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Review Article

From Infertility to Pregnancy: Understanding the Reproductive Risks and Care for Women with Systemic Lupus Erythematosus

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Abstract

Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease affecting multiple systems, particularly the kidneys, skin, and reproductive health. This review examines the intersection of SLE, fertility, and reproductive outcomes in women, highlighting the increased prevalence of infertility in this population. Notably, women with SLE experience significant reproductive challenges, including higher rates of pregnancy loss and complications during pregnancy, such as preeclampsia and infections. Indirect factors, such as the impact of cytotoxic medications like cyclophosphamide, along with psychological and lifestyle influences, contribute to decreased fertility and complicate family planning. Direct disease-related factors, including altered ovarian reserve and menstrual irregularities linked to SLE activity, are also explored. Additionally, antiphospholipid antibodies can play a role in fertility and pregnancy outcomes, emphasizing the need for comprehensive management strategies. Fertility preservation strategies, particularly critical for those undergoing immunosuppressive therapies, are discussed alongside the necessary monitoring and management of SLE during pregnancy and postpartum. This review underscores the importance of an interdisciplinary approach in the care of women with SLE, from preconception counseling through pregnancy and postpartum care, to optimize both maternal and fetal health outcomes.

Keywords: Systemic lupus erythematosus; Disease; Reproductive health; Pregnancy

Introduction

SLE is a chronic, multisystem autoimmune disorder characterized by widespread inflammation, primarily affecting the kidneys and leading to nephritis due to immune complex deposition in the glomerular tissue. It also impacts the skin, joints, brain, lungs, and blood vessels, making it a multisystem inflammatory condition. The disease varies greatly in its clinical presentation, from mild skin and mucous membrane symptoms to severe systemic involvement, including significant Central Nervous System (CNS) manifestations [1-3]. The exact cause of SLE remains unclear, but it is understood to result from a combination of genetic predisposition, environmental factors, hormonal influences, and socioeconomic status. SLE is more prevalent among women, particularly those of African American descent, and tends to affect younger individuals, though it can also occur in those over 50, with 20% of cases reported in this age group [4,5]. SLE is known for its fluctuating course, with periods of remission and relapse. Diagnosis involves both laboratory and clinical assessments, with management focusing on treating specific symptoms and preventing disease exacerbation through lifestyle measures such as using sunscreen, maintaining a healthy diet, exercising regularly, avoiding smoking, and using immunosuppressive and anti-inflammatory medications [6,7].

Endometriosis is another chronic inflammatory condition, characterized by the presence of endometrial tissue outside the uterine lining. It remains one of the most enigmatic conditions in gynecology due to its unclear etiology and affects approximately 5% to 10% of women, being a leading cause of gynecological hospitalizations. Symptoms include severe pelvic pain, particularly during menstruation and sexual intercourse, as well as back pain and nausea. Infertility is also a frequent complication, with a study showing 41% of affected individuals experiencing infertility and 99% reporting pelvic pain [8-10]. Diagnosis is confirmed through laparoscopy, and treatment options include pain management for ovulatory discomfort and

surgery, which has been shown to improve pregnancy rates and is preferred for treating infertility. Notably, the incidence of endometriosis is higher in patients with SLE, with those affected experiencing more frequent and severe lupus flares. The significant overlap between autoimmune diseases highlights the need for physicians to be vigilant about the potential for coexisting conditions that could further impact patients' quality of life [11-14].

Fertility in women with SLE

It appears that infertility might be more prevalent among women with SLE than previously thought. A study involving 136 women facing infertility issues found that 1.5% were diagnosed with SLE, a condition previously unidentified in them. Generally, women with SLE tend to have fewer children compared to their healthy counterparts, which could be attributed to their increased risk of experiencing pregnancy losses [15-18]. Despite improvements in the outcomes of pregnancies in women with SLE in recent years, there remains a significant risk of complications, including higher rates of pregnancy loss. A meta-analysis reviewing pregnancy studies from 2017 to 2019 highlighted that women with SLE faced a substantially higher risk of stillbirth (with a risk ratio of 16.49) and fetal loss (with a risk ratio of 7.55) [19]. This challenges the longstanding belief that women with SLE do not encounter difficulties in conceiving. The emerging evidence suggests that having SLE might indeed influence a woman's fertility and her ability to have a larger family.

Indirect factor

Factors indirectly leading to infertility or reduced fertility in women with SLE include the use of cytotoxic drugs and other medications, aging, and the psychological impact of the disease. Monthly treatments with Cyclophosphamide (CYC) can lead to Premature Ovarian Failure (POF) by killing the rapidly dividing granulosa cells in the follicles [20,21]. POF is characterized by early onset of amenorrhea for at least four months, low estrogen levels, and consistently high gonadotropin levels in women under 40 years old. The term primary ovarian insufficiency is now preferred over POF, as it more accurately reflects cases where the ovaries may still produce hormones and ovulate [22-24]. Recent systematic reviews and meta-analyses have identified CYC treatment and the total dosage as the most significant factors predicting POF in women with SLE; those receiving higher doses of CYC are at double the risk of developing POF compared to those on lower doses. However, using Gonadotropin-Releasing Hormone agonist (GnRH-a) therapy alongside standard monthly CYC treatments can lower the risk of POF [25-30]. Genetic factors may also play a role, as studies have shown that the CYP2C19*2 allele may offer protection against POF in women with lupus nephritis treated with CYC. The EURO-lupus CYC protocol, which involves lower doses, does not seem to affect ovarian reserve as indicated by Anti-Müllerian Hormone (AMH) levels [31-33].

With the introduction of Mycophenolate Mofetil (MMF), a less harmful alternative to CYC, its use has decreased, although CYC remains the go-to treatment for severe cases of SLE. Clinical studies comparing CYC with other immunosuppressants have shown that CYC is uniquely associated with menstrual irregularities and ovarian insufficiency [34-38]. In a study of 216 SLE patients treated with CYC, MMF, Azathioprine (AZA), or calcineurin inhibitors, those treated with CYC had lower serum AMH levels compared to those not treated with CYC, while AMH levels in patients treated with MMF, AZA, or calcineurin inhibitors were similar to those in untreated SLE patients [39-42].

Other commonly used medications in SLE treatment may also temporarily affect fertility through different mechanisms. Regular use of non-steroidal anti-inflammatory drugs can lead to infertility by causing luteinized unruptured follicle syndrome, which prevents ovulation. Additionally, high doses of corticosteroids may cause menstrual irregularities by disrupting the hypothalamic-pituitary-ovarian axis [43-45].

As women age, their ovarian reserve decreases, making it more challenging to conceive. Women diagnosed with SLE during their prime reproductive years are often recommended to postpone pregnancy until their disease stabilizes. The physical and emotional toll of living with SLE can also affect psychological health. Compared to healthy individuals, SLE patients often report lower self-esteem and higher instances of depression [46-48]. Reduced sexual desire and the physical constraints imposed by the disease can lead to less frequent sexual activity, which may indirectly lower the chances of becoming pregnant. Additionally, concerns about one's health and the potential health of future children can influence family planning decisions, potentially leading to smaller family sizes [49-52].

There are also factors that might impact ovarian reserve in the general population, though their effects on women with SLE have not been specifically studied. These include low levels of vitamin D and antioxidants, as well as being at either extreme of the Body Mass Index (BMI) spectrum. In the general population, low serum vitamin D is linked to lower AMH levels, and women with SLE typically have lower vitamin D levels than healthy individuals [53-56]. SLE is associated with increased production of free radicals and oxidative stress, which are believed to play a significant role in infertility. Although there is limited evidence that antioxidant supplements improve fertility outcomes, they are often recommended. Being underweight or overweight is known to increase infertility risk, and while the link between SLE and obesity is not well-established, both conditions could potentially raise infertility risks. It remains unclear whether dietary supplements or achieving an optimal BMI can enhance fertility, including for women with SLE [57-59].

Direct disease-related factors

Ovarian reserve

The relationship between AMH and Antral Follicle Count (AFC) levels and SLE in patients not treated with CYC remains uncertain, including whether these fertility markers correlate with the activity of SLE or other disease-specific factors. Research indicates that women with SLE may experience reduced fertility (lower AMH levels) regardless of exposure to gonadotoxic treatments [60-62]. A study comparing 33 premenopausal SLE patients with mild disease and no CYC treatment to 33 healthy individuals of the same age showed that the SLE group had lower AMH levels, with no link found between AMH levels, disease duration, or activity as measured by the SLE Disease Activity Index (SLEDAI) [63-65]. Another study involving 40 childbearing-aged women with SLE, who had not used immunosuppressive medication previously, demonstrated lower average AMH levels compared to healthy controls, with an inverse relationship between AMH levels and SLEDAI scores [66-68]. Additionally, SLE patients with regular menstrual cycles had notably higher AMH levels than those with irregular cycles or abnormal bleeding. A study focusing on 68 African-American women with SLE, who had never been treated with CYC, found they were 1.5 times more likely to have AMH levels below the 25th percentile compared to women without SLE, even after adjusting for factors like BMI and hormonal contraceptive use [69].

A study assessing ovarian reserve through transvaginal ultrasound in 20 SLE patients not treated with CYC and 20 healthy controls of the same age found that the SLE patients had lower Ovarian Volume (OV) and AFC, along with a higher rate of menstrual irregularity [70]. However, the findings in the literature are mixed. A cross-sectional study of 86 SLE patients and 44 healthy individuals, which only included SLE patients with regular menstrual cycles, found no significant difference in AMH levels [71]. While AMH levels were lower in SLE patients with major organ involvement compared to healthy controls, the difference was not statistically significant. SLE patients with mild disease and healthy individuals had similar AMH levels [72,73]. Another study comparing 40 SLE patients to 40 healthy controls found no difference in AMH levels, nor a correlation with disease duration, BMI, disease activity measured by SLEDAI, or damage measured by the Systemic Lupus International Collaborating Clinics/ American College of Rheumatology Damage Index [74]. No link was found between AMH levels and ethnicity, non-CYC immunosuppressive medication use, CYC use, or current smoking status, despite these being considered risk factors for subfertility [75-77].

Abnormal uterine bleeding

Abnormal uterine bleeding in terms of amount, duration, or frequency is more common in women with SLE, especially those undergoing CYC treatment, who are at a higher risk for experiencing irregular or diminished uterine bleeding. Although it's challenging to directly link irregular uterine bleeding to the ovarian reserve, alterations in menstrual cycles can affect the timing and probability of conception [78,79]. Women with SLE tend to experience more menstrual irregularities, particularly prolonged absence of menstruation. A study comparing 61 SLE patients with 120 healthy individuals found that menstrual disorders were three times more prevalent in the SLE group (49.2%) compared to the healthy group (16.7%), especially in those over 30 years of age and those treated with CYC [80,81].

It's difficult to definitively prove that SLE activity alone causes menstrual irregularities due to the concurrent high disease activity and the use of medications like corticosteroids and cytotoxic drugs. Corticosteroids can hinder the hypothalamic-pituitary-ovarian axis, lowering luteinizing hormone and FSH levels, while cytotoxic drugs can lead to amenorrhea and ovarian failure. However, some research supports the notion that SLE activity independently affects menstrual cycles [82-84]. In a study of 94 women with SLE, 54% experienced menstrual disorders, mainly oligomenorrhea, including 15% who were not treated. There was a significant correlation between the frequency of menstrual disorders and the SLEDAI score in patients not previously or currently treated with cytotoxic or high-dose corticosteroid therapy [85,86]. Lower progesterone levels and increased prolactin were also linked to higher SLEDAI scores in untreated patients, suggesting a potential independent impact of SLE on ovarian function. Another study involving 36 untreated SLE patients found that 53% had menstrual irregularities, with a significant association between SLEDAI scores and the presence of menstrual irregularities [87,88].

Limited evidence suggests an autoimmune cause for POF in some cases within the general population, with autoimmune oophoritis leading to ovarian damage and subsequent POF. Similar to other autoimmune endocrinopathies, the presence of antibodies against steroid-producing cells and infiltration of CD4+ and CD8+ T lymphocytes in oophoritis have been observed. While the link between SLE and this condition requires further study, one investigation found a correlation between amenorrhea, the presence of anticorpus luteum antibodies, and elevated FSH levels in SLE patients [89,90].

Antiphospholipid antibodies

Antiphospholipid Syndrome (APS) is an autoimmune disorder that can occur on its own or alongside other rheumatic conditions, often SLE. Its clinical signs include both arterial and venous thrombosis, as well as complications during pregnancy. The link between antiphospholipid antibodies (aPL) and female infertility, including the underlying mechanisms, is not well understood. aPL can be identified through either functional coagulation tests (such as Lupus Anticoagulant (LAC)) or solid phase assays (including anticardiolipin (aCL) and anti-β2 glycoprotein

I (anti-β2GPI)). Known pregnancy issues and negative outcomes related to aPL encompass miscarriages, fetal loss, stillbirths, preterm births, infants born small for their gestational age, and pre-eclampsia [91-94].

Although aPL is acknowledged as a contributing factor to fetal loss and other negative pregnancy outcomes, it is also believed to affect fertility by interfering with fertilization and implantation at the early stages of reproduction. The interaction of aPL with antigens may lead to the breakdown of phospholipid adhesion molecules in trophoblast elements; furthermore, aPL is thought to obstruct implantation through a direct effect on placental development and function [95,96]. Currently, there is no agreed-upon effect of aPL on general Infertility or *in vitro* Fertilization (IVF) failure rates. A recent thorough review concluded that there is insufficient evidence to warrant routine aPL testing in individuals facing infertility in the broader population, and another study did not find a link between IVF outcomes and the presence or quantity of aPL in 173 participants. As of now, the American Society for Reproductive Immunology does not advise testing for or treating aPL in women who have experienced multiple unsuccessful IVF attempts [97,98].

Strategies of fertility preservation in women with SLE

Based on the clinical guidelines provided by the American Society of Clinical Oncology and the recommendations of the International Society for Fertility Preservation, it is advised that fertility preservation should be a consideration for patients who have yet to complete their families and are facing treatments with cytotoxic therapies for cancer or other non-cancerous conditions. Consequently, the existing fertility preservation guidelines for women diagnosed with cancer are also relevant to young women with SLE who are about to undergo cytotoxic immunosuppressive treatments and are worried about the risk of infertility [99-101]. Patients should be made aware of the potential for premature ovarian failure due to cytotoxic treatment at the first consultation, followed by a discussion on the most suitable fertility preservation method available to them. Presently, the freezing of embryos and oocytes is recognized as the standard methods for fertility preservation in line with the latest guidelines from the American Society for Reproductive Medicine, Society for Assisted Reproductive Technology, and the American Society of Clinical Oncology. Other techniques, such as ovarian tissue freezing, the simultaneous use of gonadotropin-releasing hormone agonist with chemotherapy, and IVM, are still considered to be in the experimental stage [102-104].

Finally, it is crucial to discuss fertility preservation methods with patients, especially if they are experiencing:

- Active disease and/or complications like nephritis and vasculitis that require treatment with cyclophosphamide;
- Advanced age (over 33-35 years);
- Reduced ovarian reserve;
- Increased risk of disease flare-up;
- Incomplete family planning, even if the disease is currently in remission, as future flare-ups or complications could urgently necessitate the use of cyclophosphamide.

Pregnancy

Numerous studies have shown that pregnant women with SLE face higher risks. An analysis of 13,555 birth records in the United States over a three-year period revealed that women with SLE are more likely to experience infections, blood clotting events, early labor, and preeclampsia. Those with active SLE at the time of conception, particularly those with nephritis or lupus anticoagulants, are at an even higher risk of adverse pregnancy outcomes, including high blood pressure, ongoing or worsening kidney inflammation, and premature delivery [105,106]. Additionally, pregnant women with SLE who have organ involvement, such as pulmonary hypertension or heart disease, face a risk of severe and progressive organ damage. Given the potential for serious complications like preeclampsia, early labor, nephritis, and neonatal lupus, it is recommended that women with active kidney, heart, or lung issues related to SLE wait to conceive until their condition is under control [107-109].

Medications during pregnancy

Along with standard prenatal vitamins, certain medications for lupus are advised for pregnant women. It is recommended that women who have previously responded well to hydroxychloroquine continue with this medication during pregnancy, as it has been shown to lower the chances of experiencing lupus flares and prevent neonatal lupus. Research on hydroxychloroquine use in pregnant women has found no links to birth defects, miscarriages, or stillbirths. Women diagnosed with antiphospholipid syndrome are advised to take Aspirin (ASA) or possibly low molecular weight heparin to minimize the risk of blood clots [110-112].

NSAIDs are commonly prescribed to manage lupus-related joint pain. However, some researchers highlighted an increased risk of cardiac abnormalities in the first trimester, based on two high-quality studies. Despite this, two comprehensive reviews suggest the benefits of NSAIDs may surpass the risks until the 30th week of pregnancy, after which they should be discontinued due to the risk of causing a patent ductus arteriosus in the fetus [113-115].

Should a lupus flare-up occur during pregnancy, corticosteroids and azathioprine are considered the safest treatment options and are not associated with fetal abnormalities. However, corticosteroids do come with typical risks such as diabetes, high blood pressure, preeclampsia, premature membrane rupture, and the possibility of gastrointestinal issues. Cyclosporine

and sulfasalazine can also be safely used. On the other hand, medications like belimumab, cyclophosphamide, methotrexate, and mycophenolate mofetil are not recommended during pregnancy [116,117].

Psychosocial issues during pregnancy

It is widely recognized that quality of life is significantly affected, yet there is limited research on particular issues encountered during pregnancy. However, existing studies indicate a rise in symptoms and diagnosis of both anxiety and depression, with occurrences possibly reaching up to 60% [118-120].

Childbirth

Numerous factors contribute to a significantly increased risk of high-risk childbirth for women with SLE, leading to a maternal mortality risk that is 20 times higher. These women face elevated risks of cesarean sections, blood-related issues (such as anemia and thrombocytopenia), bleeding after childbirth, pneumonia, and blood clots in the veins. Additionally, women with SLE often have several other health conditions and are more prone to giving birth prematurely [121,122].

Clinical implications

SLE significantly affects women both before and during pregnancy. Nursing care grounded in evidence involves making sure that women with SLE develop a reproductive plan in collaboration with both OB-GYN and rheumatology professionals. Despite the eagerness of some women to start a family, it's important to inform patients that optimal outcomes are achieved when SLE is effectively managed for a considerable period before attempting to conceive [123,124].

Monitoring during pregnancy

Once a pregnancy is confirmed, it's crucial for nurses to assist patients in promptly assessing their health status and reviewing any medications they're on, particularly if the pregnancy was not planned. Pregnant women with Systemic Lupus Erythematosus (SLE) are deemed high-risk and should expect regular appointments with both a rheumatologist and an obstetrician to keep an eye on potential complications and adjust medications as necessary [125,126]. The heightened risk of conditions such as hypertensive disorders, preeclampsia, and early labor necessitates close monitoring of blood pressure and urine tests at every visit. Regular blood tests are also to be anticipated. Elevated levels of antibodies to double-stranded DNA (dsDNA) and reduced complement levels during the second trimester can signal a higher risk of miscarriage and premature delivery, while the presence of lupus anticoagulant (tested once at the beginning of pregnancy) also raises risk levels. To check for fetal heart block and growth, fetal echocardiography and monthly ultrasounds are advised [127,128].

Throughout the pregnancy, nurses play a key role in identifying whether symptoms are typical pregnancy-related issues or potential signs of SLE flares. Common pregnancy complaints like tiredness or swelling might actually indicate an increase in SLE activity and require quick action. Nurses should also be on the lookout for signs such as inflammatory arthritis and skin rashes, which are not normal during pregnancy. Differentiating between nephritis and preeclampsia can be challenging, but it's important to remember that lupus nephritis usually appears earlier in the pregnancy and comes with other lupus flare symptoms and specific biological markers like dsDNA and low complement levels. Nurses can provide valuable support by preparing patients for the numerous appointments and blood tests needed when managing pregnancy alongside SLE. This includes frequent monitoring of blood counts to detect anemia, which can be a consequence of both pregnancy and active lupus [129].

For perinatal nurses, caring for a woman with SLE during childbirth involves navigating additional complexities. If the patient has been on prednisone throughout the pregnancy, they might need an increased dose to cope with the stress of labor. A detailed history of any hematological issues related to SLE is important for identifying risks of clotting or bleeding during birth. Additionally, it's worth noting that some women may experience perinatal complications that lead to a first-time diagnosis of SLE, necessitating enhanced support and education, although this topic extends beyond the scope of this discussion [130-132].

Postpartum needs

Women with SLE can breastfeed, provided the medications they need to manage their condition postpartum are compatible with nursing. Breastfeeding does not elevate the risk of lupus flares in women with SLE. Postpartum, it's important to closely monitor for any signs of increased disease activity, as the postpartum period carries a higher risk for flares. Similar to the initial stages of family planning, advice on contraception is crucial [133].

Conclusion

In conclusion, SLE presents unique challenges for women regarding fertility, pregnancy, and overall reproductive health. The interplay between the disease's activity, treatment regimens, and psychosocial factors significantly influences fertility outcomes, often resulting in higher rates of infertility and complications during pregnancy. As evidence continues to mount regarding the impact of conditions such as antiphospholipid syndrome and the effects of cytotoxic medications, it becomes increasingly evident that a tailored, multidisciplinary approach is essential for managing these women's health.

Healthcare providers must prioritize patient education regarding the risks associated with SLE and its treatments, as well as advocate for fertility preservation options when appropriate. Close monitoring during pregnancy is crucial, particularly for those with active disease or complications,

to ensure optimal outcomes for both mother and child.

By integrating rheumatology, obstetrics, and mental health support, we can enhance the quality of care for women with SLE, empowering them to navigate their reproductive journeys more successfully. Future research should focus on addressing the gaps in knowledge surrounding fertility mechanisms and optimal management strategies to further improve outcomes in this vulnerable population.

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