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PREGNANCY PLANNING AND PHARMACOTHERAPY FOR PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

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ABSTRACT

Background: SLE is an intriguing topic of research, given the severity of the disease and the impact in can have on a pregnant body is why this analysis and future research can help to better the understanding on how to improve patients' healthcare.
Aim: This narrative review analysis the current available treatment methods for patients with SLE and the risks of SLE and pregnancy.
Material and methods: A search of relevant research databases was conducted to identify eligible papers.
Results: More research needs to be conducted to improve the understanding and improve SLE treatment in pregnant patients.
Conclusions: SLE is a complex condition the variety of symptoms and risks factors in pregnancy are why new methods of treatment, improved specialist care and novel therapies are vital in its treatment.

KEYWORDS

Systemic Lupus Erythematosus (SLE), Lupus Nephritis (LN), Antiphospholipid Syndrome (APS), Pregnancy, Antiphospholipid Antibodies

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1. Introduction

Systemic lupus erythematosus (SLE) is a chronic, systemic autoimmune disease characterized by its autoantibody production and multi-organ pathophysiology (1). SLE has an estimated prevalence rate of 43.7 (15.87 to 108.92) per 100 000 persons worldwide (2), and mostly affects mostly women in their peak reproductive ages (3).

SLE is characterized by its multisystemic involvement and periods of flares or remissions, therefore vital factors of patient care include fertility, family planning, pregnancy and prenatal care. Issues arise in cases of active disease, renal failure, thrombosis and flares which can lead to pregnancy complications and consequences including but not limited to: preeclampsia, preterm birth, neonatal lupus, and fetal loss. There are several types of antibodies if present which require more extensive pregnancy monitoring (4).

Prior to conception and pregnancy patients should have medications changed or modified to avoid possible teratogenic effects or other adverse complications. Most commonly hydroxychloroquine is the recommended of treatment strategy with the addition of aspirin to prevent preeclampsia (4).

2. Aim of the article

This systematic review aimed at summarizing the most meaningful and current information on the topic of SLE in pregnancy and the treatment possibilities in this condition. The research was performed by using search phrases in PubMed.

Results

3. Pregnancy planning

Infertility appears to be more prevalent among patients with systemic lupus erythematosus (SLE) due to psychosocial and physical impacts of the disease, delayed conception, medication, side effects, and other related factors (5). In a study evaluating 136 infertile women, 1.5% were found to have previously undiagnosed SLE (6).

Over the last couple of decades healthcare for pregnant patients with SLE has gotten better. Miscarriage rates have dropped from 43% in the 1960s to 17% between 2000 and 2003. Even though pregnancy outcomes have improved, the risk of complications, such as pregnancy loss, is still higher than average (7). Nevertheless, this progress is due to preconception counseling, planned pregnancies, and better risk assessment for women with SLE or antiphospholipid syndrome (APS), as outlined by EULAR in 2017, which provides guidance on when to exercise caution or advise against pregnancy in SLE (8).

During preconception counseling, clinicians should evaluate multiple disease-related factors to assess the chance of complications for women with systemic lupus erythematosus (SLE). Higher disease activity at conception or within the preceding 6 to 12 months, as well as serological markers such as decreased C3 and C4 levels or high anti-double-stranded DNA (anti-dsDNA) titers, can increase the risk of pregnancy complications. Extra attention is needed for patients with lupus nephritis (LN), anti-Ro/SSA or anti-La/SSB antibodies, and those with antiphospholipid antibodies (aPL) or SLE-related antiphospholipid syndrome (APS), since these groups are more likely to have complications during pregnancy and after delivery (8-11).

Lupus nephritis is a serious presentation of SLE and remains an important concern during pregnancy. It increases the likelihood of disease flare, worsening kidney function, increasing the risk of hypertension, and preeclampsia. To reduce these risks, it is best to plan a pregnancy when the disease is in remission. Systematic monitoring of blood pressure and kidney function is important, and treatment should use medications known to be safe in pregnancy, like glucocorticoids and some immunosuppressants. Having a team of specialists helps ensure the best results for both mother and baby (12-14).

Anti-Ro/SSA and anti-La/SSB antibodies are linked to neonatal lupus as a result of transplacental passage of these autoantibodies from mother to fetus. This condition affects about 1–2% of babies born to mothers with these antibodies (15).

Although preventative approaches are still being studied, hydroxychloroquine (HCQ) use during pregnancy has been linked to a lower risk of recurrent neonatal lupus in high-risk patients (16).

Antiphospholipid syndrome (APS) significantly increases the risk of pregnancy complications in women with SLE, including recurrent miscarriage, fetal loss, preterm birth, placental insufficiency, preeclampsia, and thrombosis. The highest risk is seen in patients with lupus anticoagulant or multiple positive aPL tests. Counseling involves finding high-risk patients before conception and providing guidance during pregnancy. Standard treatment often consists of low-dose aspirin, sometimes with low-molecular-weight heparin for

women who have had pregnancy loss or have high-risk aPL profiles. Also, HCQ may help by reducing placental damage (17-20).

Counseling should additionally include general maternal risk factors such as older age, hypertension, diabetes, obesity, smoking, alcohol use, and thyroid disease. These factors should be assessed together with SLE-related risks (8).

4. During pregnancy

Pregnancy in patients with systemic lupus erythematosus (SLE) requires highly specialized, multidisciplinary medical care involving collaboration among specialists from various fields, particularly a rheumatologist and an experienced obstetrician, and in selected cases, a nephrologist, a cardiologist, and other specialists as well. It has been shown that a planned pregnancy, occurring during a period of disease remission or low disease activity and managed with therapies that have a documented safety profile for the fetus, is associated with a significantly lower risk of obstetric complications and adverse pregnancy outcomes compared to pregnancy occurring during a period of active disease or while taking potentially teratogenic medications. The most important modifiable risk factors for obstetric complications in patients with SLE include high disease activity, lupus nephritis, and the presence of antiphospholipid antibodies. Proper preparation for pregnancy, adequate control of disease activity, and close collaboration between the patient and the healthcare team can significantly reduce the risk of maternal and fetal complications (21-24).

In order to assess the current status of autoantibodies, anti-Ro (Sjögren's syndrome type A) and anti-La (Sjögren's syndrome type B) antibodies should be tested for, as they increase the risk of congenital heart block and neonatal lupus. The risk of obstetric failure is directly proportional to the anti-Ro antibody titre. Therefore, in patients with high titres of these antibodies, detailed foetal electrocardiographic monitoring is recommended from as early as 16 weeks' gestation (25).

In addition, biochemical parameters such as a complete blood count, creatinine levels, transaminase levels, a general urinalysis including an assessment of proteinuria, levels of complement components C3 and C4, and anti-dsDNA antibodies should be monitored. Regular measurements of the mother's blood pressure and an assessment of foetal well-being are also recommended (26).

Scientific studies confirm that the risk of SLE flares increases during pregnancy and for three months after childbirth. It appears that the use of hydroxychloroquine reduces the risk of flares both during pregnancy and in the post-pregnancy period (27). The protective effect of HCQ has been establishment in terms of organ damage, flares, VTE, bone mass loss, and long-term survival in the general SLE population, as well as the potential to prevent disease activity in pregnant women (28).

Non-specific symptoms common to both of a normal pregnancy and those of systemic lupus erythematosus (SLE) include, amongst others, fatigue, mild joint pain, hair loss, shortness of breath, headaches, facial and palmar erythema, oedema, anaemia and thrombocytopenia (29).

Another major challenge for doctors is distinguishing between infection and inflammation (flare) in patients with SLE. If there is any doubt, it is recommended that intravenous immunoglobulin (IVIg) be used as first-line treatment. This will alleviate the inflammation without adversely affecting any infection that may be developing (30).

5. Pharmacotherapy

In women with SLE who are pregnant or planning to become pregnant, medications should be used at the minimum dose that is still effective and has a favorable safety track record, taking into consideration the benefit-risk ratio associated with their use (31). During pregnancy, such medicines include oral glucocorticoids, hydroxychloroquine (HCQ), azathioprine (AZA), cyclosporine (CsA) and tacrolimus (TAC). The use of oral glucocorticoids during pregnancy may be associated with a variety of side effects, including the development of hypertension in pregnancy, low birth weight relative to gestational age (SGA) and the development of gestational diabetes. At high doses, there is a risk of developing severe infections. In exceptional situations during pregnancy belimumab (BEL) and rituximab (RTX) may be used. However, they are generally discontinued due to a limited amount of data regarding their safety profile. They may be considered when the potential benefits outweigh the risks to the fetus (31-34).

Medicines used to treat SLE that are contra-indicated during pregnancy include methotrexate (MTX) and mycophenolate mofetil (MMF). They may increase the risk of miscarriage, congenital disabilities in the baby, or fetal mortality. For this reason, drugs with proven teratogenic effects should be discontinued before the pregnancy begins and replaced a few months before with drugs which are considered safe. Before

attempting to become pregnant, it is recommended that MTX be discontinued 1–3 months beforehand and that patients should follow CDC contraceptive eligibility criteria. In the case of MMF, it is recommended that patients discontinue treatment for at least 6 weeks and, as with MTX, use effective contraception during treatment and for 6 weeks after treatment has been completed (31, 32, 34).

When using leflunomide off-label for SLE, attempts to conceive should also be postponed for approximately 2 years due to its long half-life. As it is teratogenic, women should use effective contraception whilst taking it and for 2 years after treatment has ended. Its elimination can be accelerated by the use of cholestyramine or powdered medicinal carbon. Safe values for planning a pregnancy are considered to be when the plasma concentration of the leflunomide metabolite is below 0.02 mg/l. (31-34).

According to the available research and the American College of Rheumatology (ACR) and EULAR, the use of hydroxychloroquine (HCQ) is recommended. If there are no contraindications, it is recommended that patients with SLE who are planning to become pregnant or who are already pregnant continue treatment with HCQ or start taking this medicine. Studies have shown that, during pregnancy in patients with SLE, HCQ treatment reduces the activity of the disease, and its safety profile and potential beneficial effects are justified. This also applies to patients who, due to pain, are taking nonsteroidal antiinflammatory drugs (NSAIDs) or low-dose prednisone; as this suggests disease activity, it is also recommended that they start taking HCQ in such cases. In the case of an SLE activity flare-up, where treatment with glucocorticoids, AZA or HCQ has not yielded an adequate response, the use of TAC or CsA may be considered (31, 32, 35).

6. SLE complications

Obstetric complications associated with systemic lupus erythematosus affect both the mother and the baby. The most common include recurrent miscarriages, preeclampsia, intrauterine growth restriction (IUGR), preterm birth, congenital heart block, and neonatal lupus (36).

Recurrent miscarriages are common in women diagnosed with SLE. According to experts, the risk of miscarriage is increased by lupus nephropathy, decreased C3 complement levels, and the presence of antiphospholipid antibodies in the mother (37). The risk of pregnancy loss is significantly increased in unplanned pregnancies (OR 2.84; 95% CI 1.12–7.22) (38). A strong association has also been demonstrated between the presence of lupus anticoagulant in the first trimester and miscarriage. Miscarriage occurred in as many as 36% of women with confirmed lupus anticoagulant. By comparison, among women in whom the presence of lupus anticoagulant was ruled out, miscarriage occurred in only 9% of cases. Among patients with a reduced C3 complement component, pregnancy loss occurred in 16% of those studied (39).

A large meta-analysis involving 6,389 female patients with SLE showed that the risk of preeclampsia (PE) in this group of patients is significantly increased (RR = 2.99; 95% CI: 2.31–3.88; Z = 8.31; P < 0.001) compared to healthy women (40). It is estimated that more than 50,000 pregnant women worldwide die each year as a result of PE and eclampsia (41).

Fetal growth restriction and preterm birth are complications of SLE that affect not only the neonatal period but also the child's overall development. A retrospective study involving 147 pregnancies showed that preterm birth occurred more frequently in women with SLE (8.9% vs. 1.0%, p = 0.030) compared to healthy pregnant women. IUGR was also significantly more common in children born to mothers with SLE (21.4% vs. 0.0%, p < 0.001) compared to children born to healthy women (42).

Congenital heart block is a serious cardiac complication that occurs in children born to mothers with SLE. An analysis of 214 cases showed that as many as 94.4% of them were third-degree heart blocks, which underscores the risk posed by this complication (43). A significant factor in the development of heart block in a child is the presence of anti-SSA/Ro and anti-SSB/La antibodies in the mother. These antibodies belong to the IgG class and therefore cross the placenta to the fetus. In 2024, a case was reported of a newborn who was born with bradycardia at 42 beats per minute, and an echocardiogram revealed moderate mitral regurgitation and mild tricuspid and pulmonary regurgitation. High concentrations of antibodies against the SSA/Ro antigen and antibodies against the Ro52 antigen were detected in both the mother's and the newborn's blood. The parents declined to have a temporary pacemaker implanted, and the infant was pronounced dead on the second day of life (44).

7. Conclusions

SLE is a serious condition which threatens the well-being of pregnant patients especially patients with increased risk factors such as lupus nephritis (LN), anti-Ro/SSA or anti-La/SSB antibodies, and those with antiphospholipid antibodies (aPL) or SLE-related antiphospholipid syndrome (APS) (8-11).

It can be difficult to distinguish between the symptoms of a normal pregnancy and those of systemic lupus erythematosus (SLE) due to the overlap of many clinical manifestations. It is therefore essential that the patient is assessed by doctors with experience in managing pregnancies complicated by autoimmune diseases (29). Although treatment is sufficient in most cases in many cases additional medical care is needed in cases of miscarriage, preeclampisa, congenital heart block, IUGR and other aforementioned conditions (39) (41) (42, 43).

Further research into the healthcare for patients to decrease the complication rate and in turn improve treatment outcome for patients with SLE. This may be achieved through more clinal trials, new forms of therapy, improved access to specialists and increasing overall awareness on the disease progress, risks and symptoms.

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