ABSTRACT

Introduction: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune inflammatory disease that affects several organs and systems. This disease increases the risk of gestational hypertensive syndromes, which are clinical conditions characterized
by increased blood pressure and maternal-fetal complications, including pre-eclampsia and HELLP syndrome. Case description: Twenty-four-year-old female patient, in her first pregnancy, with a diagnosis of SLE prior to pregnancy, which progressed to severe pre-eclampsia and HELLP. Discussion: Pregnant women with lupus gain greater relevance for presenting a wide variety of outcomes, from activation of the autoimmune disease, remission or even to remain unchanged throughout pregnancy. Furthermore, greater care is essential during pregnancy due to the complications that lupus can cause, such as Pre-Eclampsia and HELLP Syndrome. In short, it is certain that, when the disease is active, it can be associated with: prematurity; fetal growth restriction; preeclampsia and eclampsia; increased risk of thrombosis, infection, thrombocytopenia and postpartum hemorrhage. Conclusion: Such clinical complications show the importance of strict control of SLE, before and during pregnancy, in order to avoid complications. Considering the importance of this topic in public health, this case is extremely relevant for the education of women with SLE, in order to promote a correct therapy before and during pregnancy through prenatal care, to avoid the evolution to this very serious pathology.

Keywords: Systemic Lupus Erythematosus, pre-eclampsia, HELLP Syndrome, pregnancy.

RESUMO
Introdução: Lúpus Eritematoso Sistêmico (LES) é uma doença crônica autoimune inflamatória e que acomete diversos órgãos e sistemas. Esta doença aumenta o risco de síndromes hipertensivas gestacionais, que são quadros clínicos caracterizados por aumento da pressão arterial e complicações materno-fetais, incluindo pré-eclâmpsia e síndrome HELLP. Descrição do caso: Paciente de vinte e quatro anos de idade, do sexo feminino, em sua primeira gestação, apresentando diagnóstico de LES prévio à gravidez e que evoluiu para pré-eclâmpsia grave e HELLP. Discussão: Gestantes lúpicas ganham maior relevância por apresentarem grande variedade de desfechos, desde a ativação da doença autoimune, remissão ou até mesmo manter-se inalterado durante toda a gestação. Além disso, um cuidado maior é primordial durante a gestação devido às complicações que o Lúpus pode causar, como por exemplo, Pré-Eclâmpsia e Síndrome HELLP. Em suma, é certo que, quando a doença está em atividade, pode associar-se a: prematuridade; restrição de crescimento fetal; pré-eclâmpsia e eclâmpsia; maior risco de trombose, infecção, trombocitopenia e hemorragia pós-parto. Conclusão: Tais complicações clínicas evidenciam a importância do controle rigoroso do LES, antes e durante a gestação, de forma a evitar complicações. Considerando a importância desse tema na saúde pública, esse caso é de extrema relevância para a instrução das mulheres portadoras de LES, de modo a promover uma terapia correta antes e durante a gravidez através do pré-natal, para evitar a evolução para esta patologia tão grave.

Palavras-chave: Lúpus Eritematoso Sistêmico, pré-eclâmpsia, Síndrome HELLP, gestação.

1 INTRODUÇÃO

Systemic lupus erythematosus (SLE) is a chronic inflammatory idiopathic autoimmune disease that affects various systems. Its clinical presentation is polymorphic
and characterized by alternating periods of disease activity with remission periods.¹ The etiology of SLE is considered related to genetic, environmental, viral, and hormonal factors, along with a dysfunction of the immune system. Patients with SLE present high concentrations of antinuclear antibodies (anti-DNA, anti-Sm, anti-RNP, anti-SSA [Ro], and anti-SSB [La]).² SLE is a rare disease but is more prevalent in young women, especially those in the fourth decade of life and in the reproductive age.¹ The most common signs and symptoms of SLE are changes in the joints, skin lesions, and renal, pulmonary, neurological, and hematological alterations.³ The diagnosis is based on the 2019 criteria of the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), taking into account clinical manifestations, laboratory changes identifying possible target organ damage, and autoantibody investigation.⁴ The treatment of SLE is individualized, using drugs to regulate immunological changes (corticoid, immunomodulatory, immunobiological, and immunosuppressive drugs) and to control the complications due to the inflammation caused by SLE.⁴

Pregnant patients with SLE can have various outcomes, including activation of the autoimmune disease, remission, or the absence of changes throughout pregnancy. Pregnant patients with SLE have a higher risk for complications, including pre-eclampsia, eclampsia, and hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome. This syndrome is a nuance of pre-eclampsia, with a high rate of maternal complications, morbidity, and fetal mortality.⁵

Pre-eclampsia is defined as an increase in blood pressure associated with proteinuria after the 20th week of gestation, and may be juxtaposed to a different hypertensive state. In the absence of proteinuria, a diagnosis can be made when there is target-organ damage, through the presence of abdominal pain, blurred vision, headache, or altered laboratory tests, such as thrombocytopenia (<100,000 platelets/mm³), renal changes (creatinine >1.1 mg/dL or twice the baseline), increased hepatic enzymes (twice the baseline), pulmonary edema, and visual or cerebral disturbances, such as headache, scotomas, or seizures.⁶ After diagnosis, the treatment is aimed at the prevention of maternal and fetal complications, such as stroke, acute pulmonary edema, worsening to severe pre-eclampsia, eclampsia, HELLP syndrome, and early placental abruption.⁷

Eclampsia is defined as generalized motor seizures (grand mal type) in pregnant patients with pre-eclampsia. Such seizures may occur in the prepartum period (50%), during delivery (20%), or in the postpartum period (11–44%). These seizures have no coincidental neurological disease etiology.⁶
One of the most serious complications of pre-eclampsia, worsening the maternal prognosis, is the HELLP syndrome. This syndrome usually affects older multiparous women and is more common in white women with a history of previous obstetric complications. Perinatal mortality can reach 40%, and maternal mortality around 5%. Currently, the only definitive treatment for this complication is delivery and removal of the placenta.  

This study aimed to show the importance of awareness in women of childbearing age with SLE in the proper control of this disease before starting pregnancy to avoid its complications and assist health professionals in the diagnosis and appropriate conduct in similar cases. Pregnancy should be well planned, and a strategy and management should be addressed in a consultation with an obstetrician before conception.

2 CASE DESCRIPTION

In May 2020, a 24-year-old primigravida female patient diagnosed prior to pregnancy with SLE and lupus nephritis sought treatment with a rheumatologist. She was 5 weeks pregnant when she reported having been treated with corticosteroid pulse therapy (methylprednisolone) combined with monthly cyclophosphamide for a total of two cycles. Subsequently, she maintained the chronic use of azathioprine, as there had been a good clinical response with a previous intravenous treatment. In the first consultation with a rheumatologist in the present pregnancy, in addition to azathioprine, she was using hydroxychloroquine, prednisone, and losartan. At that visit, the following laboratory tests were requested and had the following results: creatinine, 1.6 mg/dL (reference value for severe pre-eclampsia: ≥ 1.2 mg/dL); urea, 62 mg/dL (reference value: 15–36 mg/dL); C3 complement fraction, 57 mg/dL (reference value: 90–180 mg/dL); and C4 fraction, 16 mg/dL (reference value: 20–50 mg/dL). Anti-DNA was reagent, with a titer of 1/40, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were normal, and changes in creatinine and urea were identified.

In discussion with the obstetrics clinic, renal lupus activity was considered, and the patient was hospitalized for pulse therapy with methylprednisolone 1 g/day for 3 days. Additionally, losartan was suspended, and acetylsalicylic acid (ASA) 100 mg/day was introduced to prevent complications during pregnancy. After 3 days, the patient presented clinical improvement and was discharged from the hospital. She was then followed on an outpatient basis by a rheumatologist, with gradual weaning from corticosteroids and maintenance of azathioprine and hydroxychloroquine. In July 2020, she remained without
complaints, with good control of blood pressure levels and improvement of renal parameters and lupus activity.

Throughout the pregnancy, the patient maintained the follow-up with a rheumatologist but she could not have proper prenatal care with an obstetrician, claiming loss of health insurance. She also deliberately suspended the use of ASA, which is a medication well known for preventing the progression of pre-eclampsia. In October 2020, at 30 weeks and 1 day of pregnancy, she sought an emergency consultation at a maternity hospital, presenting intense lower abdominal pain, malaise, blurred vision, flickering scotomas, nausea, and vomiting. During the clinical investigation in that hospital, a hypertensive peak of 220/120 mmHg and facial edema were observed. Fetal heartbeat was present and within normal range, as observed by auscultation performed with a Doppler sonar. Given the severity of this clinical situation, the patient was immediately hospitalized with an initial diagnostic hypothesis of severe preeclampsia, to be investigated with laboratory tests, continuous cardiovascular and blood pressure monitoring, indwelling bladder catheterization, and intensive treatment to try to reverse the clinical picture and avoid eclampsia and its complications.

To prevent the case from progressing, the patient received four intravenous 5-mL doses of hydralazine (the maximum dose to control the hypertensive crisis), with partial improvement. She also received an initial dose of 10% magnesium sulfate to prevent eclampsia that improved the symptoms, except for the blood pressure, which remained at 170/100 mmHg. The patient was then immediately referred to a high-risk maternity hospital. Laboratory tests revealed acute renal failure (with creatinine at 3.31 mg/dL, 24-h proteinuria of 2,973 mg in a volume of 1800 mL, urinalysis with the presence of proteins and granular and hyaline cylinders, and albumin at 2.6 g/L). HELLP syndrome was also investigated with other tests, including ALT at 479 U/L (reference value: 8–35 U/L), AST at 600 U/L (reference value for HELLP: ≥ 70 U/L), lactate dehydrogenase (LDH) at 878 U/L (reference value for HELLP: ≥ 600 U/L), total bilirubin at 1.1 mg/dL (reference value for HELLP: > 1.2 mg/dL), direct bilirubin at 0.3 mg/dL (reference value: ≤ 0.4 mg/dL), indirect bilirubin 0.8 mg/dL (reference value: 0.1–1.0 mg/dL), International Standardized Ratio of 1.12 seconds, prothrombin time of 14.8 s (reference value: 10–14 s), activated partial thromboplastin time of 29.5 s (reference value: 28–40 s), and platelets at 90,000/mm³, with the reference value for HELLP syndrome being < 100,000/mm³ of blood, evidencing thrombocytopenia. The patient did not receive maintenance doses of magnesium sulfate after the initial dose due to the presence of anuria and impaired renal
function, which ruled out the possibility of adequate renal filtration of the medication, putting the patient at risk for magnesium toxicity and its complications (cardiac arrhythmia and cardiorespiratory arrest). On that same day, the patient was transferred to the intensive care unit (ICU) of a maternity hospital.

After delivery, the patient progressed with no new complaints and had the following test results: hemoglobin 10.3 g/dL, hematocrit 31%, total leukocytes 10500/mm³, platelets 150000/mm³, creatinine 4.14 mg/dL, AST 59 U/L, ALT 75 U/L, and urea 170 mg/dL. A clinical and laboratory improvement of the obstetric condition was evidenced, but the changes in renal function persisted. Therefore, a reactivation of the renal manifestations caused by the rheumatologic disease was diagnosed, and immunosuppression with corticosteroid pulse therapy and cyclophosphamide was initiated, as the newborn was not being breastfed.

Approved by the Research Ethics Committee of the Centro Universitário de Santa Fé do Sul (UNIFUNEC) under opinion number 50124721.6.0000.5428.

3 DISCUSSION

SLE is a multisystemic disease, which becomes more relevant in pregnant women because various outcomes is observed, including the activation of the autoimmune disease, remission, or the absence of changes throughout pregnancy. A study carried out in lupus pregnant women at the University Clinics Hospital of the Federal University of Paraná, in Brazil, showed that pregnant patients with SLE who presented maternal and fetal complications had at least one of the following factors in their history: history of severe SLE, history of previous obstetric complications, disease activity before conception, disease activity during pregnancy, hypertension, and the presence of antiphospholipid antibodies or antiphospholipid syndrome. Furthermore, greater care should be taken during pregnancy due to the potential complications of SLE, such as pre-eclampsia and HELLP syndrome, which occurred in this report. In Brazil, pre-eclampsia is the leading cause of maternal death, especially in its severe forms, such as eclampsia and HELLP syndrome, and it occurs in approximately 5–8% of the general population of pregnant women. However, that incidence is increased to 13–35% in pregnant lupus patients.

As for the clinical manifestations that SLE complications may cause, it has been observed that pre-eclampsia is a pregnancy-specific syndrome, characterized by recent-onset hypertension, mostly with proteinuria, in previously normotensive women after 20
weeks of pregnancy. Notably, the clinical picture of pre-eclampsia may various signs and symptoms, including pain in the right upper quadrant of the abdomen, headache, blurred vision, and edema. In addition, pre-eclampsia has an irreversible nature that affects multiple organs and is responsible for a considerable proportion of maternal and perinatal deaths; it can cause premature labor and accounts for 20% of all admissions to neonatal ICUs. It can safely be said that some identifiable risk factors for pre-eclampsia are related to Sub-Saharan African ethnicity, patients who are very young or in the late reproductive age, with multifetal pregnancies, nulliparity, chronic hypertension, diabetes mellitus, connective tissue diseases, and a history of antiphospholipid antibody syndrome. On the other hand, the risk of preeclampsia in patients with SLE is correlated to the use of prednisone, lupus nephritis, and the presence of antiphospholipid antibodies.

Eclampsia, on the other hand, is defined by seizures associated with the same criteria for pre-eclampsia. Therefore, differential diagnoses with epilepsy and other seizure disorders must be made regardless of these criteria. The management of eclampsia and pre-eclampsia cases includes the prevention of seizures, blood pressure control, cardiovascular, renal, and electrolyte status stabilization, and induction of labor. In the present report, the anticipation of labor and prematurity were the obstetric outcomes.

HELLP syndrome occurs when a patient with preeclampsia or eclampsia suffers a worsening of the disease, progressing to hemolysis, thrombocytopenia, and increased liver enzymes. HELLP syndrome is characterized by reports of epigastric pain in the right upper quadrant, malaise, and nausea. These symptoms and signs are similar to those in the case described herein, which also presented elevated LDH levels and severe anemia, with hematocrit <25%, which is common in this syndrome.

The laboratory screening to confirm the diagnosis in pregnant women with suspected HELLP syndrome should include a complete blood count with platelet count, serum creatinine, LDH, urinalysis, uric acid, bilirubin, and aminotransferases. If the platelet count is <100,000/mm³, prothrombin time, partial thromboplastin time, and fibrinogen tests must be added. The association of HELLP syndrome to the diagnosis of pre-eclampsia or eclampsia increases maternal and neonatal morbidity and mortality.

As for the safest drugs in SLE therapy during pregnancy, hydroxychloroquine and glucocorticoids (such as prednisone) stand out, even in patients presenting with a remission of the disease, as these drugs may be protective against pre-eclampsia and
Hydroxychloroquine may reduce thrombosis due to antiphospholipid antibodies, and it does not appear to be associated with an increased risk of birth defects, miscarriages, fetal death, prematurity, or decreased live births in individuals with autoimmune diseases; therefore, it is safe for the treatment of pregnant women. As for lupus nephritis, the best method of control during pregnancy is achieved with azathioprine. Discontinuation of these drugs is contraindicated and may increase the risk of lupus exacerbations and gestational problems.

Blood pressure control should be rigorous and can be done with nifedipine, methyldopa, and labetalol in pregnant women when treating hypertension. It has also been observed that low-dose ASA and calcium supplementation are recommended from the 12th week to reduce the risk of pre-eclampsia and perinatal death. Cyclophosphamide, methotrexate, and leflunomide are contraindicated because they have teratogenic effects.

In severe pre-eclampsia, eclampsia, or HELLP syndrome, the main drug used is magnesium sulfate, which is effective in preventing recurrent seizures in women with eclampsia and pre-eclampsia. Treatment was started with 4 g intravenously as an initial dose, followed by 1–2 g/h as a maintenance dose. In cases of pregnant women with renal insufficiency, it is recommended to administer half the dose and measure the serum magnesium level, which must be between 4 and 7 mEq/L. In case of anuria, it is recommended to suspend the use of magnesium sulfate for up to 2 h. Antihypertensives recommended for blood pressure >160/110 mmHg include nifedipine (10 mg orally) and hydralazine (5–10 mg intravenously). Currently, the only definitive treatment for HELLP syndrome is delivery and removal of chorionic villi because there is no specific treatment for this syndrome as little is known about its physiopathology.

It is necessary to evaluate the right time and the best route of delivery, because only then will it be possible to stop the effects of the disease. Evaluating the maternal and fetal hemodynamic profile is essential for this because the management of patients can vary from expectant to induced labor, depending on the gestational age and maternal stability. It is appropriate to induce labor in pregnancies that have reached 34 weeks, and to opt for a conservative conduct in those that have not yet reached this gestational age. The use of corticoids for fetal pulmonary maintenance must be emphasized, as this improves neonatal mortality rates in these cases, provided that conditions exist for this situation.

Prenatal consultations need to be more frequent due to the risks inherent to the disease in pregnancy, such as pre-eclampsia and HELLP syndrome. Monthly
consultations are recommended until the 20th week, biweekly consultations until the 28th week, and weekly until delivery. At each consultation, laboratory tests should be requested for routine prenatal evaluation. These tests should include a complete blood count, renal and hepatic function tests, and 24-h proteinuria, and antibody and complement protein dosages to analyze SLE activity.²

SLE exacerbations during pregnancy are associated with the activation of the disease for a minimum period of 6 months prior to conception, the presence of lupus nephritis, and discontinuation of the treatment, which may be difficult to achieve in cases with recent onset or with a recent episode of lupus nephritis.¹⁰ It is possible that longer periods than 6 months are more important for patients with renal dysfunction.¹⁷

Finally, it is evident that when the disease is poorly controlled, it can be associated with prematurity; fetal growth restriction, pre-eclampsia and eclampsia, and increased risk of thrombosis, infection, thrombocytopenia, and postpartum hemorrhage.²

4 CONCLUDING REMARKS

Pre-eclampsia and HELLP syndrome are complications that put the patient and her fetus at imminent risk of death, and this risk is greater in patients with SLE due to their compromised immune systems. Therefore, the early diagnosis and management of these conditions are important in reducing morbidity and mortality from the disease. Thus, physicians need to be aware and inform patients about the high risks of pregnancy in patients with SLE, who require adequate follow-up during prenatal care.
REFERENCES


