risk of disease flare with OC use in SLE patients, later studies did not support the findings. The conflicting results are probably attributable to differences in study design, patient selection and methods of assessing flare (Table 2).[30,31,39–42]

The results of two randomized clinical trials demonstrate that OCs do not significantly increase the risk of disease flare in a well-defined population of patients with stable SLE.[30,31] The SELENA trial was an equivalence trial specifically designed to test the hypothesis that OC use does not increase the risk of severe flare in SLE. The study randomly assigned 183 SLE patients with inactive or stable active disease to receive either an OC (triphasic 35 μg ethinylestradiol and 0.5–1.0 mg norethindrone for 12 28-day cycles) or placebo. Patients with a history of thrombosis, moderate to high titers of anticardiolipin antibodies, or a positive test for lupus anticoagulant were excluded. The rate of severe flares after 1 year was 0.084 for OC users and 0.087 for placebo. One severe renal flare was reported in the OC group and four in the placebo group. The number of mild-to-moderate flares was equivalent in both groups, as were the numbers of patients experiencing three or more mild-to-moderate flares. Furthermore, the combined rate of overall flares did not differ between groups.[30]

Sanchez-Guerrero and colleagues[31] found disease activity to be similar among 162 patients with SLE who were randomly assigned to receive one of three methods of contraception in a single-blind, 12-month trial: an OC containing 30 μg ethinylestradiol and 150 μg levonorgestrel, a progestin-only contraceptive containing 0.3 mg levonorgestrel, or a copper IUD. No difference was seen in global disease activity or rates of disease flare, including severe flares. The patients receiving progestin-only contraceptives discontinued treatment more frequently than those in the other two groups. Severe infection rate was highest in the IUD group and included two episodes of septic meningitis.[31]

On the basis of these studies, hormonal contraception seems safe for patients with inactive or stable active SLE, who do not test positive for antiphospholipid antibodies. All SLE patients should be screened for these antibodies before an OC regimen is started. Avoidance of the contraceptive patch in SLE patients might be advisable until more data are available on the effects of greater estrogen exposure than with other forms of hormonal contraceptives. The drospirenone-containing OC Yasmin® can predispose patients to developing hyperkalemia, and patients with baseline renal insufficiency should be monitored when using this OC.[6] For patients with active disease, barrier methods or progestin-only contraceptives are options. IUDs are not absolutely contraindicated in patients receiving immunosuppressive therapies, but no recommendations exist as to what degree of immunosuppression imparts meaningful risk of infection. Use of medroxyprogesterone acetate in patients receiving corticosteroids might be problematic because of the increased risk of additional bone loss.

Rheumatoid arthritis

In contrast to patients with SLE, patients with rheumatoid arthritis might benefit from treatment with OCs, because symptoms have been observed to improve during pregnancy and the risk of disease flares increases post partum.[43] Although numerous studies have focused on the question of whether OCs reduce the risk of developing rheumatoid arthritis, this issue remains unresolved.[44,45] An early report[46] found the rate of rheumatoid arthritis development to be halved in current OC users; other studies have suggested a duration-dependent effect,[47] and a protective effect for severe or seropositive RA.[48] Analysis from the Nurses' Health Study did not show a protective effect of past use of OCs, although authors could not rule out a slight protective effect of current OC use.[49]

Therapeutic use of OCs in patients with established rheumatoid arthritis has not been studied extensively, partly because patients have normal estrogen levels but low androgen levels.[50] As a result, hormonal therapy attempts have focused on androgenic supplementation, with mixed results.[51] Postmenopausal use of estrogen therapy has been evaluated in patients with rheumatoid arthritis and showed no significant effects on disease activity.[52] Thus, although OCs have no beneficial effects on rheumatoid arthritis disease activity, no evidence suggests that their use exacerbates the disease. Theoretically, a case could be made for the use of OCs containing the relatively more androgenic (second-generation) progestins, to maximize androgenic immunosuppression. Combination OCs or the transdermal patch might be effective and convenient for patients with rheumatoid arthritis. Insertion of a diaphragm or a vaginal ring, however, could be difficult for patients with severe arthritis who might desire these methods. IUDs are contraindicated in many patients taking immunosuppressive therapies, but no studies have been done specifically of rheumatoid arthritis medications, such as tumor necrosis factor inhibitors.

Other autoimmune diseases

The benefits of oral contraceptive therapy might have relevance to other autoimmune diseases, but data are scarce. Intravenous estrogen therapy has shown positive effects in severe Raynaud's phenomenon in systemic sclerosis;[53] use of oral estrogen in the form of OCs, however, does not affect patient-reported frequency or severity of Raynaud's disease attacks.[54] No specific data are available on effects of estrogen in patients with vasculitis, but estrogen should probably be avoided in these patients, as well as in those with atherosclerosis or at increased risk of ischemia.

The potential interactions of OCs with a variety of medications are well recognized (Table 3) and can reduce drug efficacy or increase the risk of toxic effects. Medications commonly used in patients with autoimmune connective tissue disease that have potential notable interactions with OCs include multiple anticonvulsants; corticosteroids, warfarin, and ciclosporin have weaker interactions.[55] Long-term immobilization is common in patients with rheumatologic disease, whether due to disease

Table 3 Potential medication interactions with oral contraceptives.[55,57]

Medication	Effect with concomitant OC
Anticonvulsants	
Carbamazepine, phenytoin, phenobarbital, Oxcarbazepine, primidone, felbamate, topiramate[a]	Decreased OC efficacy due to increased hepatic metabolism
Phenytoin	Increased phenytoin concentration due to decreased metabolism
Lamotrigine	Decreased lamotrigine concentration due to increased metabolism
Antibiotics	
Rifampin	Decreased OC efficacy due to increased hepatic metabolism
Griseofulvin	Decreased OC efficacy due to increased hepatic metabolism
Penicillins, cepalosporins, macrolides, metronidazole, sulfa, tetracyclines[b]	Possible decreased OC efficacy due to increased intestinal transport and decreased enterohepatic reabsorption
Corticosteroids	Increased steroid concentration due to decreased metabolism
Cyclosporin	Increased ciclosporin concentration due to decreased metabolism
Warfarin	Increased or decreased warfarin effect due to alteration in metabolism
Thyroid hormone	Decreased levels of free thyroxine due to increased levels of thyroxine binding globulin

[a]Benzodiazepines, gabapentin, lamotrigine, and valproic acid do not affect OC metabolism.[57] [b]OC levels probably remain stable with all antibiotics except rifampin. Abbreviation: OC, oral contraceptive.

Table 4 Benefits and disadvantages of contraceptive methods for patients with rheumatic disease.

Method of contraception	Benefits	Disadvantages
Barrier methods		
All	Low risk of STI	Low compliance and low effectiveness with typical use
Condom	No prescription necessary	None
Diaphragm	None	Difficulty of insertion for patients with severe arthritis
IUDs		
All	Effective, good compliance No prothrombotic risk	Contraindicated for some patients with immunosuppressive therapy
Copper IUD	None	Increases menstrual flow
LNG-IUS	Reduces menstrual flow (benefit for patients treated with warfarin) Decreases functional cysts	None
Combined hormonal contraceptives		
All	Effective; convenient Possibly increases bone density	Contraindicated in patients with thrombosis or moderate to high aPL Not evaluated in patients with active SLE Risk of thrombosis with immobilization or extended bedrest
Oral	No increased flare in stable SLE patients Benefit for RA patients?	Potential interactions with other medications
Patch	Good compliance	60% greater estrogen exposure
Vaginal ring	None	Difficulty of insertion for patients with severe arthritis
Progestin-only contraceptives		
All	No prothrombotic risk, can give to aPL-positive patients Reduces menstrual flow (benefit for patients treated with warfarin)	Irregular bleeding Weight gain; acne
Oral	None	Must take at same time daily
DMPA	Effective; convenient	Reversible osteoporosis Prolonged return of fertility after discontinuation

Abbreviations: aPL, antiphospholipid antibody; DMPA, Depot medroxyprogesterone acetate; IUD, Intrauterine device; LNG-IUS, Levonorgestrel intrauterine system, RA: rheumatoid arthritis; SLE, systemic lupus erythematosus; STI, Sexually transmitted infection.

flares or disease-related surgery. During the period of immobilization patients should discontinue use of OCs, the patch, or the vaginal ring, and should be given prophylactic anticoagulation, especially if they are antiphospholipid antibody positive. Combined hormonal contraceptives should be discontinued two cycles before planned surgery, as estrogen's effects on coagulation take up to 6 weeks to resolve. Prophylactic perioperative heparin therapy should be added to reduce risk of venous thromboembolism, especially in patients with other prothrombotic risk factors.

CONCLUSIONS

The variety of currently available contraceptive options enables most patients with rheumatic disease to choose a safe and effective contraceptive method. The potential effects of each contraceptive on rheumatic disease, or interactions with concomitant medications, demand that rheumatologists have a basic knowledge of the benefits and disadvantages of each contraceptive option. In general, younger patients prefer hormonal contraceptives because of convenience, efficacy and easy reversibility, and OCs are good options for those who do not have antiphospholipid antibodies, other prothrombotic risk factors, or active SLE. Progestin-only contraceptives, administered orally, intramuscularly, or via an intrauterine device, do not increase the risk of thrombosis and are recommended for patients of any age who have a contraindication to estrogen. An added advantage of medroxyprogesterone acetate and the Mirena® IUD for patients on warfarin is the decrease in menstrual blood flow, although medroxyprogesterone acetate should be used with caution in patients also receiving treatment with corticosteroids, because of the associated increased risk of bone loss. The Mirena® IUD has few side effects, but should be avoided in severely immunocompromised patients. Although combined hormonal contraceptives are sometimes used in older patients who have completed childbearing, the IUD or sterilization are as effective, and are probably safer, in these patients (Table 4).

KEY POINTS

- Most patients with rheumatic disease are able to choose a safe and effective contraceptive from the options available
- Combined oral contraceptives do not increase risk of disease flare in patients with stable systemic lupus erythematosus
- Estrogen-containing contraceptives are contraindicated in patients at increased risk for thrombosis, including patients who test positive for antiphospholipid antibody
- Progesterone-only contraceptives—oral, intramuscular, or intrauterine device—do not increase risk of thrombosis risk and are recommended for patients who have a contraindication to estrogen
- Medroxyprogesterone acetate and the Mirena® intrauterine device decrease menstrual blood flow in patients receiving warfarin

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