Current Recommendations for the Systemic Treatment of Cutaneous Lupus Erythematosus During Pregnancy

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PRACTICE **POINTS**

- Patients should consult their primary dermatologist when discussing medication options for cutaneous lupus erythematosus (CLE) prior to pregnancy.
- Hydroxychloroquine is a first-line medication for maintenance treatment of CLE, while oral steroids are effective for CLE flares in pregnancy. Second-line medications include dapsone and intravenous immunoglobulin. These classes of medications are considered safe in pregnancy.
- Cutaneous lupus erythematosus medications contraindicated in pregnancy include oral retinoids, mycophenolate mofetil, thalidomide, and methotrexate.

Cutaneous lupus erythematosus (CLE) is a heterogeneous autoimmune disease of the skin that commonly affects women of childbearing age. Some of the medications used in the treatment of CLE are safe in pregnancy, whereas others are contraindicated based on their teratogenic effects. We describe the most recent recommendations for the use of commonly prescribed CLE medications for those who are pregnant or plan on becoming pregnant.

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Cutaneous lupus erythematosus (CLE) is a heterogeneous autoimmune disease that involves the skin. Cutaneous lupus erythematosus can be classified into various subtypes.[1] These include, but are not limited to, acute CLE, subacute CLE, chronic CLE, intermittent CLE, lupus tumidus, and lupus profundus.[1,2] The CLE subtypes have variable associations with systemic lupus erythematosus. For instance, some subtypes, such as acute CLE, are more strongly associated with systemic lupus erythematosus.

Treatment of CLE is similar to other autoimmune disorders. Although the US Food and Drug Administration (FDA) has not approved any treatments for CLE,[3,4] the most common therapeutic options are disease-modifying antirheumatic drugs. Unfortunately, many of these treatments carry teratogenic effects. Because CLE predominantly affects women, particularly those of childbearing age, it is imperative to understand the available treatment options for those who are pregnant or considering pregnancy for an informed discussion with patients.[5]

For years, the gold standard when considering a medication during pregnancy was the FDA's classification system. According to this system, medications were classified into 5 letter categories based on their potential teratogenicity, including A (no fetal risk), B (potential animal risk but inconclusive human studies), C (risk cannot be ruled out), D (evidence of fetal risk), and X (contraindicated in pregnancy). In 2014, the FDA decided to no longer use this classification system for medications approved after 2000.[6] However, because many proposed treatment options for CLE were approved prior to 2001, we have summarized the commonly prescribed medications for CLE according to their prior FDA letter categories.

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The eTable is available in the Appendix online at www.mdedge.com/dermatology.

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Treatment Options for CLE During Pregnancy

Prior to initiating systemic medications for the treatment of CLE, topical medications should be considered. Recommended treatment options include corticosteroids and calcineurin inhibitors.[7] Compared with systemic medications, topical treatments carry minimal side effects, such as skin atrophy, that typically remain localized to areas of application.[8] Moreover, even with extensive application, no correlation has been found between topical corticosteroid use and fetal growth,[9] which suggests that topical steroids are safe in pregnancy and should be considered as a first-line treatment option for CLE. Calcineurin inhibitors also are considered safe based on their low level of absorption through the skin and are considered second-line topical treatment options in pregnancy.[10]

Although topical medications are effective for the treatment of CLE, many patients require the administration of systemic therapeutics for severe or refractory disease. Based on previously published reports, Figure 1 describes the current recommended systemic treatment options for CLE.[11] Unfortunately, many of these medications carry teratogenic risks during pregnancy. The risks and side effects of the medications are described in detail in the following sections and summarized in the eTable.

Category B

Systemic Steroids—Systemic steroids are one of the most prescribed medications during pregnancy.[12] Oral steroids have been associated with fast symptom relief, making this class of medications particularly effective during CLE flares; however, long-term management is not recommended because of the side effects, which include osteoporosis and impaired glucose metabolism.[13]

With low transmission across the placenta, there are 3 glucocorticoids that carry the safest profile in pregnancy: prednisone, cortisone, and hydrocortisone.[14] Dexamethasone and betamethasone should be avoided, as both readily cross the placenta and increase fetal exposure.[15] Although teratogenic effects have been associated with steroid use, most studies involving pregnant patients have inconclusive results. For instance, one study described an association between cleft lip/palate with in utero glucocorticoid exposure.[16] However, multiple follow-up studies found no association between the two.[17,18] Studies investigating the relationship between steroids and miscarriages or steroids and low birth weight also are inconclusive. Of note, if used throughout pregnancy, administration of a loading dose of glucocorticoids prior to delivery is recommended because of the increased stress brought on during labor.[19]

Sulfasalazine—Sulfasalazine is an immunomodulator commonly used for the treatment of inflammatory bowel disease and rheumatoid arthritis. However, studies also have shown that sulfasalazine is an effective treatment of CLE if standard treatments have failed.[20,21]

During pregnancy, patients exposed to sulfasalazine experienced minimal side effects despite transportation across the placenta.[22] In comparison with control, pregnant women taking sulfasalazine experienced no increased risk for low fetal weight,[23] congenital abnormalities,[24] or spontaneous abortions.[25] Of note, sulfasalazine can affect sperm, so male patients also should be counselled.

Category C

Hydroxychloroquine—Hydroxychloroquine is considered a first-line medication for those with CLE based on a symptomatic relief rate of 50% to 70%.[26] For those taking hydroxychloroquine during pregnancy, the majority of studies have shown no association between the medication and adverse fetal events, including congenital abnormalities, prematurity, or spontaneous abortions.[27-29] Therefore, hydroxychloroquine is considered safe in pregnancy, and those on the medication should continue standard monitoring, including retinopathy screening.[30]

Of note, hydroxychloroquine can be stored in tissue for weeks to months after discontinuation.[5] Therefore, if

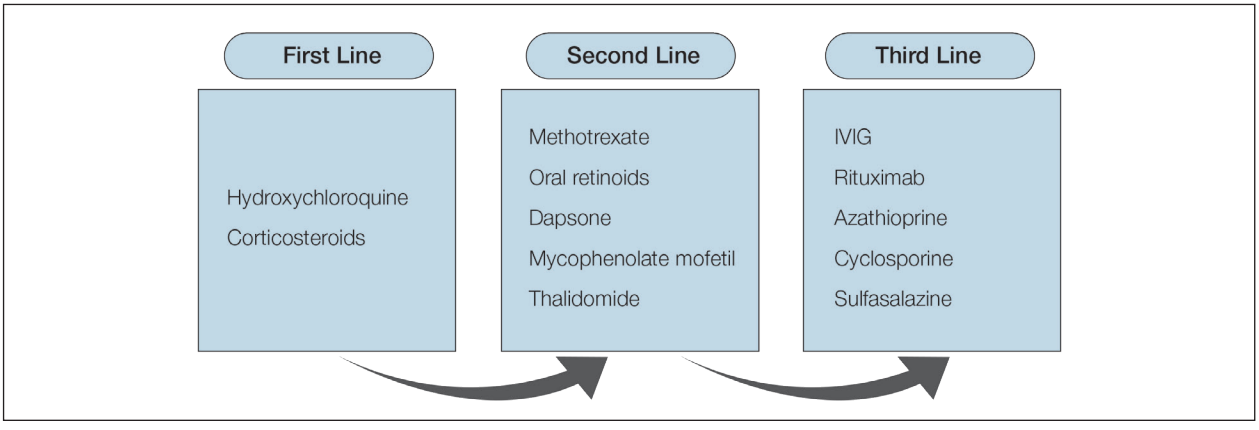

FIGURE 1. Current recommended systemic treatment options for patients with cutaneous lupus erythematosus. Abbreviation: IVIG, intravenous immunoglobulin.

patients wish to avoid hydroxychloroquine in pregnancy, one should stop taking the medication several months prior to conception.

Dapsone—Dapsone, a medication with both antimicrobial and immunomodulatory properties, is an effective second-line therapy for CLE.[31] Although large-scale human trials have not been performed, multiple case reports and observational studies have supported the safe use of dapsone in pregnancy.[32-34] However, there are notable side effects, including dose-dependent hemolysis, methemoglobinemia, and hypersensitivity reactions.[13] Therefore, once treatment is initiated or continued, folic acid supplementation (5 mg daily) and regular serum analysis, including complete blood cell counts, are recommended in pregnant patients.[19]

Rituximab—Recent studies have demonstrated that rituximab can be an effective treatment of subacute and chronic CLE.[35,36] Through inhibition of CD20, rituximab causes a decrease in circulating B cells and a reduced immune response. Therefore, experts recommend discontinuation of rituximab for 12 months prior to conception to reduce potential side effects to the fetus, which may include a transient reduction of circulating fetal B cells.[37]

If continued during pregnancy, most studies suggest discontinuation of rituximab during the third trimester, as it has been associated with neonatal infections and congenital abnormalities.[19,37] However, these results are based on limited case reports, and thus robust research is needed to better understand the effect of rituximab in utero.

Intravenous Immunoglobulin Infusion—Intravenous immunoglobulin (IVIG) infusion is a well-tolerated treatment for many autoimmune disorders.[38] Although not first line, limited case studies have demonstrated remission of refractory CLE following IVIG.[39,40] Although no studies have directly investigated the effect of IVIG on fetal development, it has been frequently administered and well tolerated during pregnancy, especially in those with multiple sclerosis or antiphospholipid syndrome.[41] Commonly reported side effects include headache and fatigue, and a rare associated side effect to be aware of is embolic events.[42,43]

Cyclosporine—Cyclosporine rarely is used in the treatment of localized CLE due to its extensive side-effect profile, most notably nephrotoxicity.[44] However, studies have shown that cyclosporine may be efficacious if symptoms extend beyond the skin, involve multiple organs, and/or other treatments have failed.[39] For those who are pregnant and wish to continue cyclosporine use, studies have associated low birth weight and premature delivery with its exposure in utero.[44]

Category D

Mycophenolate Mofetil—In conjunction with standard therapy, mycophenolate mofetil (MMF) is an adequate treatment of refractory CLE.[45] Unfortunately, case reports have demonstrated an increased risk for fetal congenital abnormalities and first-trimester spontaneous abortion with use of MMF during pregnancy.[46,47] Therefore, it is recommended that patients on MMF discontinue the medication at least 6 weeks prior to conception.[46]

Azathioprine—Although azathioprine has been shown to provide relief of discoid lupus erythematosus symptoms,[48] it currently is only utilized for refractory disease, largely due to notable side effects that particularly affect the gastrointestinal tract and liver.[4] Moreover, azathioprine use during pregnancy has been associated with prematurity, congenital anomalies, fetal cytopenia, and low birth weight.[49] With that said, and although not recommended, if patients decide to continue treatment, experts recommend limiting the dose to 2 mg/kg daily to reduce potential adverse events.

Category X

Oral Retinoids—According to the American Academy of Dermatology, retinoids such as isotretinoin and acitretin are considered second-line therapy for CLE.[50] With that being said, there are well-documented effects on

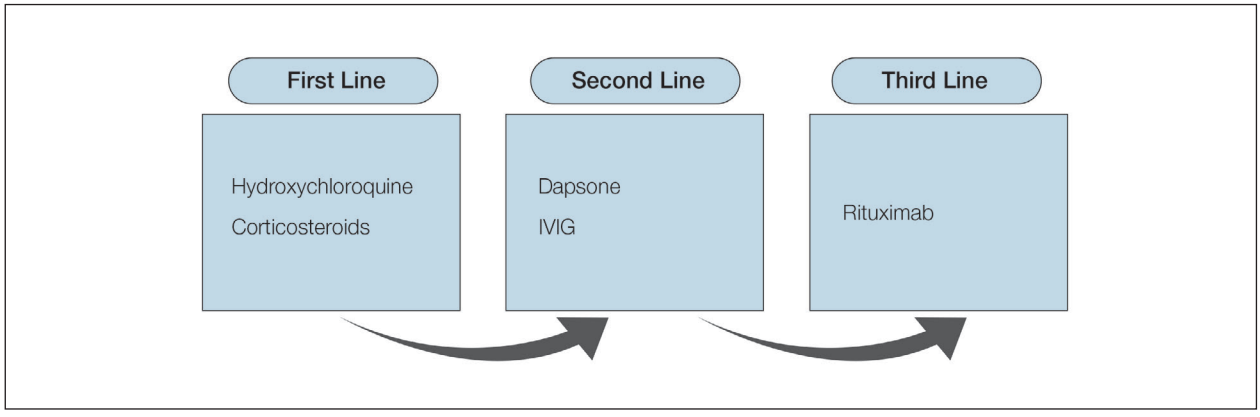

FIGURE 2. Recommended systemic treatment options for cutaneous lupus erythematosus in pregnant women. Abbreviation: IVIG, intravenous immunoglobulin.

fetal development associated with oral retinoid use, including central nervous system, cardiovascular system, and craniofacial abnormalities.[51] Therefore, its use is contraindicated during pregnancy. To prevent pregnancy while taking isotretinoin, patients must enroll in an online monitoring program called iPLEDGE. This program requires monthly updates by both the physician and the patient, including a negative pregnancy test every month for female patients actively taking the medication.[52]

The half-lives of the oral retinoids isotretinoin and acitretin are 10 to 20 hours and 50 to 60 hours, respectively.[53,54] However, alcohol consumption converts acitretin into the metabolite etretinate, which can remain in tissue for up to 120 days.[54,55] Therefore, women are advised to avoid alcohol while taking acitretin and avoid conception for 2 to 3 years after cessation of the medication.[55] For those wishing to restart retinoids after pregnancy, studies show the medication can be safely reinstated 35 days after delivery for those interested in continued treatment.[56]

Thalidomide—Although low-dose thalidomide can treat refractory CLE, its use is restricted because of its known teratogenicity, most notably limb deformities.[57] If prescribed thalidomide, women will need to enroll in the System for Thalidomide Education and Prescribing Safety program, similar to the iPLEDGE program, and use 2 forms of contraception when sexually active.[58] Contraception should be continued for 4 weeks following the last dose of thalidomide. After this point, conception is considered safe.[59]

Methotrexate—For nonpregnant patients, low-dose methotrexate (MTX) with folate supplementation is a treatment option for CLE.[60] However, for those who are pregnant, low-dose MTX is an abortive agent and has been associated with aminopterin syndrome, which includes skull deficits, craniofacial abnormalities, and limb deformities in live births.[19,61] Therefore, MTX is not recommended in pregnancy. Of note, MTX can affect sperm; male patients also should be counselled.

Final Thoughts

Overall, it is recommended to limit medication use as much as possible in pregnancy. To reduce these exposures, it is imperative to reduce triggers that may lead to symptomatic flares of CLE. Because CLE can be triggered by sun exposure, we advise topical sunscreen to prevent CLE flares that may require additional oral medication.[62,63]

Various medications are considered safe for the treatment of CLE in pregnant patients (Figure 2). Based on studies in animal and clinical trials, hydroxychloroquine is considered a safe and effective medication for CLE in pregnancy and is a first-line therapy in nonpregnant patients.[26,27] If flares occur, IVIG or a short course of oral steroids should be considered to manage symptoms.[13,39] For those with severe flares, treatment is difficult, and personalized approaches may be necessary.

Part of the question for the childbearing population is when a patient would like to conceive. For severe cases when hydroxychloroquine is not effective as monotherapy, using a treatment that can encourage remission prior to conception attempts can be a beneficial strategy. Rituximab is an excellent example of such a therapy, as the therapeutic effect outlasts the immunosuppressive effect and therefore is unlikely to affect a future fetus.[64] Thalidomide also is a potential option prior to conception, based on its short washout period and its ability to achieve notable remission rates in patients with CLE.[57,59] Regardless, patients with CLE should still consult their dermatologist and rheumatologist (if applicable) prior to conception.

Patients of childbearing potential represent a population in which discussion about life goals greatly affects medication options. Having these discussions early and often allows for an open, more successful approach so that treatment regimens are not derailed at the time of conception.

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APPENDIX

eTABLE. Risks and Side Effects of Medications for Cutaneous Lupus Erythematosus in Pregnancy

Therapy	MOA	FDA pregnancy category	Teratogenic effects	Additional recommendations
Systemic steroids	Systemic immunosuppression	B	Cleft lip/palate	Stress dose at delivery
Sulfasalazine	Systemic immunosuppression	B	No major known or documented effects	Can affect sperm
Hydroxychloroquine	Increases lysosomal pH, decreases antigen presentation	C	No major known or documented effects	Standard retinopathy screening
Dapsone	Folic acid inhibitor	C	No major known or documented effects	Daily folic acid supplementation
Rituximab	CD20 monoclonal antibody	C	Hematologic abnormalities, infection	Avoid in third trimester because of B-cell depletion
IVIG	Systemic immunosuppression	C	No major known or documented effects	
Cyclosporine	Cytokine production inhibitor	C	Low birth weight and premature delivery	
Mycophenolate mofetil	IMPDH inhibitor	D	Skeletal deformities	Discontinue 6 week prior to attempting to conceive
Azathioprine	Purine synthesis inhibitor	D	Congenital abnormalities, fetal cytopenia, prematurity, and low birth weight	Limit dose to 2 mg/kg/d
Oral retinoids	Vitamin A derivative	X	Craniofacial, cardiovascular, and CNS abnormalities	Avoid in pregnancy
Thalidomide	Immune modulator	X	Limb deformities	Avoid in pregnancy
Methotrexate	Folic acid antagonist	X	Aminopterin syndrome	Can affect sperm; men should discontinue 3 mo prior to conceiving

Abbreviations: CNS, central nervous system; FDA, US Food and Drug Administration; IMPDH, inosine-5′-monophosphate dehydrogenase; IVIG, intravenous immunoglobulin; MOA, mechanism of action.