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Management of systemic lupus erythematosus in pregnancy

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ABSTRACT

Systemic lupus erythematosus is one of the most common autoimmune disorders affecting young women. Pregnant women with lupus are generally at higher risk for certain pregnancy complications than women without comorbidities. Even so, a pregnancy with lupus can be carried to term in optimal conditions if it is properly managed by a doctor. Monitoring is generally recommended six months after the onset of lupus symptoms, and ideally there should be no active lupus symptoms prior to conception. General screening tests should include the anti-phospholipid, anti-Ro and anti-La antibodies. Women who are positive for these antibodies have an increased risk of congenital heart block in the fetus. In addition, pregnant women with lupus have an increased risk of spontaneous abortion, intrauterine fetal growth restriction, pre-term birth, while neonatal lupus syndrome is a major fetal condition. The maternal risks are faced with disease flares, pre-eclampsia and other complications. Treatment options during pregnancy are limited to a few safe medications. For example, prednisone is unlikely to cause fetal malformations, but it increases the risk of diabetes and high blood pressure in the mother. Consequently, a careful multidisciplinary monitoring is essential for optimal results in pregnancy with lupus.

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Introduction

Systemic lupus erythematosus is a chronic autoimmune disease of unknown cause that can affect all organs. It is characterized by a vast heterogeneity of clinical manifestations and immunological abnormalities that it presents. Most frequently, patients with systemic lupus erythematosus have increased levels of antinuclear antibodies (ANA), anti-double-stranded DNA antibodies (anti-dsDNA) and anti-Smith antibodies (anti-Sm) [1].

Due to the heterogeneity of clinical manifestations the diagnosis of systemic lupus erythematosus (SLE) is difficult, often being one of exclusion. For this reason, classification criteria were developed and they guide the physician towards the diagnosis of systemic lupus erythematosus [2].

In 2012, the SLICC classification criteria were developed. In order to formulate the diagnosis, we must have at least four criteria; mandatory a clinical criterion and an immunological criterion or a histopathological examination with a diagnosis of lupus nephritis [3,4].

The clinical criteria include acute skin manifestation (except the discoid lesions), chronic skin lesions, which can be associated with other autoimmune diseases, the most common being an overlap syndrome with lichen planus [3-5]. Alopecia is another criterion included. It is characterized by fragility of the hair, breaking easily not far from the emergence point; it is important to exclude alopecia areata (this is frequently associated with celiac disease) or iron depletion. Nasal or oral lesions with the appearance of ulcers constitute another criterion. Joint damage which is frequently the first sign of the disease, represent other clinical diagnostic criteria. Patients can have central or peripheral neurological symptoms, the clinical manifestations including: cranial neuropathy, myelitis, psychosis, depression, seizures, encephalitis. In the absence of uremia, serositis represents classification criteria - pleurisy or pericarditis that last for at least 24

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hours. Hemolytic anemia, leukopenia (less than 4000/mm^3 or lymphocytes less than 1000/mm^3), as well as platelets less than 100,000/mm^3 that is another criterion for the severity of the disease [3,4].

The immunological criteria are: increase above the laboratory reference value of anti-nuclear antibodies (ANA), more than two-times increase in anti-double-stranded DNA antibodies level, presence of anti-Smith antibodies, positive Coombs test, in the absence of hemolytic anemia, decrease of complement components: C3, C4, CH50 or the presence of antiphospholipid syndrome components [3,6].

Discussion

The literature search was conducted in several international databases (PubMed, Scopus, Clarivate, etc.) using the following terms: systemic lupus erythematosus, preeclampsia in lupus, lupus nephritis and immunological outcome. No date restriction was applied. Language was restricted to English, French and Spanish. Additional studies from the reference list of the articles were searched.

Generally, the fertility is not affected by systemic lupus erythematosus, but the specific treatment of the disease affects it, especially the treatment with Cyclophosphamide. Patients with systemic lupus erythematosus have a high maternal risk, the best prognosis for pregnancy is after the patient achieves remission and maintains it for six months. Active disease is a bad prognostic factor for both the mother and the fetus [6-8].

An observational study led by Buyon that included 385 patients with systemic lupus erythematosus with disease in remission or mild-moderate forms of active disease discovered 81 pregnant women (21.04%) without obstetric risk. After controlling the risk factors (for example hypertension, thrombocytopenia, flares or moderately active disease), the risk of developing obstetric complications among the Caucasian population decreased from 79% to 8%. This study did not include patients with severe systemic lupus erythematosus, active lupus nephritis, uncontrolled hypertension or diabetes [9].

A study by Clowse et al. that included 267 patients with systemic lupus erythematosus found that patients with active disease have a higher risk of abortion, compared to patients with the mild form. However, there were no statistically significant differences regarding the number of live births between the two forms (77% versus 88%) [6].

Before conception, it is important for the rheumatologist to assess the remission status of the disease, target organ damage, and hypercoagulability status. The obstetrician must discover the events that may indicate a high-risk pregnancy, for example the antecedents of small for gestational age, preeclampsia, stillbirth, abortion and prematurity. For patients with lupus nephritis, the active form, it is recommended to be in remission for at least six months before conception. Other risk factors that must be evaluated are episodes of recent transient ischemic vascular accidents, cardiac syndromes, pulmonary hypertension, diffuse interstitial pneumopathy - either due to the disease, or due to fibrosis caused by methotrexate treatment, renal failure, etc. [10,11]. Antibodies against Ro/SSA and antibodies against La/SSB must be evaluated, because they cause neonatal lupus [10].

In addition to the tests recommended for all patients who want to get pregnant, in patients with systemic lupus erythematosus it is necessary to evaluate their liver and kidney functions (transaminases, bilirubin, urea, serum creatinine, albumin/creatinine ratio, urine summary and urinary sediment). Disease-specific investigations are also mandatory: anti-Ro antibodies, anti-La antibodies, anti-double-stranded DNA antibodies, lupus anticoagulant, anti-beta2-glycoprotein I antibodies (both IgG and IgM), anticardiolipin antibodies (IgG and IgM) and complement (CH50 fractions, C3, C4) (Figure 1) [11].

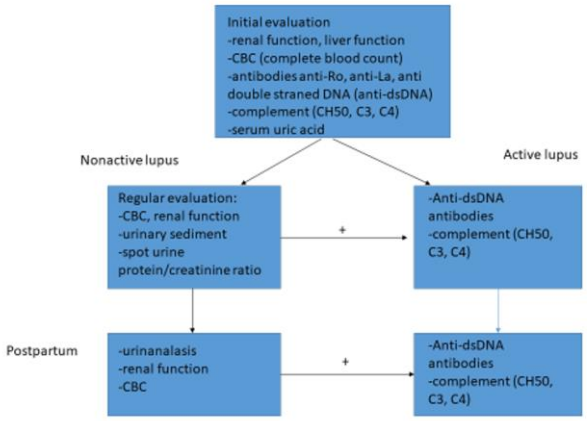

Figure 1. Evaluation protocol of pregnant women with systemic lupus erythematosus

During the pregnancy, the exacerbation of lupus is frequent with the appearance of flares. The frequency is 25-60%, depending on the geographical area and the race [8,11-13]. Risk factors for flares are represented by active disease less than six months [6], history of lupus nephritis [12-14], lack of treatment with hydroxychloroquine, primiparity [15-17], the presence of antiphospholipid antibodies and thrombocytopenia [9,18].

Another study led by Clowse et al. that included 13,555 patients with systemic lupus erythematosus concluded that they have a two to four times greater risk of developing preeclampsia, eclampsia, premature birth, intrauterine growth restriction, thrombosis, thrombocytopenia and infection [19]. Mortality is twenty times higher compared to the mortality of patients without lupus, but if the compared groups are pregnant and non-pregnant patients with systemic lupus erythematosus, the mortality in the first group was lower than in the second group [19].

A study by Yasmeen et al. analyzed the risk of hypertension associated with pregnancy, postpartum

hemorrhage, deep vein thrombosis and prematurity. The patients included in this study had a higher risk, compared to the general population of developing such complications [20].

Preeclampsia is one of the most common maternal complications that can occur. Its frequency is 16-30%, compared to 4.6% among the population without lupus [8, 21-23]. This most frequently occurs in patients with a history of lupus nephritis, the decrease in complement values as a result of its consumption and thrombocytopenia [21,24].

Prematurity is a very frequent neonatal complication, occurring between 15-50% of pregnancies, compared to 12% among the general population [16]. It is most frequently associated with lupus nephritis.

Patients with active lupus nephritis have an increased risk of abortion, especially if they also have antiphospholipid syndrome. The risk of intrauterine growth restriction is 10-30%, with higher values in patients with arterial hypertension, active systemic lupus erythematosus, lupus nephritis [20].

Neonatal lupus is more common in children from mothers with anti-Ro or anti-La antibodies. The most frequent manifestations among newborns are lupus skin eruptions and atrioventricular conduction disorders (atrioventricular blocks or bundle branch blocks). In addition to SLE, patients with Sjögren's syndrome have anti-Ro antibodies and anti-La antibodies in their serum, so newborns can show clinical manifestations of lupus [25].

During pregnancy, patients with lupus nephritis must be carefully evaluated. An observational study led by Gladman that included 104 patients with systemic lupus erythematosus, of which 81 had kidney disease, concluded that the frequency of small for age is very high [15]. A retrospective study by Saavedra et al. included 95 pregnancies with history of lupus nephritis, concluded that the risk of complications is 88%, versus 43% among patients without kidney disease. Also, the risk of flares was 54% versus 25%. Episodes of nephritis reactivation responded well to high-dose glucocorticoid therapy [16]. Patients with antiphospholipid syndrome must receive a personalized evaluation (see Table 1) [26].

The first visit to the specialist must include a general clinical exam, including blood pressure measurement, evaluation of renal and hepatic function, immunological evaluation: anti-Ro antibodies, anti-La antibodies, lupus anticoagulant, anticardiolipin antibodies, anti-double-stranded DNA antibodies, CH50, C3, C4 [27].

Maternal-fetal monitoring includes, in addition to routine monitoring, first-trimester ultrasound to accurately determine gestational age and probable date of birth. At 18 weeks, it is mandatory to evaluate the fetal anatomy, including cardiac evaluation to determine if there is a heart conduction disorder. In the third trimester, patients must undergo an ultrasound evaluation to determine if there is small for gestational age, intrauterine growth restriction or placental failure. The evaluation is performed at every four weeks if the pregnant woman does not have any of the listed complications. Evaluation by nonstress test or biophysical profile is mandatory in the last four to six weeks of pregnancy [27].

Table 1. Associated risks on patients with active disease

	Gladman	Webster	Saavedra
Study type	observational	retrospective	retrospective
No. patients	193	90	95
Renal active disease	81	47	35
Risk of premature birth	p>0.05	P=0.002	-
Maternal complications	High risk	P<=0.001	P=0.00001
Relapse	High risk	P=0.004	-
Fetal outcome	P>0.05	p>0.05	P=0.031 calculated risk for stillbirth

Preeclampsia is a frequent pathology associated with pregnancy, especially among patients with systemic lupus erythematosus. After twenty weeks of amenorrhea, all patients must have their blood pressure evaluated, proteinuria determined for twenty-four hours, and target organ dysfunction evaluated. From the gestational age of 12 weeks, low-dose aspirin should be introduced to reduce the risk of preeclampsia by 2-5%. It is very important to make the differential diagnosis with lupus nephritis. In case of kidney disease, proteinuria occurs, the urinary sediment is loaded, it shows leukocytes, red blood cells and cells arranged in clusters, the complement is low, and the antibodies against double-stranded DNA are increased. The criteria favoring preeclampsia are: thrombocytopenia, increased liver enzymes and uric acid [28-30].

On the course of pregnancy, patients can receive treatment with hydroxychloroquine which reduces the risk of flares [31-33]. A study led by Levy that included 20 pregnant women observed that there were no differences regarding the frequency of flares, but observed that patients treated with hydroxychloroquine required lower doses of glucocorticoid and had lower activity scores [34]. In addition to these benefits, hydroxychloroquine decreases the risk of neonatal heart abnormalities [35-38].

Aspirin is indicated from twelve weeks of pregnancy to all pregnant women with lupus. It appears to reduce the risk of preeclampsia [39-41].

In addition to these two, we can also administer non-steroidal anti-inflammatory, in order to keep SLE under control, but with caution after 20 weeks of amenorrhea. Keep in mind that after 30 weeks of amenorrhea they are contraindicated. There is a low risk of developing

oligohydramnios. Glucocorticoids are administered in the lowest effective dose, preferably less than 10 mg/day [42-44].

Administration in the first trimester of pregnancy can be associated with cheiloschisis (cleft lip) or cheilopalatoschisis (cleft palate) [11]. Azathioprine can be administered in a maximum dose of 2 mg/kg/day. Cyclosporine is allowed in pregnancy, tacrolimus is useful in lupus nephritis [45,46]. Immunomodulatory therapy with anti-CD20 antibodies: Rituximab or with BAFF inhibitors: Belimumab is allowed in pregnancy, because these are IgG that do not cross the fetal placental barrier [11,47-49].

During pregnancy, it is contraindicated to administer cyclophosphamide. as it can cause fetal malformations. However, in severe cases, Mycophenolate mofetil, Methotrexate and Lefunomide can be administered in the third trimester. If the patient has been administered Lefunomide, treatment must be stopped and Cholestriamine must be administered [11,47-49].

Breastfeeding is encouraged after birth. Patients following therapy with hydroxychloroquine, glucocorticoid, cyclosporine, azathioprine, tacrolimus or biological therapy can breastfeed. Breastfeeding is contraindicated if the patient is undergoing treatment with methotrexate, mycophenolate mofetil, cyclophosphamide, lefunomide [50-52].

Conclusions

Patients with systemic lupus erythematosus present an increased obstetric risk; the presence of lupus nephritis represents an important risk factor for the occurrence of preeclampsia, intrauterine growth restriction.

It is important to make a differential diagnosis after 20 weeks of amenorrhea between preeclampsia and lupus nephritis. The risks of thromboembolic disease, post-partum hemorrhage and hypertension are increased in patients with systemic lupus erythematosus.

Prematurity is two to four times more common in patients with lupus, with a higher risk in the case of lupus nephritis. In addition, an overlap syndrome between preeclampsia and lupus nephritis may occur in the pregnancy.

Medication allowed during pregnancy is represented by hydroxychloroquine, corticosteroids, non-steroidal antiinflammatory drugs, azathioprine, cyclosporine, tactolimus, biological therapy. The administration of mycophenolate mofetil, lefunomide, cyclophosphamide and mohotrexate is contraindicated.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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