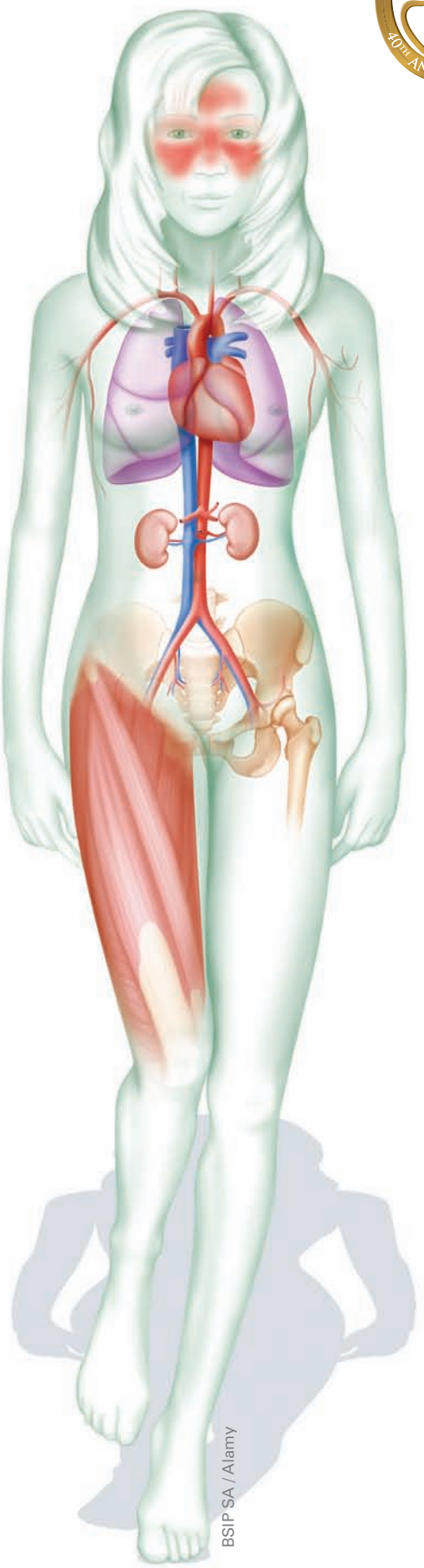


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# REPRODUCTIVE HEALTH CONCERNS IN WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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**Abstract**

Women are far more likely than men to have a diagnosis of systemic lupus erythematosus (SLE), with a peak incidence during the childbearing years. Contraceptive methods and pregnancy can both adversely affect the health of women with SLE, thus careful planning and interventions are necessary to help women manage their reproductive health choices. Women with SLE may experience infertility, difficulties conceiving and maintaining pregnancy, and ultimately have less children than they had planned. Although poor health status may account for some of this disparity, inadequate counseling and management by members of the healthcare team may also be responsible. The purpose of this article is to review the pathophysiology of SLE and its effects on reproductive health, as well as to highlight recent literature supporting evidence-based practices in reproductive health counseling, nursing care during pregnancy, and monitoring for disease complications in women with SLE. Nurses play a central role in care coordination and patient education for women with SLE making decisions about family planning.

**Keywords***:* Nursing; Reproductive health; Systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is a still incompletely understood autoimmune disorder and can affect every body system, with potential for significant physiologic and psychological impact on a patient's life (Fu, Deshmukh, & Gaskin, 2011; Sutanto et al., 2013). Women are seven to nine times more likely than men to have a diagnosis of SLE, with a peak incidence during the childbearing years (Tedeschi, Bermas, & Costenbader, 2013). Women with SLE must contend with a chronic illness, as well as complex physiologic and pharmacologic effects on their reproductive health. The purpose of this article is to review the pathophysiology of SLE, its effects on reproductive health, and to highlight recent literature supporting evidence-based practices in reproductive health counseling and nursing care during pregnancy and childbirth for women with SLE.

## Search Strategy

A search for peer-reviewed literature within the last 5 years included CINAHL, Academic Search Premier, Google Scholar, and PubMED for the search terms: "SLE and reproductive health needs," "SLE and pregnancy," "family planning services and SLE," "SLE and fertility," and "SLE and contraception counseling." Exclusion criteria included articles not written in English or with a non-U.S. sample, case studies, editorials, animal models, and articles that did not focus on childbearing women or were not specific to women with SLE. The focus was primary research articles or integrative literature reviews. These articles are the basis for the review of the physiologic factors related to SLE and their implications for the reproductive health of women with SLE presented as follows.

## Pathophysiology

An unclear combination of genetic predisposition, environmental factors, and hormonal triggers instigate the antibodies to self that are the central abnormality identified with SLE (Bertsias, Cervera, & Boumpas, 2012; Choi, Kim, & Craft, 2012). Although many genetic aberrations are linked to SLE, a preponderance is connected to human lymphocytic antigen and complement functions (Fu et al., 2011). Different genetic polymorphisms are linked with SLE and some (e.g., Foxp3) are X-linked (Tedeschi et al., 2013), providing a possible explanation for the disproportionate numbers of women with SLE as compared to men. However, a genetic aberration alone does not appear sufficient to have a diagnosis of SLE (Bertsias et al.; Fu et al.).

Several potential triggers to the immunologic abnormalities of SLE are identified in the literature. Models in mice and observational studies in some humans suggest viral infections, such as Epstein Barr, may trigger a cascade of events in the immune system that lead to SLE (Bertsias et al., 2012; Fu et al., 2011). Although not a causative agent in lupus, sunlight is a well-known exacerbating factor for individuals with SLE (Bertsias et al.). Additional environmental factors include smoking, and for Black women, exposure to silica (Hahn, 2012). Finally, data from the Nurses Health Study indicate early menarche (≤10 years old) is associated with an increased risk (pooled RR, 1.2; 95% CI [1.4–3.2]) (Costenbader, Feskanich, Stampfer, & Karlson, 2007).

The result of this combination of factors is immune system dysfunction, producing both inflammation from cytokine activation and autoantibodies that create tissue damaging antigen/antibody complexes (Choi et al., 2012). Abnormalities in SLE appear to be centered in T and B cell dysfunction. Signaling from T cells and subsequent B cell activation lead to autoantibody production. These autoantibodies (e.g., dsDNA) bind with self-proteins and create immune complexes that then bind with healthy tissue (Hahn, 2012). This enhances production of complement and macrophages leading to inflammation in a variety of organ systems (Choi et al.).

Although the precise combination of factors that cause SLE and the reasons for the variability in disease expression are still unclear (Fu et al., 2011), diagnostic criteria help organize an understanding of the various systemic problems women with SLE may experience. Current diagnostic criteria require at least 4 of 17 possible sequeli to be present. An exception is patients with biopsy-proven lupus nephritis and a positive double-stranded anti-DNA or positive ANA. The most common symptoms are fatigue, cutaneous symptoms (photosensitive butterfly rash), musculoskeletal involvement (arthritis), hematologic problems (anemia, leukopenia, thrombotic risk secondary to antiphospholipids), neurologic symptoms (headaches), and renal dysfunction (Petri et al., 2012). At least one abnormal laboratory finding such as a positive antinuclear antibody or low complement levels is necessary (Petri et al.).

> WOMEN ARE SEVEN TO NINE TIMES MORE LIKELY THAN MEN TO HAVE A DIAGNOSIS OF SLE, WITH A PEAK INCIDENCE DURING THE CHILDBEARING YEARS.

### Physiologic Effects on Fertility

Although there is debate whether or not infertility is more common in women with SLE and the mechanisms involved if true (Gleicher, Weghofer, & Barad, 2012), data indicate women with SLE have fewer children than healthy women (Ekblom-Kullberg et al., 2009) and fewer children than desired (Clowse, Chakravarty, Costenbader, Chambers, & Michaud, 2012). In a review of the literature, Hickman and Gordon (2011) suggest several likely causes: disease activity itself, medication side effects, and a women's intentional decision to delay or abandon procreation.

Unintentional infertility related to disease activity in women with SLE may have multiple causes including genetically at-risk subgroups (Gleicher et al., 2012). Significantly lower ovarian function in women with SLE, as measured by anti-müllerian hormone, has been reported (Lawrenz et al., 2011; Ma et al., 2013). Hickman and Gordon (2011) theorize that another possible disease-associated cause of infertility is due to an increased risk of infection, specifically sexually transmitted infections

that are linked to infertility in all women (Centers for Disease Control and Prevention, 2013). Medications used to treat SLE (e.g., cyclophosphamide) cause premature ovarian failure and psychosocial issues (depression and partner conflict) may impair intended fertility in women with SLE. Age-related infertility may occur as providers encourage patients to "wait" to conceive until SLE is well controlled (Hahn, 2012; Hickman & Gordon, 2011).

### Physiologic Effects During Pregnancy

Once a woman with SLE becomes pregnant, the already intricate and widespread pathological changes are further complicated by the yet unclear immunologic changes in normal pregnancy that prevent rejection of the fetus (Barbhaiya & Bermas, 2013). This lack of understanding in normal pregnancy limits the current knowledge of the pathophysiology of SLE during pregnancy. What is known is that women with SLE experience either no changes in disease state or a worsening, perhaps related to an increase in T helper type 2 cytokine production (Barbhaiya & Bermas). Increases in such inflammatory mediators also may limit placental vessel development (Ostensen & Clowse, 2013). Unclear hematological complications in women with antiphospholipid syndrome lead to an increase in miscarriages (Andreoli et al., 2012).

WOMEN WITH SLE HAVE FEWER CHILDREN THAN HEALTHY WOMEN AND FEWER CHILDREN THAN DESIRED.

## Conception Planning and Control

Conception planning is critical for women with SLE in order to limit risk to both mother and baby from medications taken to control SLE, from threats to fertility, and from uncontrolled disease during pregnancy and childbirth (Barbhaiya & Bermas, 2013; Lateef & Petri, 2013). Data indicate women with SLE (Clowse et al., 2012) have fewer children than planned and that the effects of SLE on potential parenthood are a significant component of living with SLE (Sutanto et al., 2013). There are minimal data documenting rates of contraceptive counseling for women with SLE, with only one small ($N$ = 206) study showing 59% had no such counseling in the past year (Yazdany et al., 2011). A recent review article for nurses on SLE by Ferenkeh-Koroma (2012) did not include information on family planning.

### *Contraception Risks and Benefit*

There are two concerns for women with SLE related to contraception method: worsening of existing disease/flares and adequate use of contraception to avoid unwanted/untimely conception. The latter is particularly important as the likelihood for good pregnancy outcomes for mother and baby are linked to timing of conception during a period of low disease activity and avoidance of pregnancy while on teratogenic medication (Barbhaiya & Bermas, 2013; Lateef & Petri, 2013). There is a paucity of research regarding self-reported contraception use in patients with SLE, but in a small ($N$ = 53) specialty SLE clinic population, Schwarz and Manzi (2008) report that 55% of women at risk for pregnancy used no contraceptive method in the previous month.

Women with SLE are often advised against using contraception with an estrogen component; however, recent research indicates safety. In a research review, Lateef and Petri (2012) report that oral estrogen/progesterone hormonal contraception does not increase the risk of worsening of lupus symptoms in women with *stable* disease and may carry an additional benefit of protecting women with SLE, who are at higher risk, from osteoporosis and bone fracture. Estrogen is contraindicated in women with elevated risk for thrombosis such as positive anticardiolipin antibody and lupus anticoagulant (Lateef & Petri, 2012).

Alternatives include progestin-only contraception, barrier methods such as condoms and spermacides, and intrauterine devices and systems. The use of progestin-only formulations must be balanced with risk of lower bone mineral density and somewhat lower efficacy of method if oral formulations are used (Lateef & Petri, 2012). Adding emergency contraception (progestin-only) or barrier methods are safe and can increase efficacy, but may have unacceptable high failure rates if used alone (Ostensen, 2011; Schwarz & Manzi, 2008).

TABLE 1. Risk Factors for Increased Rates of Infertility in Women With SLE

| Risk | Cause | Action |
|---|---|---|
| Medications to treat SLE that are gonadotoxic: *cyclophosphamide | Premature ovarian failure | Counsel women about possible fertility preservation prior to treatment; refer to infertility specialist as desired |
| Severe disease; lupus nephritis, anti dsDNA | Premature ovarian failure related to self antibodies directed to reproductive system in SLE or elevated prolactin levels in lupus nephritis | Assess individual family planning desires |
| Sexually transmitted infection (STI) or risk of STI | Inflammation and scarring of vaginal/cervical tissue | Follow CDC (2013) guidelines for screening and treatment of STIs, ensure routine obstetric and gynecologic care |
| Advancing age | Natural decline in fertility | Assess family planning desires; educate about risks to fertility in SLE; help ensure follow-up and care coordination |

### Fertility Preservation

Several risks to their fertility (Table 1) exist in women with SLE. Cyclophosphamide can induce ovarian failure, but careful planning of lower dosing schedule may mitigate this risk (Hickman & Gordon, 2011). Although still a young body of research, fertility preservation via ovary and embryo preservation appears safe and effective for women with SLE (Henes et al., 2012).

### Appropriate Timing of Conception

Disease activity should be well controlled prior to conception, and screening for autoantibodies that increase pregnancy risk such as anti-Sjögren's-syndrome-related antigen A, and anti-Sjögren's-syndrome-related antigen B, antiphospholipid antibody, and lupus anticoagulant should take place (Barbhaiya & Bermas, 2013; Lateef & Petri, 2013). No clear guidelines exist for practices such as perinatology referral prior to conception attempts. Even with controlled SLE, there is a two- to fourfold increase in risk for complications of pregnancy (Clowse, Jamison, Myers, & James, 2008). Counseling for these risks, as well as routine preconception advice (smoking, alcohol use, folic acid, and weight management) is important for women with SLE (Andreoli et al., 2012).

## Pregnancy

Several studies demonstrate increases in risk for pregnant women with SLE. A 3-year retrospective exploration of records from 13,555 births in the United States demonstrates an increased risk of infection, thrombotic events, preterm labor, and preeclampsia in women with SLE (Clowse et al., 2008). Women with active disease, especially nephritis, and lupus anticoagulant at time of conception have even greater risk of poor pregnancy outcomes with complications such as hypertension, continued and worsening nephritis, and premature birth (Lateef & Petri, 2013; Ostensen & Clowse, 2013). Women with organ involvement such as pulmonary hypertension or cardiac disease are also at risk for severe and worsening organ damage during pregnancy. Due to the risk of poor outcome (such as preeclampsia, preterm labor, nephritis, and neonatal lupus), women with active renal, cardiac, or pulmonary involvement are advised not to attempt conception until their disease is controlled (Andreoli et al., 2012; Ateka-Barrutia & Khamashta, 2013; Lateef & Petri, 2013).

### *Medications During Pregnancy*

In addition to routine prenatal vitamins, some lupus medications are recommended for use during pregnancy. Women who have tolerated hydroxychloroquine prior to conception should continue during pregnancy as this medication reduces the risk of flares during pregnancy and of neonatal lupus (Barbhaiya & Bermas, 2013). A literature review of hydroxychloroquine in pregnant women (Abarientos et al., 2011) reports no association with congenital abnormalities, spontaneous abortion, or fetal death. Women with antiphospholipid syndrome should be on aspirin (ASA), or possibly low molecular weight heparin (Andreoli et al., 2012) to reduce thrombotic risk.

NSAIDs are used to control arthralgia, a common manifestation of SLE. In a systematic literature review, Adams, Bombardier, and van der Heijde (2012) note an increased risk (OR = 1.86) for cardiac defect in the first trimester, with only two studies of adequate quality. Two large review articles suggest that benefit of NSAIDs may outweigh risk until week 30 of gestation, when risk of patent ductus arteriosus necessitates discontinuation (Andreoli et al., 2012; Barbhaiya & Bermas, 2013).

Nurses who are knowledgeable about SLE can help women with SLE obtain optimal perinatal outcomes through interdisciplinary care coordination and assessment for SLE symptoms.

If a disease flare occurs during pregnancy, corticosteroids and azathioprine have the best safety profile and do not appear to cause fetal abnormalities. Corticosteroids carry standard risks such as diabetes, hypertension, preeclampsia, and premature rupture of membranes as well as the potential for gastrointestinal toxicity (Andreoli et al., 2012). Cyclosporine and sulfasalazine may also be continued. Other medications such as belimumab, cyclophosphamide, methotrexate, and mycophenolate mofetil are contraindicated (Barbhaiya & Bermas, 2013).

***Psychosocial Issues During Pregnancy***

Although it is well established that has a significant impact on quality of life (Sutanto et al., 2013), the literature is sparse regarding specific problems during pregnancy but suggests increases in both anxiety and depression symptoms and diagnosis (Bachen, Chesney, & Criswell, 2009; King et al., 2010). The incidence may be as high as 60% (Bachen et al.).

## Childbirth

Several issues create a high-risk birth scenario for women with SLE and contribute to a 20-fold higher risk of maternal mortality (Clowse et al., 2008). Risks are elevated for cesareans, hematological complications (anemia, thrombocytopenia), postpartum hemorrhage, pneumonia, and venous thrombotic embolism (Andreoli et al., 2012). Women with SLE are more likely to have multiple comorbidities as well as preterm birth (Andreoli et al.).

## Clinical Implications

SLE has significant impact on women prior to and during pregnancy. Evidence-based nursing care includes ensuring women with SLE have a plan for contraception and procreation made in conjunction with both OB-GYN and rheumatology care providers. Although women may be anxious to begin a family, nurses should help educate patients that the best outcomes occur when SLE is well controlled for several months prior to conception (Ostensen, 2011). Internet resources for both nurses and patients include those of the American College of Rheumatology (www.rheumatology.org) and the Lupus Foundation of America (www.lupus.org).

### Monitoring During Pregnancy

Once pregnancy has occurred, nurses need to help patients access immediate evaluation for disease status and current medications, especially if the pregnancy was unplanned. A woman with SLE who is pregnant is considered high risk and can expect frequent visits to a rheumatologist and obstetrician to monitor for complications and manage medications (Barbhaiya & Bermas, 2013). Due to increased risk of hypertensive disorders, preeclampsia, and preterm labor, blood pressure and urinalysis are important markers at each visit. Patients should expect frequent blood analysis. Antibody to double-stranded DNA (dsDNA) and low complement levels in the second trimester indicate an increase in the risk for pregnancy loss and preterm birth (Clowse, Magder, & Petri, 2011) and lupus anticoagulant (measured once at pregnancy onset) also increases risk (Ostensen & Clowse, 2013). Fetal echocardiography and monthly ultrasounds are recommended to monitor for fetal heart block and growth (Lateef & Petri, 2013).

Throughout pregnancy, nurses can help monitor and distinguish symptoms between normal pregnancy-related complaints and possible indications of disease flares (Barbhaiya & Bermas, 2013). Minor, normally routine complaints of pregnancy such as fatigue or edema may signal increased disease activity and need prompt evaluation. Nurses can

## Suggested Clinical Implications

- Discuss family planning, including contraceptive methods and timing of conception with all childbearing women who have SLE.
- Help ensure women with SLE are under the care of both obstetricians and rheumatologists immediately upon conception.
- Monitor women who are pregnant closely for proteinuria, blood pressure, dsDNA and complement levels, and psychosocial stressors.
- Evaluate common pregnancy complaints such as fatigue and edema carefully in pregnant women with SLE, as they may indicate worsening of disease.
- Be alert for bleeding complications during birth as well as neonatal complications.

help monitor for symptomatology such as inflammatory arthritis and rashes, which are not normal pregnancy-related symptoms. Nephritis can be difficult to differentiate from preeclampsia, but nurses should note that lupus nephritis often occurs earlier in pregnancy and is associated with other symptoms of a lupus flare and biological markers such as dsDNA and low complement (Ateka-Barrutia & Khamashta, 2013). Anticipatory guidance includes helping patients anticipate the frequent appointments and blood testing that comes with being pregnant and having a diagnosis of SLE. For example, blood counts may need to be monitored frequently to identify anemia, which can be related to both pregnancy and lupus activity.

Perinatal nurses can anticipate increased complexity when a woman with SLE presents for birth. If prednisone has been taken throughout pregnancy, patients may require additional dosing for the stress of birth (Ateka-Barrutia & Khamashta, 2013). A careful history for hematological involvement secondary to SLE can help identify women at risk for clotting or hemorrhage. Conversely, though beyond the scope of this article, is being aware that women who experience perinatal complications discussed here may be ultimately diagnosed with SLE for the first time and require increased support and education.

### Postpartum Needs

Breastfeeding can be implemented in women with SLE depending on medications necessary in the postpartum period to control illness. Costenbader et al. (2007) report no increased risk in lupus flares among women with SLE who breastfeed. Other issues postpartum relate to careful monitoring for disease activity as the risk for flares is increased postpartum (Barbhaiya & Bermas, 2013). Just as it is with initial family planning, contraceptive counseling is essential.

## Conclusion

SLE is a serious chronic illness disproportionately affecting childbearing women, who therefore must make difficult decisions about their reproductive life. The findings of the Sutanto et al. (2013) thematic synthesis of qualitative studies on the experiences of those living with SLE serve as an important reminder to all nurses that the impact of SLE on reproductive health is significant. Research suggests healthcare providers are not attending to these concerns or providing adequate counseling regarding reproductive options (Yazdany et al., 2011). Some long-held beliefs about limiting these choices are no longer appropriate and women with SLE can conceive and give birth safely with careful planning and multidisciplinary care (Barbhaiya & Bermas, 2013; Lateef & Petri, 2013). Nurses are perfectly situated to provide evidence-based patient education and dispel myths about reproductive choices as well as guide fertility and conception planning. Assisting patients with navigation of the complex care system with both OB-GYN and rheumatology specialists may increase the chances of planned conception, preserved fertility, and good pregnancy outcomes for mother and baby. ✣

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