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Lupus (S Keeling, Section Editor)

Treatment of Systemic Lupus Erythematosus (SLE) in Pregnancy

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Abstract

Purpose of review To identify known teratogenic medications that may be used to treat SLE and discuss alternative therapeutics that can be used throughout pregnancy in order to manage maternal autoimmune diseases.
Recent findings Teratogenic immunosuppressive medications include methotrexate, mycophenolatemofetil, and cyclophosphamide. In anticipation of pregnancy, such medications should be discontinued and replaced with immunosuppressive medications including azathioprine and cyclosporine and assessed for disease stability.
Summary Pregnancy is an important aspect to women's lives, and a diagnosis of SLE should not necessarily preclude the ability to bear children. Pregnancy outcomes among SLE women are favorable when disease is well controlled prior to conception and teratogenic medications are avoided. Several immunosuppressive therapies that are compatible with pregnancy are available to treat flares that may occur during pregnancy. Hydroxychloroquine use throughout pregnancy is associated with improved outcomes for both mother and infant. Risks of medication use need to be balanced with risks of active maternal disease.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that predominantly effects women of childbearing age. As multiple organ systems are involved throughout the disease course, management of disease activity and maintenance of clinical quiescence is critical to limit damage accrual over time.

Improvements in disease management have made childbearing feasible among these women. However, concerns remain about the safety of implementation of disease-modifying therapy and use of biologics during pregnancy. Teratogenicity has always been a significant issue when considering medication use during pregnancy as the effects can be life threatening and permanent. It must be remembered that the rate of congenital malformations in the general population is 3–5% and has remained unchanged over time despite the introduction of many hundreds of medications [1]. Moreover, generating data on human teratogenicity is difficult at best and case reports of congenital anomalies are often confounded by polypharmacy and active underlying maternal disease, making attribution to any particular therapeutic agent challenging. As with many other diseases that may coincide with pregnancy, studies have shown that pre-conception counseling and effective management of SLE prior to conception often improves pregnancy outcomes [2]. Effective pregnancy risk assessment and counseling requires a multidisciplinary approach that involves a team of obstetricians, rheumatologists (and other specialists as required), an individual management plan, regular reviews, and early recognition of flares and complications [3].

Impact of disease activity on pregnancy outcomes

Before discussing the potential risks of medication use during pregnancy in women with SLE, it is important to understand the risks associated with untreated or undertreated disease activity in affected women. For the past 80 years, it has been widely recognized that pregnancy in women with SLE could have potentially devastating effects on both mother and fetus. In fact, during the mid-twentieth century, SLE women were strictly counseled to avoid pregnancy because of the unacceptably high maternal and fetal mortality rate. Since that time, advances in medical management of both SLE and pregnancy have allowed the majority of women with SLE to avoid or modify known risk factors for adverse pregnancy outcomes and go on to have healthy pregnancies. However, even in the best cases, adverse pregnancy outcomes among SLE women are higher than that of healthy pregnant women comparators [4••]. Research has shown that among the most significant risks to SLE pregnancy is active SLE at conception or flares that develop during pregnancy. The relative risk of overall SLE flares during pregnancy compared to flare rates among the non-pregnant SLE population remains controversial. Fortunately, most flares appear to be mild to moderate in nature. There is more consensus, however, in reported rates of serious SLE flares during pregnancy. It is estimated that approximately 10–20% of SLE pregnancies will be complicated by severe flares—active nephritis, cerebritis, or significant cytopenias that require urgent immunosuppressive therapy [3].

It is well known that risks of disease flares during pregnancy are associated with the degree of lupus activity within the 6 months prior to conception [3]. Therefore, it is imperative to work diligently to achieve clinical quiescence or low disease activity before pregnancy and to avoid pregnancy during times of active underlying SLE [3]. More recent data has suggested that the organ involvement of flare during pregnancy is most highly predicted by the organ involvement with active disease in the 6 months prior to conception [5]. Although active disease carries the highest risk for adverse pregnancy outcomes, other risk factors include elevated blood pressure, reduced renal function, proteinuria, and thrombocytopenia at conception [6]. Therefore, it is important

to achieve disease control and modify other risk factors as much as possible using medications that are compatible with pregnancy, as an abrupt discontinuation of or change in immunosuppressive therapy can portend a flare in underlying disease.

In the past, clinicians relied on the Food and Drug Administration (FDA) pregnancy classification criteria to help guide prescribing practices during pregnancy. Unfortunately, the ABCD and X categories were often misinterpreted as a "grade" of safety (regarding teratogenicity) for use during pregnancy when, in fact, they served as descriptors of the type and amount of pregnancy data available at the time of licensure. Unless data suggested more definitive teratogenic risks, categories were rarely updated as additional data became available. The FDA has since replaced the former system with a new, more comprehensive, assessment of risk for use in pregnancy and lactation that will be more informative for clinicians and patients alike and will require periodic updates as new evidence becomes available [7].

Immunosuppressive agents with known teratogenic potential

When considering medication use in anticipation of or at the discovery of pregnancy, it is perhaps most important to recognize medications with known teratogenic potential that should not be used during pregnancy. Women of childbearing potential should be made aware of the teratogenic nature of these medications, and use of reliable contraception be assured for the duration of exposure. For rheumatologists, the most commonly used known teratogens are relatively few and include methotrexate (MTX), mycophenolatemofetil (MMF) and cyclophosphamide (CYC).

MTX is an antifolate metabolite commonly used to treat cutaneous and articular manifestations of SLE. In addition to teratogenicity, MTX is a known abortifacient and is often used for the treatment of ectopic pregnancies. Exposure during the first trimester increases the risk of neural tube defects, craniofacial abnormalities, and central nervous system abnormalities; second and third trimester exposure involves limb malformations and growth retardation [8]. In doses typically used to treat rheumatic conditions (up to 25 mg weekly), rates of spontaneous abortion reach approximately 40%, and the rate of fetal malformation is estimated to be < 15% [9, 10••]. Although this remains high and contraception is critical during MTX exposure, this means that the majority of pregnancies with early exposure to MTX that survive beyond 10 weeks will not necessarily be affected by the fetal aminopterin syndrome. Therefore, women who inadvertently become pregnant while taking MTX should not necessarily be encouraged to terminate an otherwise wanted pregnancy until fetal assessments have been made to determine the risk of malformations. High dose folic or folinic acid supplementation should be continued throughout pregnancy if prenatal or early antenatal exposure has occurred.

Mycophenolatemofetil (MMF) is metabolized by the liver to its active moiety, mycophenolic acid, which irreversibly inhibits inosine monophosphate dehydrogenase, an enzyme involved in purine de-novo synthesis in proliferating B and T lymphocytes. MMF is a known teratogen: limb and facial anomalies are the most common congenital malformations, including microtia, hypoplastic nails, shortened fifth finger, cleft lip and palate,

congenital diaphragmatic hernia, and congenital heart defects [11, 12]. The National Transplantation Pregnancy Registry (NTPR) reported in 2010 that the incidence of congenital anomalies is 23% and rate of spontaneous abortion is 49% among MMF-exposed pregnancies [13, 14]. Therefore, MMF remains contraindicated during pregnancy and for the first 6 weeks following discontinuation of MMF. The FDA has initiated a voluntary REMS program for prescribers of MMF that provides comprehensive details of teratogenic potential of MMF and outlines effective contraceptive options for use during MMF exposure [7]. Again, the rate of malformations is high, necessitating contraception; however, if an inadvertently exposed pregnancy is discovered, careful fetal assessment should be considered to help the patient determine teratogenic risks if wishes to proceed with the pregnancy.

In contrast, CYC is a teratogenic and gonadotoxic alkylating agent. It is a definitive teratogen with exposure during the first trimester of pregnancy. In contrast to MMF and MTX which are often used for long-term maintenance of disease quiescence and may be used for many years in a given individual, CYC is currently used in the acute setting as induction therapy for severe disease manifestations including active lupus nephritis or cerebritis. Indeed, with the increased use of alternative therapies, CYC is rarely used beyond 6 months before changing alternatives including MMF or azathioprine (AZA) for maintenance therapy. Therefore, in addition to teratogenic and abortifacient risks to the pregnancy from CYC exposure itself, the pregnancy is also at high risk for adverse outcomes due to the severity of active underlying disease that necessitated CYC use to begin with. Should they continue, these pregnancies carry extremely high risks for serious adverse outcomes for both mother and fetus and termination should be considered. In rare cases, CYC may be considered for use during the latter half of pregnancy for severe life- or organ-threatening maternal disease that is refractory to other agents [15]; however, these pregnancies remain at high risk due to maternal disease in addition to CYC use.

Immunosuppressive agents that are compatible with pregnancy

Azathioprine (AZA) is a prodrug used to induce and maintain disease remission and limit the use of corticosteroids in management of many SLE manifestations. In severe disease with renal involvement, AZA has been used as maintenance therapy following induction with cyclophosphamide and MMF [16]. AZA is rapidly metabolized to 6-mercaptopurine (6-MP), which passes into fetal circulation. However, the fetal liver lacks the enzyme necessary to metabolize 6-MP into its active metabolite, thioinosinic acid. While thiopurines were listed as pregnancy category D by the FDA based on initial animal data [17], AZA is widely considered acceptable to use during pregnancy and has not been associated with increased risk of adverse pregnancy outcomes or congenital abnormalities [17, 18]. Additionally, studies involving pregnant women with renal transplants, as well as those with IBD, continue to support the use of AZA throughout pregnancy to induce and maintain disease remission, preventing intra-partum flares that are associated with adverse outcomes. Therefore, AZA has become one of the most commonly used chronic immunosuppressive medications during pregnancy as it can be effective in maintaining remission in many SLE manifestations and reduced steroid requirements without teratogenic

associations. Indeed, for women with a history of renal disease or other active manifestations who have had disease stability with MMF or CYC, it is recommended that they change to AZA therapy and then be followed for 6 months to assure disease quiescence before proceeding with pregnancy. In cases of inadvertent pregnancy occurring with MTX, MMF, or CYC exposure, it is advisable to change to AZA rather than simply discontinue the teratogenic medication in order to reduce risk of disease flare.

Calcineurin inhibitors, such as tacrolimus and cyclosporine, are similarly considered compatible with pregnancy based largely on accumulated data from solid organ transplant recipients [19]. Improvement in management of lupus nephritis with the use of DMARDs has resulted in an increasing number of women with prior or current renal involvement becoming pregnant. Lupus nephritis during pregnancy increases morbidity and mortality of both mother and baby [20]. These agents have been used in induction therapy of lupus nephritis in pregnancy, when other immunosuppresive agents (MMF, CYC) have failed or were not tolerated [21•]. Additionally, tacrolimus and cyclosporine may achieve partial or complete remission without the need for induction or dose escalation of oral steroids [22, 23]. Calcineurin inhibitors do enter fetal circulation, and the blood levels detected are approximately half of levels in maternal circulation [24]. Reviews of cyclosporine use during pregnancy have not identified an increased incidence of congenital malformations or fetal growth restriction [25, 26]. However, continuous exposure in utero seems to impair T-, B-, and NK-cell development and function in neonates and these effects may extend into the first year of life, the clinical consequence of which is uncertain [27]. Tacrolimus and cyclosporine are compatible throughout pregnancy at the lowest effective dose and are often used in conjunction with AZA if additional disease control is required.

Biologic agents

Most antibody-based therapeutics are immunoglobulins with an IgG1 construct. In general, antibodies are large molecules that are unable to passively cross from maternal to fetal circulation. Starting in the second trimester, IgG1-based antibodies (natural or therapeutic) are actively transported to the fetal circulation. At term, the fetal concentration of IgG1 antibodies is higher than the maternal circulation so that the neonate may benefit from passive maternal humoral immunity for the first months of life. Therefore, therapeutic antibodies essentially do not cross the placenta for the first trimester, with increasing fetal concentrations as the pregnancy continues to term. Therapeutic antibodies used for the treatment of SLE are generally limited to belimumab and rituximab. Belimumab is FDA approved for monthly intravenous infusion for the treatment of mild-to-moderate manifestations. To date, there is little human data on pregnancy outcomes with exposure to belimumab, but recommendations are to avoid use during pregnancy until risks are better known. Unlike small molecule therapeutics, belimumab does not need to be discontinued in advance of pregnancy and can be safely stopped once a pregnancy is confirmed [28•]. Rituximab is licensed for the treatment of rheumatoid arthritis, ANCA-associated vasculitis, and B-cell malignancies. While not licensed for SLE, it is used as a second line agent for more severe manifestations including nephritis

and refractory cytopenias. While human data to date has not identified any associations with congenital anomalies, rituximab is not recommended for routine use during pregnancy. However, in the setting of severe maternal disease including refractory nephritis or clinically significant cytopenias, rituximab has been used successfully during all trimesters of pregnancy [29]. Given that the disease-modifying effects of rituximab usually last at least 6 months, the consideration of use during pregnancy is usually limited to a single course of therapy. Intravenous immunoglobulin (IVIg), concentrated natural antibodies used for therapeutic purposes, is also compatible with use during pregnancy, particularly in cases of severe exacerbation of disease. The infused antibodies will behave identically to maternally derived antibodies and will cross to fetal circulation in the same manner. Given the increased blood volume of pregnancy, caution must be observed during IVIg infusion to avoid fluid overload.

Corticosteroids

Corticosteroids are among the first line therapies for acute flares of disease during pregnancy. Ideally, SLE would be treated to low disease state without requirement of moderate to high dose steroids before pregnancy is undertaken; however, disease flares may still occur during pregnancy even in the best of circumstances. Corticosteroids have the benefit of very rapid onset of action and are able to control active disease more quickly than most other immunosuppressive therapies. In cases where rapid control of disease is required, non-fluorinated corticosteroids should be initiated as quickly as possible and then titrated to the lowest effective dose as soon as it is safe to do so. There is extensive experience with corticosteroids during pregnancy as they are used for so many indications. Even pulse dosing (one gram intravenously daily for 3 days) has been used in pregnancy to treat severe maternal disease. There has been debate in the past regarding an increased risk of cleft palate with first trimester exposure to 20 mg or more of prednisone daily; however, large meta-analyses have failed to confirm such association [30]. Because of the myriad of adverse effects of glucocorticoid use, recommendations for use during pregnancy are the same as in a non-pregnant patient: to use the lowest dose for the shortest possible time. To treat maternal disease, it is important to use non-fluorinated glucocorticoids (prednisone, prednisolone) as the placenta converts active glucocorticoids into inactive metabolites and therefore little active drug reaches the fetal circulation. In contrast, when glucocorticoids are used for fetal indications (lung maturation), fluorinated agents (betamethasone, dexamethasone) are preferred as the majority of active drug will reach the fetus.

Hydroxychloroquine

The use of hydroxychloroquine (HCQ) during pregnancy has perhaps undergone the most dramatic change in recommendations over the past few decades. In the past, it was recommended that antimalarials should be discontinued at least 6 months prior to pregnancy based upon animal studies showing ocular and ototoxicity of the offspring and case reports of human abnormalities with chloroquine exposure [31]. At the same time, in the non-pregnant SLE population, the Canadian Hydroxychloroquine Withdrawal study demonstrated the

importance of maintaining HCQ and the high risk of SLE flare upon discontinuation [32•]. Case reports and increasingly larger case series were published showing no adverse fetal outcomes with HCQ exposure, first in early pregnancy and then throughout pregnancy. In 2001, a small randomized controlled study evaluated outcomes of 10 SLE pregnancies randomized to HCQ and 10 SLE pregnancies randomized to placebo [33]. This small study demonstrated no congenital abnormalities of any offspring despite detailed ophthalmological examination, but also showed a significant increase in active SLE during pregnancy among women receiving placebo. Based on this data, recommendations for HCQ use during pregnancy evolved from discontinuation to continued use of HCQ by patients if desired. As a consequence of subsequent larger observational studies, the initiation or continuation of HCQ has become recommended for women with SLE prior to or during pregnancy.

Summary

Over the past few decades, there have been dramatic changes in the recommendations regarding the safety of pregnancy itself in women with SLE as well as in recommendations regarding use of immunosuppressive agents during pregnancy. The mid-twentieth century recommendations were to avoid pregnancy altogether, and extreme caution was applied to medication use during pregnancy out of concern for teratogenicity. The past several decades have brought about improved disease control for women with SLE and have also brought a more nuanced understanding of medication use during pregnancy for many different indications. Certainly, concerns for active maternal disease during pregnancy have been more widely recognized, and with more SLE women considering and completing pregnancies, accumulated experience has helped to understand risk factors for adverse outcomes, as well as a more balanced consideration of risk and benefits of medication use during pregnancy.

With the proliferation of new therapeutics that can be used to treat SLE, only a small number are known teratogens and must be avoided during pregnancy. Fortunately, in most cases, there are alternative medications that are compatible for use though the duration of pregnancy that can successfully manage disease. Certainly, we should never become complacent or cavalier about prescribing medications during pregnancy; however, the last few decades have taught us that successful pregnancy is achievable for most SLE women and medication use during pregnancy should not be routinely avoided but rather that informed and judicious use of available therapeutics will increase the probability for healthier mother and infant.

Compliance with Ethical Standards

Conflict of Interest

Erin Shirley declares that she has no conflict of interest. Eliza F. Chakravarty declares that she has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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