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Review

Pregnancy in systemic autoimmune diseases: Myths, certainties and doubts☆

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ABSTRACT

Systemic autoimmune diseases especially affect young women during childbearing age. The aim of this review is to update systemic lupus erythematosus, antiphospholipid syndrome and systemic sclerosis management during pregnancy.

These diseases present variable maternal and foetal risks. Studies show that an appropriate disease control and a reasonable remission period prior to pregnancy are associated with satisfactory obstetric outcomes. Antiphospholipid autoantibodies profile, anti-Ro/anti-La antibodies, pulmonary pressure and activity evaluation are crucial to assess the pregnancy risk.

Monitoring requires a multidisciplinary team, serial analytic controls and Doppler ultrasound of maternal and foetal circulation. Evaluation of the activity of the disease is essential.

El embarazo en las enfermedades autoinmunes sistémicas: mitos, certezas y dudas

Palabras clave:
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Síndrome antifosfolípido
Esclerosis sistémica
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RESUMEN

Las enfermedades autoinmunitarias sistémicas suelen afectar a mujeres jóvenes en edad reproductiva. El objetivo de esta revisión es actualizar el tratamiento del embarazo en el lupus eritematoso sistémico, el síndrome antifosfolípido y la esclerosis sistémica.

Las 3 enfermedades pueden presentar complicaciones y riesgos maternos y fetales. Diversos estudios han confirmado que si la enfermedad está bien controlada y se ha mantenido en remisión durante un período razonable es más probable que el embarazo llegue a término sin mayores complicaciones. El perfil de anticuerpos antifosfolipídicos, los anticuerpos anti-Ro/anti-La, la presión pulmonar y la evaluación del nivel de actividad son determinantes para definir el riesgo del embarazo.

El seguimiento requiere de un equipo multidisciplinar, controles analíticos seriados y ecografía con doppler de la circulación maternofetal. El tratamiento estará destinado a controlar adecuadamente estas enfermedades y emplear la terapéutica efectiva para la enfermedad al menor riesgo para el feto, optimizando así los resultados obstétricos.

Systemic autoimmune diseases (SAD) often affect young women of reproductive age, so pregnancy is often a cause for concern and consultation to clinicians attending these patients. For many years, and until not so long ago, the presence of an SAD meant, in many cases, immediate contraindication of pregnancy. Today the situation has changed and, knowing the risks and precautions to be

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taken in conjunction with a suitable schedule of controls, most patients can become pregnant and have children without major problems.[1,2]

This review aims to update the SAD treatment more commonly faced by clinicians, describing their main risks, how to prevent them, which controls to perform and how to treat complications. Much of the treatment of these diseases requires a multidisciplinary team where the clinician is a link in a chain comprising obstetricians, sonographers, neonatologists, clinical laboratory and nursing staff.

Systemic lupus erythematosus and pregnancy: potential risks and necessary controls

An initial concern is on the relationship between systemic lupus erythematosus (SLE) and fertility. Pre-treatment with cyclophosphamide (CPM), the organic commitment and the degree of activity of SLE can affect fertility. It is well-recognized that cumulative doses below 9–10 g are rarely associated with early menopause.[3]

A second aspect to consider is the complications faced by a lupus patient during the gravid-puerperal period. Population studies establish that 2–8% of pregnancies in women with SLE develop complications with hypertension or preeclampsia, which is a major cause of maternal and foetal morbidity and mortality.[4–6] Moreover, gestational diabetes, hypertension, renal failure, venous thromboembolic disease and stroke can be between 2 and 8 times more frequent in patients with SLE compared to the general population. The risk of complications such as preterm birth and intrauterine growth restriction is also considered 2–4 times higher (Table 1).[7,8]

The PROMISSE study, which describes a prospective follow up in a cohort of 389 patients with inactive SLE or low levels of activity at the time of conception has been recently published. The study confirms that 81% of pregnancies did not present complications, 5% ended in foetal or neonatal death and less than 3% had lupus flare.[9]

On the other hand, the relationship between pregnancy and lupus activity has been controversial. Nowadays it is well-recognized that pregnancy increases the risk of having a lupus flare, particularly in those patients with activity close to the time of conception. Indeed, the PROMISSE study confirms that most patients with low levels of activity or no activity at the time of pregnancy progress favourably. In turn, it has been shown that if the disease is inactive for a long time, the risk of lupus flare during pregnancy is reduced very significantly.[9–11]

Table 1
Potential complications of systemic autoimmune diseases during pregnancy.

Systemic lupus erythematosus	Abortion Foetal loss Prematurity IUGR Lupus flare Increased irreversible organ damage Arterial hypertension Preeclampsia
Antiphospholipid syndrome	Abortions Foetal loss Prematurity IUGR Thrombocytopenia Preeclampsia Thrombosis
Systemic sclerosis	Increased gastroesophageal reflux Scleroderma renal crisis Increased restriction secondary to pulmonary interstitial lung disease Worsening of pulmonary hypertension

IUGR: intrauterine growth retardation.

Table 2
Differential diagnosis between preeclampsia and renal lupus flare.

	Preeclampsia	Lupus flare
Hypertension	Increase	Decrease
Proteinuria	Present	Present
Uric acid	Increase	Normal
C_3 and C_4	Normal or increased	Decreased[a]
Anti-DNA antibodies	Negative	Positive[a]
Urinary sediment	Proteinuria	Proteinuria Hematic or cellular casts Leukocytes/erythrocytes

[a] Observe variations compared to pre-pregnancy values.

In any case, the presence of lupus flare during pregnancy is a major complication for both mother and foetus. For the first, because of the possibility of severe manifestations and because it is associated with an accumulation of irreversible organ damage, adding the fact that therapeutic resources are reduced during pregnancy. For the foetus, because the presence of maternal lupus activity has been linked with an increased risk of abortions, prematurity and perinatal death, and because the use of certain drugs could have adverse effects.[8–12]

The diagnosis of lupus flare during pregnancy is often a challenge. It is well established that the flare manifestations may be similar to those determined by the pregnancy itself, such as arthralgia, fatigue or oedema.[12] To further complicate things, the possibility of a renal flare is often a problem to the extent that manifestations may be confused or overlap with the clinical manifestations of preeclampsia. Protein excretion in urine during pregnancy may increase in patients with residual proteinuria, so it does not always mean nephropathy activity. Meanwhile, proteinuria, hypertension and impaired renal function may be observed in preeclampsia. However, the presence of active urinary sediment, particularly the presence of hematic or cellular casts, supports the diagnosis of renal flare. The increase in titres of anti-DNA and decreased levels of C_3 and C_4 can support the diagnosis of renal flare, particularly if the preconception level is known. In contrast, uric acid may increase in preeclampsia, but, often, it does not alter during renal flare (Table 2).[13–16]

Another factor that has been linked to the development of lupus flare during pregnancy is the discontinuation of hydroxychloroquine. In some series it has been found that patients remain under treatment with hydroxychloroquine have lower lupus activity and require lower doses of prednisone.[17–19]

Consequently, it is necessary to know the factors that decrease the likelihood of developing lupus flare during pregnancy. First, the disease needs to have been in remission for a long period, generally a minimum of 6 months is accepted, which should be longer in situations of severe organic disease such as renal or neurological. Second, treatment with hydroxychloroquine should be maintained throughout pregnancy and should be initiated if the patient diagnosed with SLE was not receiving it. Finally, patients should be closely controlled in order to detect early any alterations that could alter the course of gestation.[20]

Another aspect to consider is the complications to which foetuses of mothers with anti-Ro/anti-La antibodies are exposed. Importantly, these complications are related to the antibodies themselves and not with the underlying disease of the mother, that is, these occur in cases of when there is a maternal diagnosis of SLE, Sjögren's syndrome or other connective tissue disease as well as in asymptomatic carriers. Antibodies, as well as the rest of immunoglobulins, cross the placenta by active transport from week 16 of pregnancy and can cause neonatal lupus. Clinical manifestations include cutaneous lupus, congenital heart block (CHB), cytopenias, particularly thrombocytopenia, and liver disorders. The most common complication is neonatal cutaneous lupus, which