



Revision

Drugs employed during pregnancy and contraceptive methods in rheumatic disease. New evidence

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ABSTRACT

Voluntary birth control, the ability to identify the best moment for becoming pregnant depending on disease activity, and the need to avoid conception during the administration of teratogenic drugs are the main reasons for the use of contraceptive methods among women with rheumatic diseases.

This article reviews the risks that antirheumatic drugs represent during conception, pregnancy and lactation and the contraceptive methods that are currently available to patients. Hormonal therapy has developed considerably and can further our understanding of safety aspects, especially for systemic lupus erythematosus patients. Recently the methods of administration have evolved, and now include transdermal and intravaginal routes, a progesterone-releasing intrauterine device, and an extended-cycle oral contraceptive.

Rheumatologists work increasingly in conjunction with patients to assist in choices regarding contraceptive methods and pregnancy planning. Each decision should be individualized according to the personal preference and the stage of reproductive life.

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Fármacos durante el embarazo y métodos contraceptivos en enfermedades reumáticas. Nuevas aportaciones

RESUMEN

El control voluntario de la natalidad, el hecho de poder establecer el mejor momento de la gestación en función de la actividad de la enfermedad y la necesidad de evitar el embarazo debido a la indicación de fármacos potencialmente teratógenos constituyen las razones principales para la utilización de métodos contraceptivos en pacientes afectas de enfermedades reumáticas.

En este artículo se revisan los posibles riesgos durante el embarazo de las medicaciones utilizadas en reumatología y los diversos métodos contraceptivos disponibles actualmente. En los últimos años se ha producido un mejor conocimiento de la seguridad de los métodos contraceptivos hormonales con datos especialmente relevantes de su utilización en pacientes con lupus eritematoso sistémico. La evolución de la contracepción hormonal con nuevas vías de administración, como la transdérmica, la intravaginal y los dispositivos intrauterinos o los implantes liberadores de progestágenos, han significado avances evidentes en este campo.

La implicación del reumatólogo, como responsable de la atención de estos pacientes, es requerida con mayor frecuencia y el conocimiento de todos los métodos disponibles, con todas sus ventajas, desventajas y efectos adversos ayudará a facilitar información para que la pareja pueda escoger en cada caso la mejor opción.

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"The first great commandment is not to allow yourself to be frightened"

E. Davis

Voluntary birth control is the main indication for the use of contraceptive methods. In patients with inflammatory rheumatic

disease, the need to avoid pregnancy due to the use of potentially teratogenic effects or disease activity and the fact that they allow the establishment of the optimal time for conception in relation to the disease are added reasons.

The decision to use a certain contraceptive method is usually taken jointly between the person or persons implicated and the health provider. In the case of patients with rheumatic disease it is the rheumatologist, as the physician responsible for the attention of these patients, who is more often consulted. We should have enough knowledge of all of the available methods, with all of their advantages, disadvantages and adverse

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effects in order to help the couple choose the method of their preference, with the duty and responsibility of providing opportune instructions and recommendations, leading to improved efficacy and protection.

Effects of the drugs on pregnancy

One of the main indications for contraception in rheumatic diseases resides in the possible side adverse effects of certain drugs during pregnancy. For some years, the Federal Drug Administration (FDA) has established a classification of the different drugs in relation to their effect on the course of pregnancy, with inclusion of most of the treatments employed in our specialty.

In its classification, the FDA establishes 5 categories in relation to the risk of a certain drug on pregnancy. Drugs in "category A" are those that are adequate for use during pregnancy due to the availability of properly performed studies which have shown that they do not pose a risk for the fetus. "Category B" includes those that pose a risk in animals but not humans, or in the case of no studies in women being available but which have not shown to be associated to risk in animals. "Category C" includes drugs in which no studies on pregnant women are available but that have shown risk in animals or when no human or animal studies are available. "Category D" has shown risk for the fetus in studies or prior experience, but beneficial effects may justify their use, and "category X" include drugs in which studies have shown a clear risk for the fetus which surpasses any benefit for the patient.

The insert of the different drugs usually includes its indication or not during pregnancy and several systematic reviews exist on the use of drugs during pregnancy and lactation. As a summary, we will review the main characteristics of the most frequently used drugs in the following lines.^{1,2}

Steroids: one of the most used drugs in rheumatic disease. Cortisone and hydrocortisone cross the placenta but hydrocortisone is converted into cortisone, which is biologically inactive, by the enzymatic action of 11-beta dehydrogenase, and is therefore considered in the B category. If the mother requires steroids, cortisone, hydrocortisone or prednisone should be employed. Dexamethasone and betamethasone are not inactivated by this enzyme and are considered in the C category. If the fetus requires steroids, for example in the case of respiratory distress, these would be the drugs of first choice. Steroids increase the risk of cleft palate if used at high doses during the first trimester of pregnancy. Low levels are usually detected in maternal milk, although in the case of using high doses it is recommended that lactation occur 4 hours after the last steroid dose.

Non steroidal anti-inflammatory drugs (NSAID): for some authors, traditional NSAID are in the B category and the newer COX-2 inhibitors in the C category, but if they are administered in the third trimester of pregnancy then they are considered in the C or D categories.³ They increase the risk of fetal and postpartum hemorrhage due to their anti-platelet effect. They have also been associated with closure of the ductus arteriosus with hypertension. It is advisable to avoid them during the first trimester and especially in the 6 to 8 weeks before labor, starting at week 32. They can be administered during lactation but, by displacing bilirubin, may increase the risk of jaundice and kernicterus.

Hidroxicloroquine: it is considered in the C category, although it can continue to be administered during pregnancy. It must be remembered that chloroquine accumulates 2,5 times more than hydroxicloroquine. It crosses the placenta, but no fetal toxicity has been reported at recommended doses in the placenta (visual alterations, deafness, growth retardation). Concentrations of 2% have been measured in maternal milk, which do not lead to

ocular complications, making it safe to be administered during lactation.

Methotrexate: belongs in the X category due to its teratogenic and abortive effects. Fetal exposure can lead to cranial and central nervous system abnormalities such as anencephaly or myelopathy, as well as defects in the formation of the extremities. It is imperative to instruct the patient on the use of contraception when taking methotrexate. The drug should be discontinued at least 4 months before pregnancy and folic acid must continue to be taken and for the rest of the pregnancy. It is also contraindicated during lactation. In males, there are very few studies but the drug is recommended to be suspended 3 months prior to conception.

Leflunomide: included in the X category. Before starting its administration, the clinician must be sure that the patient is not pregnant and adequate contraceptive measures must be recommended. It may remain in the organism for a long time due to entero-hepatic circulation; therefore in order to speed its elimination, cholestiramine at a dose of 8 grams 3 times a day for 11 days must be recommended, and after administering it, levels of leflunomide must be determined to be under 0.02 mg/l in 2 separate determinations 2 weeks apart. For a subsequent pregnancy, a waiting period of 3 menstrual cycles after the administration of cholestiramine is recommended. It is also contraindicated during lactation.

Sulphasalazine: included in the D or B categories. It does not increase fetal morbidity or mortality. It has not been shown to displace bilirubin or cause jaundice. It is considered as safe to use during pregnancy.

Azathioprine: category D. Crosses the placenta, but the newborn's liver lacks the enzyme to create inosinate pyrophosphorylase active metabolites. It is not considered teratogenic, although isolated cases have been reported related to growth retardation, neonatal leucopenia, lymphopenia and hypogammaglobulinemia that can determine a greater number of cytomegalovirus infection and Gram negative. Development during adolescence is normal. Controlled studies have shown no differences in abortions, birth defects, tumors or infections. If it is necessary for the control of autoimmune disease, it is considered an option during pregnancy. Contraindicated in breastfeeding.

Cyclophosphamide: category D. It can cause infertility and amenorrhea, as well as increase the risk of malformations. There have been reports of growth retardation, craniosynostosis, blepharophimosis, flattened nasal bridge, abnormal auricles, oligodactyly...should be avoided during pregnancy, especially the first trimester and during lactation.

Cyclosporin A: category C. Crosses the placental barrier. Most studies have been conducted in transplant patients and have not seen growth retardation or increased blood pressure. A meta-analysis has not shown an increased risk of malformations. It is not recommended during nursing.

Mycophenolate mofetil: initially included in category C, is currently considered category D (positive evidence of fetal risk) according to data from the United States National Transplantation Pregnancy Registry. There have been reports of fetal losses in the first trimester of pregnancy and birth defects (micrognathia, hypertelorism, anomalies of limbs ...).⁴ It is advisable to remove the drug six weeks before conception.⁵ There have been no cases of malformations when the father is taking mycophenolate at the time of conception. Avoid while breastfeeding.

Anti-TNF: considered category B. Some cases of vertebral abnormalities have been reported in association with etanercept, as have anal atresia, esophageal and renal anomalies (VATER Syndrome), but most are uncomplicated term pregnancies. In recent communications with a significant number of cases, there appears to be an increase in fetal malformations among patients receiving anti-TNF.⁵⁻⁹ Undetectable infliximab levels in breast milk, although high levels in the case of etanercept, have been

observed, and it is generally advised not to administer during lactation.

Anakinra: category B. Studies in animals have shown that it does not interfere with fertility, but there are no studies in humans. Caution should be exercised if necessary. It is not known if it is secreted in breast milk, but avoidance of breast-feeding is advised.

Rituximab: category C. There is more experience than with other drugs introduced in recent years for autoimmune diseases due to its prior use in some types of lymphoma.¹⁰ Cases of uncomplicated pregnancies and cases of mild, transient and reversible granulocytopenia and lymphopenia have been published. It can be considered a possible future option, but right now its administration should be avoided during pregnancy and lactation.

Abatacept: although animal studies have not observed effects on fetal development, there is insufficient data on the use of abatacept in pregnant women and its use is not advised. During treatment of women of childbearing age, effective contraception should be used until 10 weeks after the last dose.⁵ It is not known whether abatacept is secreted in breast milk.

The indications for many of these drugs should trigger strict contraceptive measures because of the risk posed to the fetus. This, together with voluntary birth control on the part of the patient and the possibility to set the best moment for pregnancy, according to disease activity, are indications for contraception.

After establishing the indication for contraception due to any of the circumstances described, we must differentiate between temporary and permanent methods. For the latter, it should be noted that in these diseases there is no contraindication for tubal ligation or vasectomy. Patients, or the couple, must decide whether method of choice should be definitive.

Among the temporary methods, barrier methods, including the diaphragm, the female and male condoms, with or without a spermicide, must first be mentioned. For these there is no published data that examines the effectiveness and side effects in patients with rheumatic diseases, although there seems no apparent reason to contraindicate their use. These temporary methods, the main problem lies in the use of oral contraceptives (OC) in patients with autoimmune diseases and above all in patients with systemic lupus erythematosus (SLE) and antiphospholipid syndrome.

Hormonal contraception

Since the introduction of the so-called birth control pill in 1960, the variety of available hormonal contraceptives has changed considerably. Currently hormonal contraceptives include a combination of estrogen and progestin or progesterone alone and routes of administration include oral, intramuscular, transdermal and vaginal. The most common hormonal combinations usually differ in the amount of estrogen, type of progesterone and dosage during the cycle. The effects of these treatments can have effects on menstruation, and some of the treatments used reduce the number of menstrual periods to four a year.

The classic combination of OC includes ethinylestradiol at doses of 20–50 µg and progesterone. The second-generation OC containing ethinylestradiol and lower amounts of any of the following progestins: levonorgestrel, and Lynestrol norethindrone. The latter, considered a third-generation progesterone, include desogestrel, norgestimate or gestodene and are characterized by fewer androgenic effects such as acne, nausea, or unfavorable changes in lipid profile, more common in second generation.¹¹ The combination transdermal hormone patches (Ortho Evra®) releases 20 mg of ethinyl estradiol and 150 µg of norelgestromine daily. These patches should be used weekly for 3 consecutive weeks, followed by a week without its use. The contraceptive vaginal ring (Nuvaring®) offers 15 µg of ethinyl estradiol and etonogestrel 120 µg daily and is

used for 3 consecutive weeks followed by the removal of the ring for a week.

Contraceptives containing only progesterone include norethindrone, norgestrel or desogestrel (Cerazet®) and are used less frequently than combined contraceptives because they cause irregular vaginal bleeding, but are an alternative in those cases where estrogens are contraindicated. Within this group, the administration of medroxyprogesterone acetate intramuscularly every 12 weeks or etonogestrel (Implanon®) stands out and is employed as a subcutaneous implant that lasts for three years and is an alternative to be considered in patients with poor adherence to other treatments; side effects include irregular vaginal bleeding, weight gain and bone loss related to decreased secretion of estrogen. The so-called “morning after pill” contains levonorgestrel (Norlevo® and Postinor®) is effective within the first 72 hours after intercourse. Finally, the intrauterine device (IUD), Mirena® is characterized by not containing copper, but rather releases levonorgestrel and maintains its efficacy for 5 years.¹² It has been associated with a 75% decrease in menstrual bleeding, which would put it in a clear advantage over other contraceptive methods, especially in patients requiring anticoagulation. Regular IUDs have been linked with an increased risk of pelvic infection in the first month after insertion and early removal of the device. Mirena® may cause irregular vaginal bleeding during the first 3 months of use, although during the first year of use up to 20% develop amenorrhea.¹³ Contraindications of IUD use include pregnancy, history of previous ectopic pregnancy, the presence of pelvic inflammatory disease, vaginal bleeding of unknown cause and a history of cervical or uterine neoplasia. Important immunodeficiency in a particular disease or because of a drug may represent a relative contraindication that will need individualized evaluation.

Side effects associated with the use of CO are usually mild and include nausea, swelling and soreness of the breasts. Other less common effects are impaired glucose tolerance or hypertension. Estrogens increase HDL cholesterol levels and lowers LDL, while progestins tend to have a reverse effect. In combined hormonal OC, the effect on the lipid profile is often negligible, as in the case of third generation progesterone alone. Medroxyprogesterone does not usually affect glucose tolerance, but may increase blood pressure and increase cholesterol levels.¹⁴ Serious side effects are rare and include venous thromboembolism (VTE), cerebral vascular accident (CVA) or myocardial infarction. Its effects on cervical cancer or breast cancer are under discussion¹⁵ and it is associated with prothrombotic effects mediated by an increase in the levels of procoagulant factors, lower levels of antithrombin III and fibrinolysis.¹⁶ The incidence of thromboembolic events in young healthy women is 1 in 10,000, but in patients treated with OC it increases to 3–5. Both estrogen and progestins contribute to increased risk of venous thrombosis and third-generation progesterone induce resistance to C protein activity in twice as many cases as the second generation does, although an increase in risk of stroke has not been seen. The development of thromboembolic effects has also been associated with hormonal treatment duration and dose used; the risk is higher during the first year and then is reduced more than half. The risk of stroke decreases with a decreasing dose of estrogen. The ring or patch presentations appear to have similar risks than traditional oral administration. We must consider the presence of other risk factors such as genetic or acquired thrombophilia, smoking, age or obesity. Thus, it appears that the risk of ischemic stroke is increased in patients treated with OC when they are older than 35 years, are smokers or have hypertension or migraine, and in the case of normotensive, nonsmokers healthy women, under 35, there has been an increased risk of ischemic or hemorrhagic stroke.^{17,18}

Absolute contraindications include the use of OC in patients with a history of thrombosis, stroke or coronary artery disease, uncontrolled hypertension, diabetes with vascular complications, smokers over 35

years, presence of estrogen-dependent neoplasms, breast cancer, active liver disease, complicated migraines and thrombotic disorders. Relative contraindications considered are hyperlipidemia, migraine, and prolonged immobilization.

Contraception in SLE patients

OC in the United States are the most widely used contraceptive methods in women of 15–44 years of age. In a study conducted in five centers, only 10% of patients with SLE were treated with OC as opposed to 55% who had taken them before diagnosis of the disease, and another series showed only 4% of women with Hopkins Lupus Cohort were treated with OC after, compared with 67% of those who had taken prior to diagnosis.¹⁹ This gives us an idea of the change of strategy in relation to contraception that occurs in women with SLE. Let's review if there are sufficient reasons to justify these changes.

There are many reported cases of the temporal association between the onset of SLE and the use of OC and some studies have indicated an increased risk for developing SLE associated with prior use of OC, however, this data has not been confirmed in subsequent studies.^{20–22}

A recent, just-released study shows an increased risk of developing SLE in women who have recently begun using high-dose OC.²³

In addition, increased activity of SLE associated with use of CO has been controversial, possibly motivated by differences in study design. Thus, a study published more than 25 years ago,²⁴ showed that 43% of SLE patients with an outbreak of renal involvement occurred during the administration of OC. However, later studies²⁵ with lower doses of ethinyl estradiol did not observe an increase of SLE outbreaks. More recently, the study *Safety of Estrogens in Lupus Erythematosus National Assessment* (SELENA), a multicenter prospective study that includes two major sub-studies, analyzed the effect caused by estrogen therapy on disease activity. In the first study²⁶ estrogens were indicated as HRT during menopause and showed a small increase in the risk of outbreaks of mild-moderate intensity in women who continued HRT. The authors recommended avoiding HRT in older lupus patients with active disease, renal failure and when antiphospholipid antibodies (aPL) were positive, which confer an increased risk of coagulopathy. The other so-called OC-SELENA study, published shortly after,²⁷ included 183 women with SLE (76% active and 24% stable inactive), of which 92 were taking placebo and 91 OC with 35 µg of triphasic ethinyl estradiol and norethindrone. Patients with a history of thrombosis or moderate-high levels of antiphospholipid antibodies (aPL) were excluded. After a year of monitoring, the risk of an outbreak was 0.084 for patients treated with OC and 0.087 in the placebo group. A renal flare was observed in a patient with OC and 4 in the patients with placebo. Overall, there was no increased risk of outbreaks during the period of administration of OC and therefore it was considered a safe method in patients with inactive or stable SLE with a low risk of thrombosis. These results were similar to another study published in the same issue of the journal²⁸ which analyzed 162 women with SLE who were randomized into three groups: one received OC (30 µg of ethinyl estradiol and 150 µg levonorgestrel), another group received single oral progesterone (30 µg of levonorgestrel), and the third group received a copper IUD. There were no significant differences between groups of women in relation to adverse events, disease activity, maximum SLEDAI activity score and the incidence and time of appearance of the first outbreak. The authors recorded four thrombotic events that occurred during the study in patients with SLE and all had positive APL, therefore it is recommended that OC are avoided in patients with APL.

Based on these studies, OC, preferably combined with low doses of estrogen, appears to be safe in those patients with inactive or stable SLE

without aPL. In patients with active disease, barrier methods or IUDs may be an alternative to consider. IUD's can be used in patients with SLE but should be avoided in patients receiving immunosuppressive therapy, although there are few studies on this subject.

The use of progesterone alone may be another alternative to consider in patients with active disease or aPL as it is not associated with increased activity or a clear increased risk of thrombosis. Progestin pills should be taken daily to maintain effectiveness. The quarterly administration of medroxyprogesterone acetate may be another option in cases of low compliance. Medroxyprogesterone acetate has not been associated with an increase in the thrombotic risk, but can cause reversible osteoporosis and delay the recovery of fertility after its suspension.

A significant reduction in menstrual bleeding has been observed with DMPA and the Mirena® IUD,²⁹ so it might be useful in patients under anticoagulant treatment. An additional benefit of contraception with progestins is the decreased risk of ovarian cyst rupture.

The second-generation progestones have less effect on coagulation than estrogen³⁰ and might thus be indicated in patients with AAF if no barrier methods are thought to be adequate. There are however some side effects from the use of progestins alone, such as a higher incidence of ectopic pregnancies, reduced effectiveness, irregular menstruation and changes in the lipid profile and glucose intolerance.³¹ The third-generation progestogens (desogestrel and gestodene) have shown a greater suppression of ovarian activity, have fewer androgenic properties and reduced effects on the lipid profile, and might thus have less effect on thrombosis. However, some studies have found that the risk of VTE is increased even in OC containing third generation progestogens, more than in those containing second generation progesterone^{32,33} apparently by inducing resistance to activated C protein, but no increase in the risk of stroke has been seen.^{34,35} More recent studies have indicated that etonorgestrel (Implanon) does not increase the risk of thrombosis.³⁶ We must also consider the use of medroxyprogesterone acetate in patients receiving glucocorticoids due to an increased risk of bone loss.³⁷

Contraception in patients with antiphospholipid antibodies

The combination of aPL and prothrombotic genetic risk factors increase the risk of thrombosis. Patients who have had a thrombotic phenomenon or fetal loss associated with aPL are more likely to have a hereditary risk of thrombosis than asymptomatic patients with aPL.³⁸ In a cohort study of patients with SLE, Leiden's factor V and a mutation in prothrombin contribute to the risk of VTE and increased the risk when combined with lupus anticoagulant or anticardiolipin antibodies.³⁹ There have been no studies that have examined whether OC increases the risk of thrombosis in patients with aPL, however many cases of the association between the use of OC and the development of thrombosis have been published. The SELENA study excluded patients with aPL that had not presented prior thrombosis and there was an increase in the thrombotic events in patients treated with OC compared to placebo.

Avoiding the use of OC in all patients with moderate to high levels of aPL seems most reasonable. The risk in patients with low titers and no history of thrombosis is doubtful, and in these cases the detection of hereditary risk factors may help the decision. It is unknown if the risk persists in those patients under anticoagulant treatment. In cases at risk, barrier methods, IUDs or the use of progesterone alone may be an alternative to consider.

Contraception in patients with rheumatoid arthritis

Contrary to what occurs in SLE, patients with rheumatoid arthritis (RA) may benefit from treatment with OC, as it has been shown to

improve symptoms during pregnancy and the risk of polyarticular outbreaks increases in the postpartum. But several studies that have analyzed the influence of OC in the risk of developing RA have shown no conclusive results.⁴⁰⁻⁴² Nor does the use of OC in patients with established RA seem to have beneficial effects on disease activity, although its use does not cause flares of joint symptoms.⁴³ The use of OC or in patch combination therapy appears to be the better choice in patients with RA, since the use of the diaphragm or estrogen vaginal ring can cause placement problems in patients with significant joint disease of the hands. IUD's may be contraindicated in patients on immunosuppressive therapy, but there are no studies in patients specifically treated with TNF inhibitors.

Contraception in other autoimmune diseases

Although OC had initially been discouraged in patients with Raynaud's phenomenon, subsequent studies showed that intravenous estrogen therapy had a positive effect on the Raynaud's phenomenon of patients with scleroderma.⁴⁴ However, studies with non-oral estrogen showed no effect on the frequency and severity of episodes of Raynaud's.⁴⁵

No data exist on the use of estrogens in patients with vasculitis, but it seems reasonable to avoid them as is done in patients with atherosclerosis and other risk factors.

We must also consider potential drug interactions in patients treated with OC because their effectiveness may be reduced or toxicity increased. Within the drugs to be considered, anticonvulsants and to a lesser extent corticosteroids, warfarin or cyclosporine should be included.³³ It is also advised to avoid the use of OC during long periods of immobilization that may occur during a major outbreak of disease or after surgery related to the disease, and anticoagulant prophylaxis should be indicated, especially in patients with aPL. It is advisable to discontinue hormonal contraception for two cycles prior to elective surgery.

Disclosures

The authors have no disclosures to make.

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