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Contraception and preconception counseling in women with autoimmune disease

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A B S T R A C T

Appropriate contraception and preconception counseling are critical for women of reproductive age with systemic autoimmune diseases (AIDs) because clinical diagnosis, rheumatology medications, and disease activity may impact the safety or efficacy of certain contraceptives as well as the risk of adverse pregnancy outcomes. The presence of antiphospholipid (aPL) antibodies (anticardiolipin, *anti*-β2 glycoprotein I, and lupus anticoagulant) is the most important determinant of contraception choice, as women with these antibodies should not receive estrogen-containing contraceptives because of the increased risk of thrombosis. Prepregnancy counseling generally includes the assessment of preexisting disease-related organ damage, current disease activity, aPL antibodies, *anti*-Ro/SS-A and anti-La/SS-B antibodies, and medication safety in pregnancy. Quiescent AID for six months on pregnancy-compatible medications optimizes maternal and fetal/neonatal outcomes for most patients.

Introduction

Systemic autoimmune diseases (AIDs) are variable in terms of both clinical manifestations and degree of severity. AIDs include a broad spectrum of systemic disorders related to dysregulation and overactivity of the immune system. Systemic lupus erythematosus (SLE) usually involves multiple organ systems, with symptoms ranging from sun-induced rash to life-threatening renal or neurologic disease. Joint inflammation and damage are the hallmarks of rheumatoid arthritis (RA) and other types

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of inflammatory arthritis. Systemic vasculitides, defined by the presence of vascular inflammation in small-, medium-, or large-sized arteries, usually lead to end-organ damage if untreated. Systemic sclerosis, characterized by progressive fibrosis and vasculopathy, imparts risk of interstitial lung disease and renal crisis with malignant hypertension. Antiphospholipid syndrome (APS) manifestations are largely limited to thrombosis (arterial, venous, or small vessel) and pregnancy morbidity, including pregnancy loss and adverse pregnancy outcomes (APOs) such as preterm delivery and small-for-gestational age (SGA) infants. AID may affect pregnancy outcomes, and pregnancy may impact AID activity or exacerbate manifestations of chronic disease-related damage.

There is an overall increased risk of APOs and maternal morbidity for patients with most AID diagnoses; outcomes are generally improved with controlled disease and pregnancy planning [1,2]. While risk is most often significant for women with SLE and APS, almost every AID presents an increased risk as compared to the general population, even RA [3]. As a result, choice of contraception and planning for pregnancy are particularly important.

The most significant issues affecting contraceptive choice are concern for flare of underlying disease, increased risk of thrombosis, and potential medication interactions. Contraception is imperative for sexually active patients who have severe organ damage that precludes pregnancy due to high maternal risk, those with active disease inflammation that can impact maternal and pregnancy outcomes, and those on teratogenic medications.

Prepregnancy counseling should include discussion regarding the importance of quiescent disease at conception and the significance of relevant autoantibodies such as antiphospholipid (aPL) and *anti*-Ro/SS-A and/or anti-La/SS-B. Even when renal function is adequate, a history of nephritis increases the risk of adverse outcomes, particularly preeclampsia and eclampsia [2]. Expectations for pregnancy and plans for monitoring and management will vary according to diagnosis, autoantibody status, disease activity, and patient history (medical and obstetric). Contraception and pregnancy discussions and decisions benefit from ongoing communication between obstetrician-gynecologists (OB-GYNs) and rheumatologists to provide optimal patient outcomes.

Contraception

The use of safe and effective contraception may be the single most important measure to improve AID pregnancy outcomes because the presence of active disease and the use of teratogenic medications are common and may impact both maternal and fetal/neonatal outcomes.

Utilization of contraception by women with AID

Increasing utilization of safe and effective contraception is an important goal for physicians caring for women with AID. Survey studies have documented the low use of effective contraception in these patients. Approximately 1 in 4 patients with SLE at risk for pregnancy do not use consistent contraception [4–9]. Patients with SLE taking teratogenic medications are no more likely to use effective contraception than those not on these medications [6]. Twenty-seven percent of patients at a Swiss inflammatory arthritis clinic on teratogenic drugs were not using any form of contraception, and most were aware of the potential teratogenicity [7]. One half of patients with SLE who used contraception regularly used less effective barrier methods [6].

Large database studies confirm underutilization of effective contraception. One study utilizing data for 11,649 women with and without chronic medical conditions including SLE and RA found contraception prescription rates to be significantly lower for women with chronic conditions and lowest of all for those with SLE and RA (21.7% and 20.0%, respectively) than a 41.1% rate for women without chronic illness ($p < 0.001$) [8]. A single-center administrative database study of contraception use among women with any AID ($N = 2455$) found that while 32.1% used prescription contraception, only 7.9% used highly effective prescription methods. More than 70% of these women were taking at least one teratogenic medication, but this was not associated with prescription contraception use [9]. A recent study highlights additional concerns regarding the risk of adverse side effects for women with AIDs. Eight percent of women in a large SLE cohort surveyed were using oral estrogen–progestin

contraceptives; however, 55% of the treated patients had one or more contraindications to use including aPL, hypertension, and migraine with aura [10].

Multiple factors may explain low rates of use. Medical management of acute illness may overshadow health maintenance issues for rheumatologists, and there may be an assumption that contraceptive counseling should be provided solely by OB/GYNs. Other issues may play a role, such as limited time or lack of familiarity with the subject area [11]. In one SLE cohort (n = 68), one-third of patients did not receive contraceptive counseling from their rheumatologist when starting a new medication. In addition to higher SLE disease activity, older age, white race, and depressive symptoms were independently associated with lack of counseling [12]. For OB/GYNs, uncertainty regarding the medical issues of a patient's underlying disease or medications may lead to hesitation in prescribing certain contraceptives for fear of adverse effects.

There are increasing efforts at education regarding reproductive health issues for rheumatologists. Three of 20 SLE quality indicators published in 2009 focused on reproductive health, including effective contraception [13]. The online Mycophenolate REMS program provides education and counseling for patients and physicians regarding the unique contraceptive issues related to the use of mycophenolate, a drug commonly used in SLE [14]. A recent study demonstrated improvement in rates of contraceptive counseling after provider interventions [15], and ongoing initiatives utilizing the electronic medical record may further improve counseling. The American College of Rheumatology (ACR) has prepared its first-ever guideline on reproductive health care for patients with rheumatic and musculoskeletal disorders, which includes specific recommendations for contraception and pregnancy assessment as well as for the management of patients during assisted reproductive techniques, pregnancy, and breastfeeding.

Risks of contraception in women with AID

Both the OB/GYN and the rheumatologist should discuss contraception and plans for pregnancy beginning early in the physician–patient relationship. The choice of contraceptive will depend on efficacy, safety, and individual preferences. Postponing pregnancy if disease is active generally leads to improved pregnancy outcomes. For example, in the PROMISSE (Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus) study, a multicenter observational study of pregnancy outcomes in women with SLE and/or aPL antibody, APOs developed in 19% of all patients with SLE (n = 386); however, for patients who did not have identified risk factors such as active disease at conception, hypertension, or positive aPL, the risk of APOs was lower, 7.6% [16].

Long-acting reversible contraceptives (LARC) including intrauterine devices (IUDs) (levonorgestrel (LNG) and copper IUDs) and the etonogestrel implant are highly effective [17] and are recommended for patients with AID. Other effective forms of contraception for patients unable or unwilling to utilize LARC include estrogen–progestin methods, progestin-only pill, and depo-medroxyprogesterone acetate (DMPA). Less effective methods such as condoms are discouraged unless more effective options are not possible. The potential benefit of condoms in preventing sexually transmitted infections should be discussed; however, the safety of over-the-counter emergency contraception for all patients with AID should also be discussed.

Major medical factors influencing the choice of contraception for women with AID include risk of flare, risk of thromboembolism, and potential interactions with medications.

Disease flare

Early reports suggested increased flares in patients with SLE exposed to estrogen–progestin oral contraceptives (OCs), and hence, their use was avoided. However, in 2005, two randomized controlled clinical trials demonstrated no significant increase in the risk of flare in well-defined SLE populations with stable disease activity using estrogen–progestin OCs versus other progesterone-only OCs, copper IUD, or placebo [18,19].

The Safety of Estrogen in Lupus Erythematosus National Assessment (SELENA) trial randomized 183 patients with lupus who had inactive or stable active disease to triphasic ethinylestradiol 35 μg (EE)/

norethindrone 0.5–1 mg or placebo. Patients with a history of thrombosis or positive aPL were excluded as were patients with active disease. Severe flare rates at one year did not show significant difference (0.084 vs. 0.087 for the treatment group vs. the placebo group, respectively); mild-to-moderate flares and overall combined flare rates were equivalent [18]. Another study compared the use of EE 30 μg/LNG 150 μg/day with the use of oral LNG 0.3 mg/day or a copper IUD in patients with SLE. Disease activity was similar among the three groups, including rates of severe flare, global disease activity, and overall flare [19].

These reassuring results may not be generalizable to estrogen–progestin contraceptives with higher estrogen content or a different administration method such as the transdermal patch or the vaginal ring. Formulations yielding higher serum estrogen levels are discouraged. Study patients also had low stable disease activity at entry, and hence, women with active SLE disease, especially with nephritis, are discouraged from using estrogen–progestin OCs.

Use of estrogen-progestin OCs in other patients with AID has not generated concern regarding flare. Several early studies suggested patients with RA might potentially benefit with improved disease control from treatment with estrogen-containing OCs; however, data remain inconclusive. One case–control study of 176 women with RA found a relative risk of developing severe disease with estrogen–progestin OC use for >5 years to be 0.1 (95% CI 0.01–0.6) [20]; however, a systematic review was not able to confirm any beneficial effect of estrogen–progestin OCs on RA progression [21].

Effects of the LNG IUD, etonogestrel implant, or DMPA on disease activity in AIDs including SLE have not been specifically studied, but progestins alone have not been suggested to increase disease activity in any AID.

Thromboembolic risk

Thrombotic risks of combined estrogen–progestin OCs are well established and depend on both estrogen and progestin components. Estrogen risk is dose dependent. The odds ratios (ORs) for risk of venous thromboembolism (VTE) with estrogen–progestin OCs (20–50 μg EE) vary for pills with the same EE content from 2.24 to 6.61 depending on the type and dosing of progestin. Third- and fourth-generation progestins impart almost twice the risk of second-generation progestins (RR 1.79) [22].

Thrombosis risk with estrogen–progestin OCs should be considered for all patients with AID, as many are at a slightly increased risk for thrombosis even if they are aPL negative [23–26]. In general, however, aPL represents the most significant risk factor for thrombosis. Lupus anticoagulant (LAC) and/or high-titer IgG anticardiolipin (aCL) appears to confer the highest risk [27]. The presence of additional prothrombotic risk factors including genetic variants, medical comorbidities such as nephrotic syndrome, or exogenous factors such as bed rest or smoking additionally increases thrombotic risk associated with aPL [28]. Estrogen–progestin OCs should be avoided in patients with positive aPL or other significant risk factors for thrombosis.

While reports describe aPL-positive patients with venous or arterial thromboses attributed to estrogen-containing contraceptives [29], no controlled studies have addressed this question because of the perceived risk. A marked increased risk for stroke with aPL and estrogen–progestin OC was demonstrated in the RATIO study; however, a case–control study evaluated stroke and myocardial infarction in women <50 years old. OR for stroke was 43.1 (12.2–152.0) in the presence of LAC and increased to 201.1 (14.5–523.0) with LAC plus estrogen–progestin OC [30].

Use of progestin-only contraceptives (POCs) is widely accepted as a lower risk for patients with AID unable to use estrogen-containing methods, although the degree of thrombotic risk – if any – is debated. POCs may offer an advantage in patients on anticoagulation by reducing heavy menstrual blood flow. Combined data on POC use in the general population do not show an increase in VTE risk. A meta-analysis of 8 publications (including 2 studies with patients at high risk for VTE) demonstrated that POCs overall are not associated with an increased risk of VTE when compared with nonusers, RR = 1.03, (0.76–1.39). In a subgroup analysis, however, the two studies that included small numbers of patients using DMPA did find a significant increased risk of VTE with DMPA, RR = 2.67 (1.29–5.53) [31]. In contrast, the progesterone-only pill VTE risk was not elevated (RR = 0.90, 0.57–1.45) as was the risk with the LNG-IUD (RR = 0.61, 0.24–1.53) [31]. Several more recent studies of women with elevated VTE

risk did not identify a higher risk with the use of non-DMPA progestin contraceptives [32–34]. There is little information, however, on thrombosis risk with the etonogestrel subdermal implant.

Data on POC use in patients with AID are limited. The Sanchez-Guerrero et al. trial that compared estrogen–progestin OC with a progesterone-only pill and the copper IUD did not find a difference in VTE rate between the two hormonal groups [19]. One case series surveyed 23 anticoagulated APS patients with LNG-IUDs placed for the treatment of menorrhagia associated with anticoagulation: 58.8% of patients reported decreased bleeding, and there were no thromboses [35]. A small series of patients with SLE (with and without aPL) on POC (including progestin-only pill, DMPA, subdermal implant, and LNG-IUD) found that over the course of one year of follow-up, BMI increased slightly but there were no thromboses [36].

Given the limited data on aPL-positive patients, the Centers for Disease Control and Prevention guidelines for medical eligibility for contraceptive use do not recommend POCs for women with SLE having positive (or unknown) aPL. Risk is considered Category 3, where "theoretical or proven risks outweigh advantages [37]." By contrast, the American College of Obstetricians and Gynecologists (ACOG) guidelines for contraceptive use in women with chronic medical conditions recommend POCs as safer alternatives than estrogen–progestin OCs for women with SLE having aPL, active nephritis, and vascular disease [38].

Rheumatology medications

Patients with AID are often on multiple medications, and it is important to identify potential pharmacological interactions before recommending hormonal contraception. Medications that have potential interactions with hormonal contraceptives include mycophenolate, cyclosporine, warfarin, and anticonvulsants [39,40]. Most antibiotics, with the exception of rifampin, do not significantly affect efficacy [41]. Some herbal medications, particularly St. John's wort, may increase the clearance of estrogen-progestin OCs, decreasing efficacy [42]. A common concern for AID patients is the use of mycophenolate medications, commonly used for the treatment of lupus nephritis. Because mycophenolate may interact with both estrogen and progestin, recommendations are to use either an IUD or two alternative forms of contraception [15].

The chronic use of immunosuppressive medications may raise the concern for an increased risk of IUD-associated infection. There are no direct studies on infection risk with IUD use in rheumatology patients, but the CDC guideline recommends IUD use in patients with SLE to be acceptable (Category 2) [37]. Furthermore, studies have shown no increased infection risk in HIV-infected or solid-organ transplant patients [43–46]. On the basis of these data, IUDs (progestin or copper IUDs) are recommended for use in women with AID requiring immunosuppressive medications.

Recommendations

For all patients with AID, it is appropriate to ask about contraception and pregnancy planning at the first or early visit, or when starting a new medication, and to emphasize the benefits of safe and effective contraception in preventing adverse maternal and pregnancy outcomes. APL should be measured in patients with SLE, SLE-like AID, or relevant clinical history because aPL is an important determinant of contraceptive safety. Testing should include LAC, aCL, and *anti*-β2 glycoprotein I (aβ2GPI) antibodies. A summary of the advantages and disadvantages of common contraceptives for patients with AID is presented in Table 1.

APL-negative patients including those with stable SLE

LARC should be encouraged for all patients, although there are no data specific to rheumatology patients for the etonogestrel implant. Use of DMPA in patients with osteoporosis or significant risk factors is discouraged because of the potential for decreased bone density [47].

For patients with aPL-negative SLE, disease activity should be assessed when considering estrogen–progestin OCs; these should be avoided if the disease is active. If the patient is aPL-negative with quiet/stable SLE but is unable or unwilling to use LARC, then it is appropriate to consider the use of

Table 1
Advantages and disadvantages of common contraceptive methods for patients with AID.

Contraceptive method	Advantages	Disadvantages
LARC:	Highly effective	
LNG IUD	May decrease menstrual blood flow in anticoagulated patients No increased thrombosis risk – OK for patients who are aPL+ OK for patients on immunosuppressive therapy	
Copper IUD	No increased thrombosis risk – OK for patients who are aPL+ OK for patients on immunosuppressive therapy	May increase menstrual blood flow in anticoagulated patients
Etonogestrel implant		Limited data overall No data in patients with AID
Estrogen–progestin:	Effective	Cannot be used in patients who are aPL+; caution with other thrombosis risk factors (e.g., nephrotic syndrome) Drug interaction with mycophenolate Not evaluated in patients with active SLE – avoid
Pill	No increased risk of flare in patients with stable SLE	
Transdermal patch		Not studied in SLE Concern for flare risk given higher serum estrogen levels
Vaginal ring		Not studied in SLE
Progestin-only:	All effective	Drug interaction with mycophenolate
Pill	No increased thrombosis risk – OK for patients who are aPL+ May decrease menstrual blood flow in anticoagulated patients	
DMPA	May decrease menstrual blood flow in anticoagulated patients	May increase the risk of thrombosis (limited data) May lower bone density – avoid in patients with osteoporosis or risk factors
Barrier methods:		Less effective
Male condom	Some protection against STI Over the counter	
Emergency contraception	Option for all patients with AID (even those with active disease or + aPL) Over the counter	

AID: Autoimmune disease.
SLE: Systemic lupus erythematosus.
LARC: Long-acting reversible contraception.
LNG IUD: Levonorgestrel intrauterine device.
Copper IUD: Copper intrauterine device.
aPL: antiphospholipid antibody.
DMPA: Depo-medroxyprogesterone acetate.

estrogen–progestin OCs [18,19]. No studies have been reported in patients with SLE using the vaginal ring or transdermal patch, but the patch has been suggested to result in increased serum levels of estrogen [48]. Fourth-generation progestins (such as drospirenone) in combined OCs have been suggested, but not proven, to increase the risk of hyperkalemia [49]. They should be used with caution in patients with SLE who have nephritis or who are on angiotensin-converting enzyme inhibitors (ACE-I).

Patients with positive aPL or other significant thrombotic risk factors

LARC should be encouraged for all aPL-positive patients (or other patients at significant thrombotic risk), although there are no data specific to aPL-positive patients for the etonogestrel implant. The LNG-IUD is a good alternative for APS patients on anticoagulation therapy because of the expected decrease

in menstrual bleeding [35]. If the patient is unable or unwilling to use LARC, the progestin-only pill should be considered. As limited data suggest a possible increased risk of thrombosis with DMPA [31], it may be reasonable to avoid this as a long-term contraceptive until more data are available.

Preconception counseling

A general assessment for patients considering pregnancy should be performed regardless of the specific autoimmune diagnosis. Determination of risk includes the identification of serious organ damage that might affect the ability to safely carry a pregnancy, evaluation of disease activity, serologic evaluation for the identification of autoantibodies associated with adverse fetal or neonatal outcome, and review of current medications and their safety in pregnancy (Fig. 1).

Severe organ damage

Severe disease may preclude pregnancy because of a high risk of maternal morbidity and mortality; such organ damage may include severe presentations of cardiomyopathy, cardiac valve disease, neurologic manifestations, renal insufficiency, or pulmonary arterial hypertension (PAH). Although mortality risk with PAH has decreased in recent years, it is prohibitive even with current aggressive therapies. Deaths generally occur in the postpartum period, mostly within 72 h of delivery and because of right heart failure [50]. Because of the high risk, baseline testing to rule out PAH (echocardiogram and pulmonary functions tests) may be considered in patients with high-risk diseases such as systemic sclerosis and mixed connective tissue disease.

Pre-existing renal disease is a relatively common issue, especially with SLE or vasculitis. The most important predictors of permanent renal disease in pregnant women are GFR <40 ml/min/1.73 m^2 and proteinuria greater than 1 g/24 h [51]. Patients with milder disease are at a much lower risk: a recent meta-analysis including 2751 pregnancies in patients with lupus nephritis who have a mild disease found good renal prognosis, with 2% patients developing deterioration in renal function and only 1% requiring dialysis [2].

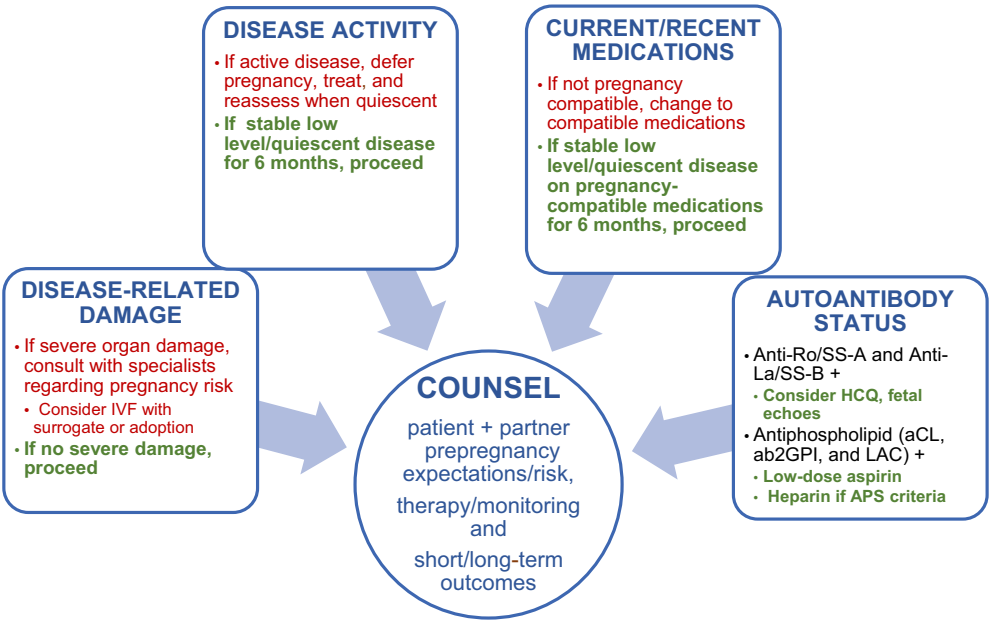

Fig. 1. Prepregnancy assessment and counseling for patients with AID.

If patients with severe disease-related damage are intent on having a biological child, they can consider in vitro fertilization (IVF) with surrogacy. A patient unable to safely carry a pregnancy may incur less risk with more limited duration and physiological changes associated with IVF. Issues surrounding surrogacy may be complex, depending on financial, legal, or other constraints.

Disease activity

It is essential to assess for recent or current disease activity in patients considering pregnancy: if patients have ongoing active disease, then they should defer pregnancy, use appropriate contraception, receive treatment, and be reassessed after 4–6 months of inactive disease.

Numerous studies confirm the importance of stable disease at conception and the adverse effect of flare during pregnancy for SLE and other patients with AID [52–56]. A high level of lupus disease activity during pregnancy has been associated with a lower chance of live birth, greater chance of perinatal death, and lower chance of full-term delivery [54]. Women with long-standing remission in SLE are more likely to complete their pregnancies uneventfully [55]. Most patients with systemic sclerosis without severe disease-related damage have successful pregnancies, but patients with early diffuse disease are advised to defer pregnancy for several years, as they are thought to be at increased risk for developing renal crisis during pregnancy [57].

In general, pregnancy outcome in RA is comparable to that in the general population, and up to 50% of patients with RA develop a pregnancy-induced remission [58]. Even in patients with RA, however, disease activity during pregnancy may impact outcome: studies suggest a small increase in the risk of lower birth weight and preterm delivery for patients with RA who have active disease during pregnancy, with a slight increase in perinatal mortality and higher frequency of cesarean sections [59,60].

Assessment of autoantibodies

Assessment of aPL and *anti*-Ro/SS-A and/or anti-La/SS-B autoantibodies helps to determine the risk, type, and frequency of pregnancy monitoring and need for potential additional therapy.

Antiphospholipid antibodies

Every patient with SLE and patients with an adverse obstetric history or history of thrombosis should be evaluated for the presence of aPL. Usual testing includes LAC, aCL, and aβ2GPI. Patients should be counseled regarding associated pregnancy risks, including recurrent miscarriage, fetal loss, preterm birth, intrauterine growth restriction (IUGR), and preeclampsia/eclampsia [61]. The diagnosis of obstetric APS generally requires the presence of moderate-to-high titers of aCL or aβ2GPI and/or a positive LAC on two or more occasions, 12 weeks apart [62]. APOs are most strongly associated with the presence of LAC [63]. Other risk factors include history of thrombosis, history of prior fetal loss, and presence of underlying SLE. Patients with low-titer aCL and aβ2GPI, especially those without a history of prior fetal loss or thrombosis, have significantly lower risk [63].

Patients with aPL are recommended to take low-dose aspirin for preeclampsia prevention [64]. Patients with obstetric APS or thrombotic APS will require the addition of unfractionated or low-molecular-weight heparin (LMWH), prophylactic or therapeutic, respectively, once pregnant. Patients should be aware of the plans for monitoring during the third trimester, with nonstress tests, umbilical artery Doppler tests, or serial ultrasound scans [61].

Patients with SLE, RA, undifferentiated connective tissue disease, and Sjogren's syndrome should be evaluated for *anti*-Ro/SS-A and/or La/SS-B antibodies. Positive patients are at risk of delivering an infant with neonatal lupus erythematosus (NLE) and should be counseled regarding the spectrum of transient NLE manifestations (rash, thrombocytopenia, and liver function abnormalities), as well as the risk of serious and permanent congenital heart block (2%). Risk of congenital heart block in the offspring of a patient who has already had a child with NLE is elevated, approximately 17% [65].

Antibody-positive patients require periodic fetal echocardiograms from 16 to 26 weeks to assess for fetal heart block: for high-risk patients (those with a previous child with NLE), echocardiograms are recommended weekly. Use of hydroxychloroquine (HCQ) may reduce the risk of complete heart block

[66]. Patients who are negative for *anti*-Ro/SS-A and anti-La/SS-B do not require fetal echocardiograms, as the risk is associated with demonstrated antibody.

Medication review

Medications should be reviewed early in the planning process. If current medications are contraindicated, options include tapering and discontinuation if disease permits, or a change to pregnancy compatible medications. The disease should be stable on compatible medications for 4–6 months before conceiving. In addition to prednisone, immunosuppressive medications compatible with pregnancy include azathioprine, cyclosporine, and tacrolimus [67]. Cyclophosphamide is teratogenic in the first trimester but has been used rarely in the second or third trimesters for life-threatening disease.

Certain biological therapies are also compatible with pregnancy. Tumor necrosis factor (TNF) inhibitors are a mainstay of inflammatory arthritis treatment and are increasingly continued during pregnancy for active disease [67]. These include adalimumab, certolizumab, etanercept, golimumab, and infliximab. All except certolizumab pass through the placenta after the first trimester because of the active transfer of the IgG Fc chain. Reports are reassuring concerning safety with use immediately before conception and in the first trimester. A common approach for women with RA on combination, methotrexate, and TNF-inhibitor, therapy is to stop methotrexate, continue the TNF-inhibitor, and wait three months before trying to conceive. Once pregnancy is confirmed, patients may continue the TNF-inhibitor throughout pregnancy if necessary. If possible, the TNF-inhibitor is stopped by the third trimester to reduce the risk of significant drug levels in the neonatal circulation at birth. Infants of women treated throughout pregnancy are recommended to avoid live vaccines during the first six months of life [68].

Non-TNF-inhibitor biological therapies based on IgG constructs may be continued up to the time pregnancy is diagnosed, but lack of data does not support continuation during pregnancy. Rituximab may be used during pregnancy for organ or life-threatening disease. Small-molecule medications for inflammatory arthritis, such as tocilizumab or apremilast, have not been well studied and are generally avoided [67].

Non Rheumatology medications should be modified if necessary. ACE-I are changed to pregnancy-safe substitutes several weeks before attempting to conceive, with follow-up of blood pressure and proteinuria after discontinuation. Warfarin is usually changed to LMWH and monitored with factor Xa levels. LMWH is usually started before conception; otherwise, the change must be made before the sixth week of pregnancy to avoid warfarin embryopathy.

Continuation of HCQ, commonly used in SLE, is encouraged. Women with SLE on HCQ have been shown to have lower disease activity and to be on lower prednisone doses at delivery [69]; in contrast, patients discontinuing HCQ within three months of conceiving have a greater risk of flare [70]. The offspring of HCQ-treated *anti*-Ro/SS-A- and/or La/SS-B-positive patients may have a lower risk of complete congenital heart block [66]. If patients with SLE or patients with *anti*-Ro/SS-A or La/SS-B antibodies have no contraindications to HCQ, there are likely benefits for both mother and child.

The addition of low-dose aspirin during pregnancy in patients with AID has varying support: it is used for preeclampsia prevention in patients with demonstrated risk factors [70] and has been recommended for patients with SLE or aPL [71], although no controlled studies have been done in patients with AID.

Patients on the folate antagonist sulfasalazine, a pregnancy-compatible medication for inflammatory arthritis, are generally advised to further increase their folic acid intake before and during pregnancy [67].

Counseling

Counseling is important for both the patient and her partner, and education should include the risks of pregnancy for the given diagnosis and on the basis of the patient's clinical profile. Each patient should understand potential risks to both maternal health and the health of the infant (most often complications associated with preterm birth or SGA).

Pregnancy risk and outcome

AID pregnancy outcomes have improved in recent years, yet many diagnoses are still associated with an increased risk of APOs when compared with the general population. Patients with SLE have a 2- to 4-fold increase in pregnancy complications including preeclampsia, preterm labor, and IUGR; medical complications are similarly increased, including thrombosis, major infection, and thrombocytopenia [72]. Most reviews of pregnancies in other AIDs find increased rates of preterm birth and/or SGA infants [73]. Risk of flare during or after pregnancy exists even when the disease is quiescent at conception.

Delivery

In general, cesarean section is reserved for those with obstetric indications. While rare, orthopedic impairments due to severe hip arthritis or hip replacements with limited range of motion may preclude vaginal delivery. Patients with severe rheumatoid or spondylitic involvement of the cervical spine should be assessed, as with any surgery, for instability should endotracheal intubation be necessary. Patients with a history of vasculitis, primarily Takayasu's, may require baseline vascular imaging and hemodynamic monitoring during delivery.

Pregnancy outcomes

The major risk to the child is the constellation of complications associated with prematurity and SGA, often with long-term implications for disability. Long-term outcomes of children of mothers with SLE and APS have been studied, and a small increase in the risk of learning disability has been suggested, although numbers are small and results may be confounded by effects related to preterm birth [74].

Postpartum period

Postpartum risk of flare should be anticipated, with a treatment plan in place. Breastfeeding is encouraged when possible. Prolonged breastfeeding may be a concern for patients with severe osteoporosis because it may further lower bone density, leading to increased risk of fracture.

Many rheumatology medications are compatible with breastfeeding. Glucocorticoids in low dose are safe. For doses >20 mg daily, discarding breast milk for 4 h after medication is suggested. Aspirin, heparin, warfarin, hydroxychloroquine, and sulfasalazine may be used in patients who are breastfeeding. Immunosuppressive therapies compatible with breastfeeding include azathioprine, cyclosporine, and tacrolimus. Biological medications based on an IgG construct, including TNF-inhibitors, belimumab, and others, are compatible with breastfeeding because very little IgG is transferred into breast milk [67].

Patients on prophylactic LMWH therapy during pregnancy are generally advised to continue this for 6–12 weeks postpartum to minimize the risk of postpartum thrombosis; those requiring long-term anticoagulation may switch back to warfarin.

Summary

Decisions regarding contraception and pregnancy ultimately depend on the individual patient, her medical condition, and her preferences. Long-acting methods of birth control, such as the IUD, are most effective and are recommended for use in women with AID. Estrogen–progestin OCs may be used in most patients with AID but should not be used in those with active SLE or those with increased risk for thrombosis due to positive aPL, history of thrombosis, nephrotic syndrome, or active vasculitis. POCs are good alternatives for most patients and may be useful for decreasing heavy menstrual blood loss in anticoagulated patients.

Optimal contraception and pregnancy planning in patients with AID depend on the rheumatologist, obstetrician, and patient working together as a team, with identification and understanding of

potential risks. Good maternal and fetal outcomes are most likely for the patient without severe organ damage and with well-controlled disease on pregnancy-compatible medications.

Conflicts of interest

None.

Practice points

- LARC are most effective and are recommended for women with AID.
- Estrogen–progestin oral contraceptives may be used in most patients with AID but should not be used in those with active SLE or those at increased risk for thrombosis, such as those with positive aPL, history of thrombosis, nephrotic syndrome, or active vasculitis.
- Progestin-only methods are good alternatives for patients who are unable to take estrogen and may decrease menstrual blood loss in patients on anticoagulation.
- Good maternal and fetal outcomes are most likely for the patient with AID without severe organ damage and with well-controlled disease on pregnancy-compatible medications.

Research agenda

- LARC safety and efficacy have not been well defined in AID populations.
- Firm recommendations for monitoring and therapy for complete heart block in *anti*-Ro/SS-A- and anti-La/SS-B-positive patients will require further data.
- Optimal therapy for obstetric APS treatment failures with LMWH/low-dose aspirin is unknown.

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