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2019 American College of Rheumatology Reproductive Health in Rheumatic and Musculoskeletal Diseases Guideline

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Abstract:

Objective: To develop an evidence-based guideline for rheumatic and musculoskeletal disease (RMD) patients regarding contraception; assisted reproductive technology

(ART); fertility preservation; pregnancy assessment, counseling, and management; medication use before, during and after pregnancy; and hormone replacement therapy (HRT).

Methods: We conducted a systematic review of evidence relating to contraception, ART, fertility preservation, pregnancy and lactation, and HRT in RMD populations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology to rate the quality of evidence, and a group consensus process to determine final recommendations and grade their strength (conditional or strong). Good practice statements (GPS) were agreed upon when indirect evidence was sufficiently compelling that a formal vote was unnecessary.

Results: This ACR guideline provides 12 ungraded GPS and 131 graded recommendations for reproductive health care in RMD patients. These recommendations are intended to guide care for all patients with RMD, except where indicated as being specific for patients with systemic lupus erythematosus (SLE), those positive for antiphospholipid antibody (aPL) and/or those positive for anti-Ro/SSA and/or anti-La/SSB antibodies. Recommendations and GPS support several guiding principles: use of safe and effective contraception to prevent unplanned pregnancy, pre-pregnancy counseling to encourage conception during periods of disease quiescence and while on pregnancy compatible medications, and ongoing physician-patient discussion with obstetrics/gynecology collaboration for all reproductive health issues given the overall low level of evidence available for RMD patients in this area.

Conclusion: This guideline provides evidence-based recommendations developed and reviewed by panels of experts and RMD patients. Many recommendations are conditional, reflecting a lack of data or low-level data. We intend that this guideline be used to inform a shared decision-making process between patients and their physicians on issues related to reproductive health that incorporates patients' values, preferences and comorbidities.

Introduction:

The management of reproductive health issues for patients with rheumatic and musculoskeletal diseases (RMD) differs from that of well persons. As a result, rheumatologists and other clinicians caring for these patients must often discuss with and counsel their patients about contraception, pregnancy and lactation (including medications), assisted reproductive technology, fertility preservation, and hormone replacement therapy, and they must collaborate with specialists in the fields of obstetrics-gynecology (OB-GYN), maternal-fetal medicine (MFM), and reproductive endocrinology and infertility (REI).

Pregnancy in women with RMD may lead to serious maternal or fetal adverse outcomes; accordingly, contraception, tailored to the patient's situation with emphasis on safety and efficacy, should be discussed and encouraged. Because risk for pregnancy complications depends on diagnosis, disease activity and damage, medications, and the presence of anti-Ro/SSA, anti-La/SSB, and antiphospholipid (aPL) antibodies, pre-pregnancy assessment is critical to informing pregnancy management, therapy, and outcomes. Achieving pregnancy may itself be an independent concern for some patients, and so minimizing risk of gonadal insufficiency is important. RMD patients with sub-fertility value advice from their rheumatologists about oocyte preservation and in vitro fertilization (IVF) procedures.

It is difficult to avoid use of medication during RMD pregnancy. Not all medications are safe for pre-conception use by men and women or in pregnancy and lactation, but uncontrolled systemic inflammatory disease is itself associated with poor pregnancy outcomes(1–6) . In addition, post-partum patients are also vulnerable to disease flare (7,8), but the American Academy of Pediatrics (AAP) recommends that infants be exclusively breastfed for six months (9). In many cases medication safety is uncertain because most data derive from case reports, small series, and observational studies; direct data from randomized controlled trials are scarce. As a result, it is challenging for clinicians to easily identify the appropriate screening, management and medication use for RMD patients.

Given the primary goal of providing recommendations for care of all adult RMD patients throughout the reproductive lifespan, the scope of this Guideline is broad. Aspects of reproductive health care other than pregnancy have received little attention in patients with RMD, and the ACR recognizes the imperative for guidance in reproductive health issues for RMD patients.

Methods:

These recommendations follow the ACR guideline development process, using a systematic literature review (SLR) and GRADE methodology; for details, see Appendix 1, available online. When no direct data in RMD patients were available from the SLR, indirect data collected in additional, less formal literature reviews (Appendix 2) performed by Core Team members (Appendix 10) supplemented discussion and voting; these data were not part of the SLR and are listed as "not graded" in evidence tables. Results of the SLR were compiled in an Evidence Report (Appendix 3).

A **strong recommendation** suggests that most informed patients would choose the recommended management; while usually reflecting a higher level of evidence, it may also reflect the severity of a potential negative outcome.

A **conditional recommendation** suggests that choice will vary with individual values and preferences. Conditional recommendations generally reflect no data, limited data, or conflicting data that lead to uncertainty.

Finally, **good practice statements** are those in which indirect evidence is sufficiently compelling that a formal vote is unnecessary, and are presented as "suggestions" rather than formal recommendations.

Recommendation numbers are denoted in Appendix 4 as numbers in parentheses, allow for cross referencing of recommendations with tables/appendices, and reference the order in the original list (i.e. may not be consecutive in the appendix.)

Results/Recommendations:

The detailed tables of recommendations appear in Appendix 4. Concise recommendations within the table and throughout the manuscript are grouped into categories of contraception, assisted reproductive technologies (ART), fertility preservation with gonadotoxic therapy, use of menopausal hormone replacement therapy, pregnancy assessment and management, and medication use (compatibilities are reported for paternal, maternal and breastfeeding use).

Most recommendations are general; where relevant, RMDs are specifically identified, most often for systemic lupus erythematosus (SLE), or according to presence of specific autoantibodies (aPL and anti-Ro/SSA and La/SSB antibodies). In general, aPL should be tested in patients with SLE or SLE-like disease and in patients with suggestive histories or physical findings; whether to check these antibodies in other RMD patients with a lower likelihood of positive results should be decided by physician-patient discussion. The presence of aPL modifies the recommendations in many circumstances, and therefore is considered separately. “Positive aPL” throughout this guideline refers to laboratory criteria only (10): persistent (two positive tests at least 12 weeks apart) moderate-high titer anticardiolipin antibody (aCL) ($\geq$ 40 units or $\geq 99^{th}$ percentile), moderate-high titer anti-beta2 Glycoprotein I antibody (aβ2GPI)($\geq$ 40 units or $\geq 99^{th}$ percentile), or positive lupus anticoagulant (LAC). Detailed definitions of aPL and antiphospholipid syndrome (APS) are presented in Appendix 5, available online. Briefly, included within the positive aPL group are asymptomatic aPL patients who have no history of thrombosis or pregnancy morbidity (i.e. meet laboratory but not clinical APS criteria), obstetric APS (OB APS) patients and thrombotic APS patients. OB APS refers to patients with laboratory criteria for APS and prior pregnancy complications consistent with APS (with other causes ruled out). These include three consecutive

losses prior to 10 weeks gestation, a fetal loss at or after 10 weeks gestation, or delivery < 34 weeks due to preeclampsia, intrauterine growth restriction, or fetal distress. Thrombotic APS refers to patients with laboratory criteria for APS and a prior thrombotic event (arterial or venous), regardless of whether they have had obstetric complications. The aPL definitions in the Guideline refer to patients with and without other underlying autoimmune disease unless specifically stated.

Patients with lower titer aCL and/or aβ2GPI (or non-criteria aPL) that do not meet laboratory classification criteria may still have some degree of risk that is difficult to quantify. Recommendations for these patients are not offered in this guideline; decisions regarding therapy rest on discussion between the patient and the physician, taking into account additional relevant risk factors.

Contraception:

Appendix 4,Table A presents formal recommendations regarding contraception; strength of evidence and justifications for strong and conditional recommendations are presented in Appendix 6. Figure 1 details the contraception decision-making process, and Table 1 offers efficacy data and comments on available contraceptives.

RMD patients typically underutilize effective contraception (11–13). The most important reason for effective contraception for women with RMD is to avoid risks of unplanned pregnancy, which include worsening disease activity that may threaten maternal organ function or life, adverse pregnancy outcomes (pregnancy loss, severe prematurity, and growth restriction), and teratogenesis. Members of a one-day patient focus group, convened as part of the guideline process, emphasized their desire that clinicians caring for patients with RMD routinely discuss family planning, as they view their rheumatologists as “the doctors who know them and their medications best”. We suggest that rheumatologists treating reproductive-aged women with RMD discuss contraception and pregnancy plans at an initial or early visit and periodically thereafter, and always when initiating treatment with potentially teratogenic medications. One Key Question® (powertodecide.org) has been suggested in the literature as a simple way of

addressing the issue of family planning with patients: “would you like to become pregnant in the next year”? (14). In whatever way one chooses to discuss this topic, counseling regarding contraception should include issues of efficacy and safety, with consideration of individual values and preferences.

Effectiveness of reversible forms of contraception varies. For long-acting reversible contraceptives (LARC) – copper or progestin IUDs and subdermal progestin implants (15) – ideal use and “real world” use effectiveness are similar, with pregnancy rates < 1% per year (“highly effective”). Combined estrogen-progestin methods, depot-medroxyprogesterone acetate (DMPA) injections and progestin-only pills yield pregnancy rates of 5-8% per year (“effective”) (16). Condoms, fertility-based methods (e.g. rhythm), and spermicide are less effective and yield pregnancy rates of 18-28% per year (17). Barrier methods confer some protection against sexually transmitted diseases.

While LARC are encouraged as first line contraceptives for all appropriate candidates, including nulliparous women and adolescents (17), lack of data specific to RMD and variability in clinical situations, values and preferences may affect a patient’s choice. Clinical factors that affect appropriateness of various contraceptive methods include diagnosis and activity of SLE, presence of aPL, osteoporosis, and some potentially interacting medications (Appendix 7 and “Special RMD situations” section, below). “Hormonal contraceptives” refers to any contraception containing a hormone, including estrogen-progestin contraceptives and progestin-only contraceptives. The term “fertile women” refers to women of reproductive age who do not have documented menopause, hysterectomy, or permanent sterilization (that is, women who may become pregnant).

In fertile women with RMD who have neither SLE nor positive aPL we strongly recommend use of effective (i.e. hormonal contraceptives or IUDs) over less effective options or no contraception; among effective methods, we conditionally recommend the highly effective IUDs or progestin subdermal implant (LARC) because they have the lowest failure rates.

We strongly recommend discussing use of emergency contraception with all patients, including those with SLE or positive aPL, because risks of emergency contraception are low compared to those of unplanned pregnancy. Levonorgestrel, the over-the-counter option, is widely available and has no medical contraindications to use, including thrombophilia (18).

SLE patients:

Controlled studies of estrogen-progestin contraceptives in SLE enrolled only women with stable, low disease activity; they specifically excluded those with high disease activity and history of thrombosis (19,20). Prospective studies (evidence level moderate) in patients with stable SLE found no increased risk of flare due to estrogen-progestin pills (19,20), and no data suggest increased SLE flare risk of progestin-only pills or copper IUDs (20,21).

For SLE patients with stable or low disease activity who do not have positive aPL, we strongly recommend effective (i.e. hormonal contraceptives or IUDs) over less effective options or no contraception, and we conditionally recommend highly effective IUDs or progestin subdermal implant because they have the lowest failure rates.

We conditionally recommend against use of the transdermal estrogen-progestin patch in patients with SLE. Although not directly studied in SLE patients, the transdermal estrogen-progestin patch results in greater estrogen exposure than do oral or transvaginal methods (22,23), raising concern for potential increased risk of flare or thrombosis**.**

We strongly recommend progestin-only or IUD contraceptives over combined estrogen-progestin contraception in SLE patients with moderate or severe disease activity, including nephritis, because estrogen-containing contraceptives have not been studied in SLE patients with moderate or severe disease activity.

aPL positive patients:

We strongly recommend against combined estrogen-progestin contraceptives in women with positive aPL because estrogen increases risk of thromboembolism. **We strongly recommend IUDs (levonorgestrel or copper) or the progestin-only pill for women with positive aPL.** For aPL-positive patients, we do not recommend DMPA due to concern regarding thrombogenicity, and we do not comment on the relatively new progestin implant due to lack of data.

The risk of venous thromboembolism (VTE) in healthy women using combined estrogen-progestin contraceptives is 3-6x higher than the baseline annual risk of 1/10,000 women (24). Although whether there is any increase in thrombosis risk with progestin-only contraception is debated, progestin-only methods are widely accepted as a lower risk option for patients for whom estrogens are contraindicated but who still require effective contraception (18,25,26). The specific progestin and serum level affect thrombosis risk: in healthy women taking estrogen-progestin contraceptive pills that vary progestin type but not estrogen, VTE risk odds ratios range from 2.2 to 6.6 (24). However, VTE risk in healthy women using either the progestin-only pill (RR = 0.90, 0.57-1.45) or the progestin IUD (RR = 0.61, 0.24-1.53) is not increased (27). Furthermore, thromboses do not increase when progestin (levonorgestrel) IUDs are used in non-RMD patients with increased (non-aPL-associated) thrombosis risk (27–29). VTE data for the newer progestin (etonogestrel) subdermal implant are inadequate to permit recommendations (the prior progestin implant containing levonorgestrel is no longer available in the United States). Very limited data in non-RMD patients suggest that injectable DMPA imparts a higher VTE risk than do other progestin-only contraceptives, RR = 2.67 (1.29-5.53), similar to that of oral estrogen-progestin contraceptives (27). For this reason, we do not include DMPA among the progestin contraceptives recommended for use in patients with positive aPL.

The copper IUD is a highly effective alternative that does not increase risk of VTE, but it may increase menstrual bleeding and cramping for several months after insertion;

progestin-IUDs may decrease these symptoms, a potential benefit for patients on anticoagulation(30).

We suggest the progestin-only pill (which is an effective, but not highly effective contraceptive) as a low-risk alternative for patients unable or unwilling to use an IUD. The lack of data specific to aPL-positive patients using the progestin-only pill or IUD must be weighed against the risk of pregnancy-related VTE in the general population, which is more than ten times that seen with estrogen-progestin contraceptive use. Pregnancy-related thrombosis risk for aPL-positive patients is not well-quantified, but VTE risk is 197/10,000 women-years for pregnant patients with a single prothrombotic mutation and 776/10,000 women-years (31) with multiple prothrombotic mutations.

Other special RMD situations:

Since IUDs are the most effective contraceptive options, we strongly recommend the IUD (copper or progestin) for women with RMD on immunosuppressive therapy, despite hypothetical infection risk. IUD-associated infection risk in immunosuppressed RMD patients has not been specifically studied, but studies in women with HIV show no increase (32), and IUDs are recommended for all solid organ transplant patients, including adolescents (33,34). One arm of a SLE contraceptive trial used a copper IUD; although the number of patients on immunosuppressive agents was not reported, there were no cases of pelvic inflammatory disease (20).

In women with RMD at increased risk for osteoporosis from glucocorticoid use or underlying disease, we conditionally recommend against using DMPA as a long-term contraceptive because data suggest up to 7.5% decline in bone mineral density over 2 years of use in a healthy population (35)**.** Although no data suggest increased fracture risk, the American College of Obstetrics and Gynecology (ACOG) recommends caution regarding DMPA use for women with or at increased risk for osteoporosis (17).

We conditionally recommend that women with RMD taking mycophenolate mofetil/mycophenolic acid (MMF) use an IUD alone or two other methods of contraception together, because MMF may reduce serum estrogen and progesterone levels (in turn reducing the efficacy of oral contraceptives). The Mycophenolate Risk Evaluation and Mitigation (REMS) program suggests use of an IUD alone (copper or progestin is not specified), or an estrogen-progestin contraceptive or the progestin implant together with a barrier contraceptive (36). It is not known whether these medications reduce efficacy of progestin IUDs, which contain varying amounts of hormone and have a largely intrauterine effect. Other recommendations vary: while the package insert states that MMF may reduce effectiveness of oral contraceptives and use of additional barrier contraceptive methods is recommended(37), the European Medicine Agency recently updated recommendations regarding use of contraception for women taking MMF to state that "two forms of contraception are preferred but no longer mandatory"(38). Voting panel members disagreed on the need to use additional contraceptive measures. As befits a conditional recommendation, clinicians should be aware of and discuss this hypothetical risk with their patients.

Assisted reproductive technology (ART):

Appendix 4, Table B presents the ART recommendations with strength of supporting evidence; detailed justifications for strong and conditional recommendations are in online Appendix 6. Figure 2 details the ART decision-making process.

While fertility is typically normal in women with RMD (who have not been treated with cyclophosphamide, or CYC), it decreases with age. Some RMD patients may require assisted reproductive technology (ART). ART techniques include ovarian stimulation, which markedly elevates estrogen levels, in vitro fertilization (IVF), and embryo transfer. Ovarian stimulation cycles for IVF generally require more aggressive stimulation than do those for intrauterine insemination; they involve surgical extraction of oocytes and IVF, followed by embryo transfer. Frozen embryo transfer does not usually require ovarian stimulation.

As is the case with any underlying significant medical disease, women undertaking ovarian stimulation must be cleared medically by the appropriate specialist. Similarly, women with APS,

thrombotic or otherwise, should be cleared medically by their rheumatologist. The rheumatologist should consult with the REI regarding adjustments to the ovarian stimulation protocol in order to minimize the risk to the patient. Women undergoing fertility therapy with these underlying conditions should only do so in centers where the appropriate expertise is readily available.

We strongly recommend proceeding with ART if needed in women with uncomplicated RMD on pregnancy-compatible medications who have stable/quiescent disease and negative tests for aPL. Compared to benefit of a successful pregnancy, risk for sub-fertile patients is low; nonetheless, risks associated with ART, especially thrombosis and lupus flare (39,40), should be discussed with patients. The level of evidence is very low for RMD patients (41,42), but evidence supports the safety of ART in a general population (43,44).

SLE patients:

We strongly recommend deferring ART procedures for any RMD while disease is moderately or severely active; this recommendation is based on extrapolated evidence that RMD disease activity increases pregnancy risks. For pregnancy planning, six months of stable inactive or low level disease is most often suggested but individual clinical factors may influence this decision**.** For patients with SLE, there is theoretical concern that ovarian stimulation with elevated estrogen levels may worsen active disease.

We conditionally recommend against an empiric dosage increase of prednisone during ART procedures in patients with SLE; instead, we suggest following the patient carefully and treating for flare if it occurs. No studies have evaluated prescription of prophylactic prednisone to prevent SLE flare during ART.

aPL positive patients:

For sub-fertile RMD patients who desire pregnancy, have stable/quiescent disease, and have asymptomatic positive aPL, obstetric APS (OB APS), or treated

thrombotic APS, we conditionally recommend ART with anticoagulation, as follows.

We conditionally recommend <u>prophylactic</u> anticoagulation therapy with heparin or low molecular weight heparin (LMWH) for asymptomatic aPL-positive patients during ART procedures (41,42)**.** The increased risk of organ- or life-threatening thrombosis due to high estrogen levels greatly outweighs the low risk for bleeding or other complications of unfractionated heparin or low molecular weight heparin (LMWH).

During ART procedures we strongly recommend <u>prophylactic</u> anticoagulation with heparin or LMWH for women with OB APS and strongly recommend <u>therapeutic</u> anticoagulation for women with thrombotic APS. The strength of these recommendations rests on the severity of the risk of organ- or life-threatening thrombosis during ovarian stimulation. An added risk for thrombosis is ovarian hyperstimulation syndrome (OHSS), an important, uncommon complication consisting of capillary leak syndrome (with pleural effusion and ascites) and, in severe cases, arterial and venous thrombosis and renal failure (43). Underlying thrombophilia increases the risk for severe OHSS (44). While there are few data to guide prophylactic anticoagulation in aPL-positive patients, thromboprophylaxis is recommended to prevent thrombotic complications of moderate-to-severe OHSS as it is for patients with known inherited or acquired thrombophilia (45,46). Reports of thrombosis in aPL-positive patients undergoing IVF are uncommon, but most reported patients received empiric anticoagulation (41,42). In a recent series, two of four reported thromboses occurred in women who self-discontinued LMWH after oocyte retrieval (41).

LMWH is used most commonly. Prophylactic dosing of enoxaparin is usually 40 mg daily, started at the beginning of ovarian stimulation, held 24-36 hours prior to oocyte retrieval and resumed following retrieval. Optimal duration of prophylactic LMWH for asymptomatic aPL positive patients undergoing ovarian stimulation has not been studied; this is a decision best made in consultation with the REI specialist; it is often continued until estrogen levels return to near physiologic levels if no pregnancy occurs.

OB APS patients will continue therapy throughout pregnancy. Aspirin is not commonly used prior to oocyte retrieval (it will be started after retrieval if indicated) given concern that its prolonged action may increase bleeding risk at the time of the retrieval. Patients on chronic anticoagulation with vitamin K antagonists for thrombotic APS should transition to therapeutic-dose LMWH for ART (usually enoxaparin 1 mg/kg sq q12h), holding it for retrieval and resuming after to continue throughout pregnancy. Since ovarian stimulation protocols vary, discussion with the REI specialist is appropriate. In addition to anticoagulation, patients at risk for thrombosis or OHSS may benefit from ovarian stimulation protocols that yield lower peak serum estrogen levels, such as those incorporating aromatase inhibitors (47).

Embryo and oocyte cryopreservation:

Embryo and oocyte cryopreservation are good options to preserve fertility in patients who are stable enough to undergo ovarian stimulation but are either not able or not ready to pursue pregnancy at the time of stimulation. A carefully monitored ovarian stimulation/IVF cycle followed by embryo transfer to a surrogate is an option if available for patients with severe disease-related damage who desire a biological child, are able to undergo ovarian stimulation and oocyte retrieval, but cannot safely undergo pregnancy.

We strongly recommend continuation of necessary immunosuppressive and/or biologic therapies (except cyclophosphamide, which directly impacts maturing follicles) for treated, stable patients when the purpose of ovarian stimulation is oocyte retrieval for oocyte or embryo cryopreservation. This includes continuation of mycophenolate or methotrexate. There is an anticipated risk of uncontrolled disease from withdrawal of effective medication. However, no data directly address oocyte retrieval during treatment with most immunosuppressive or biologic therapies other than cyclophosphamide.

Fertility preservation with cyclophosphamide:

Appendix 4, Table C shows the formal recommendations for fertility preservation and strength of supporting evidence. Detailed justifications for strong and conditional recommendations are in online Appendix 6.

Fertility preservation in RMD women:

To prevent inducing primary ovarian insufficiency in premenopausal women with RMD receiving monthly IV CYC, we conditionally recommend monthly gonadotropin releasing hormone agonist (GnRHa) co-therapy. Ovarian insufficiency risk depends on patient age and cumulative IV monthly CYC dose (48); measures of ovarian function remained stable during treatment with the Euro-lupus protocol (49). A recommendation for GnRHa therapy for ovarian protection during monthly CYC therapy is based on evidence supporting benefit in early breast cancer (50,51); evidence for RMD patients is less robust, but positive, with limited clinical trials of GnRHa (usually leuprolide acetate) that used heterogeneous RMD populations and outcome measures (52–56).

Thus far studies have addressed GnRHa co-therapy only in RMD patients treated with monthly IV CYC. Acknowledging this lack of data, it is reasonable to consider GnRHa use for patients treated with oral CYC. Theoretically, GnRHa co-therapy may not be necessary for patients receiving the lower cumulative CYC dose of the Euro-lupus regimen (49). Expense including insurance coverage issues and difficulty coordinating administration (timing is preferred 10-14 days prior to CYC administration) may impact the ability to use GnRHa for the first CYC infusion, especially in the setting of urgent need for therapy.

Fertility preservation in RMD males:

We conditionally recommend against testosterone co-therapy in men with RMD receiving CYC, as it does not preserve fertility in men undergoing chemotherapy for malignancy (57). **Because sperm cryopreservation prior to treatment preserves a man's ability to conceive a healthy child, we strongly suggest sperm cryopreservation as good practice for men undergoing CYC who desire it.** We

acknowledge the difficulty of coordinating sperm banking when CYC therapy is urgently indicated. Because CYC causes the most damage to the post-meiosis spermatids and sperm developing during therapy have the highest degree of genetic damage (58), sperm should be collected prior to CYC. If collected after CYC treatment, urologists recommend waiting a minimum of three months after completion of therapy (59).

Menopause and hormone replacement therapy:

Appendix 4, Table D shows formal recommendations with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are in the online Appendix 6. Figure 3 details the hormone replacement therapy (HRT) decision-making process. Postmenopausal women include women with surgically induced menopause.

Current population recommendations (60–62) suggest limiting HRT use in healthy postmenopausal women and using the lowest dose that alleviates symptoms for the minimal time necessary. Studies of long-term HRT therapy show that risks outweigh benefits, including stroke and breast cancer (63). Risks of HRT depend on the type, dose, route of administration, duration of use, and timing of initiation. Benefit-risk balance is most favorable for severe vasomotor symptoms in women ≤ 60 years old or within 10 years of menopause onset (61).

Vasomotor symptoms, as defined by the North American Menopause Society (NAMS), include hot flashes and night sweats. Hot flashes are recurrent, transient episodes of flushing, perspiration, and a sensation ranging from warmth to intense heat on the upper body and face, sometimes followed by chills. Night sweats are hot flashes that occur with perspiration during sleep(64). General contraindications to use of HRT include history of breast cancer, coronary heart disease, previous venous thromboembolic event or stroke, or active liver disease.

We strongly suggest as good practice the use of HRT in postmenopausal women with RMD without SLE or positive aPL who have severe vasomotor symptoms, have no contraindications, and who desire treatment with HRT.

SLE patients:

In women with SLE without positive aPL who desire HRT, we conditionally recommend treatment for patients with severe vasomotor symptoms who have no contraindications and who desire treatment with HRT. Moderate quality direct evidence supports use of oral HRT in aPL-negative women with SLE who have stable low-level disease activity and no contraindication to use (65–68) although no studies directly address use of HRT in patients with moderate-high disease activity. The recommendation is conditional because there was a small increase in risk of mild-moderate (but not severe) lupus flares with use of oral HRT in the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA) study (65), and because the studies did not include women with active disease.

aPL-positive patients:

In women with asymptomatic aPL, we conditionally recommend against treating with HRT. We strongly recommend against use of HRT in women with obstetric and/or thrombotic APS. We also conditionally recommend against HRT use in patients with APS who are anticoagulated, and patients with APS with currently negative antibodies. We conditionally recommend consideration of HRT, if desired, in women who have a history of positive, but currently negative, tests for aPL and no history of clinical APS.

Risk of VTE may be increased with HRT use in the general population (69,70). Types of estrogen and progestin and route of administration (71–74) affect risk. In the Women's Health Initiative study, VTE risk increased 2-fold over placebo with oral estrogen-progestin (70), and oral HRT in patients with factor V Leiden or prothrombin G20210A mutations increases VTE risk 25-fold compared to mutation-free non-users (75,76). In contrast, recent studies show that transdermal estrogen does not increase

VTE risk in healthy women (71,74), even those with prothrombotic mutations or high body mass index (75,77). No studies, however, specifically assess thrombotic risk of oral or transdermal HRT in women with aPL.

Direct evidence regarding thrombosis risk with HRT in SLE patients with or without aPL is low, as studies were of risk of flare in SLE, not thrombosis, and some studies excluded patients with prior thrombosis (65,67). One study randomized 106 SLE patients, regardless of aPL status but excluding those with recent thrombosis, to oral estrogen-progestin HRT or placebo. Roughly one-third in each group had some (unreported) level of aPL (78). In 24 months of follow-up three thrombotic events occurred in the treatment group and one in the placebo group, a not significant difference.

Available evidence supports the use, when indicated and desired, of HRT in RMD patients without aPL, including those with SLE (65). Given the demonstrated lower VTE risk of transdermal administration as opposed to oral estrogen-progestin preparations even in women at increased prothrombotic risk (77), it may be reasonable to consider transdermal estrogen as initial therapy.

Pregnancy:

General RMD pregnancy assessment, counseling and management:

OB-GYN or maternal fetal medicine specialists (MFM) necessarily assume primary management of a pregnancy of a woman with RMD. An understanding of basic pregnancy physiology is helpful for rheumatologists to identify and treat active disease during pregnancy and coordinate care with obstetrical providers.

Pregnancy changes may impact manifestations of RMD. Pregnancy-related increased intravascular volume may worsen already abnormal cardiac or renal function. The expected 50% increase in glomerular filtration rate during pregnancy may increase preexisting stable proteinuria. Pregnancy-induced hypercoagulability increases RMD-associated thrombosis risk. The calcium demand of fetal bone development and

breastfeeding may worsen maternal osteoporosis. In addition, normal pregnancy symptoms such as malar erythema, chloasma gravidarum, anemia, elevated erythrocyte sedimentation and diffuse arthralgias may falsely mimic symptoms of active RMD. Pregnancy-induced hypertension syndromes (preeclampsia) may be confused with lupus nephritis, scleroderma renal crisis, or vasculitis flare. HELLP syndrome (hemolysis, elevated liver enzymes and low platelets) or eclampsia may resemble severe disease flare. Distinguishing among these syndromes requires the expertise of rheumatologists and OB-GYN or MFM working together.

Most information regarding pregnancy management in RMD comes from observational studies, primarily in patients with SLE and APS. Very few controlled trials exist. Data about pregnancies in rare rheumatic diseases usually derive from small case series. For these reasons, many recommendations are conditional, supported by collective experience of the Voting Panel members and patient input.

Appendix 4, Table E shows formal recommendations with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are in online Appendix 8. Figure 4 details the pregnancy management process for RMD patients. Appendix 7 shows assessment and management suggestions for specific RMD's.

As standard good practice, we strongly suggest counseling women with RMD who are considering pregnancy regarding the improved maternal and fetal outcomes (based on many studies) associated with entering pregnancy with quiescent/low activity disease(75,77,79–98)**. As additional good practice we suggest maintaining concurrent care with OB-GYN, MFM, neonatologists, and other specialists as appropriate.**

Patient participants expressed a strong desire that their physicians discuss family planning "early and often", including before planning of pregnancy. Discussion with patients should include information on medications and impact of disease activity,

autoantibodies, and organ system abnormalities on maternal and fetal health. In rare situations with significant disease-related damage, such as pulmonary arterial hypertension, renal dysfunction, heart failure or other severe organ damage, pregnancy may be contraindicated due to the high risk of maternal morbidity and mortality.

In women with RMD planning pregnancy who are taking medication incompatible with pregnancy, we strongly recommend switching to a pregnancy-compatible medication and observing for sufficient time to assess efficacy and tolerability of the new medication. There are no data to support a specific period of time for observation on pregnancy-compatible medications. Timing will vary depending on individual clinical factors; in clinical practice this is usually a minimum of several months.

In women with RMD who are currently pregnant and have active disease that requires medical therapy, we strongly recommend initiating or continuing a pregnancy-compatible steroid-sparing medication, as both active RMD and chronic high-dose glucocorticoid have potential for maternal and fetal harm(99)**.**

Pre-pregnancy or early pregnancy laboratory testing for relevant autoantibodies is recommended. Ascertaining anti-Ro/SSA, anti-La/SSB and aPL antibodies improves counseling regarding pregnancy and fetal risk. **We strongly recommend testing for anti-Ro/SSA and anti-La/SSB one time before or early in pregnancy in women with SLE or SLE-like disorders, Sjogren's, systemic sclerosis, and RA. Given the relative persistence and unchanged titers of these antibodies, we strongly recommend against repeating the test during pregnancy.**

In women with SLE who are considering pregnancy or are pregnant, we strongly recommend testing for lupus anticoagulant (LAC), anticardiolipin (aCL), and anti-beta 2 glycoprotein I (aβ2GP-1) antibodies one time before or early in pregnancy, and against repeating these tests during pregnancy.

Scleroderma renal crisis:

We strongly recommend use of ACE-inhibitor or angiotensin receptor blockade therapy to treat active scleroderma renal crisis in pregnancy because the risk of maternal or fetal death with untreated disease is higher than the risk associated with use of these medications during pregnancy. While scleroderma renal crisis is rare in pregnancy (an estimated 2% of scleroderma pregnancies), it can easily be confused with preeclampsia. ACE-inhibitor drugs, which can be renal protective and life-saving (100), however they are contraindicated in the second and third trimesters because of potential oligohydramnios or permanent fetal renal damage (101) and should only be considered for active scleroderma renal crisis.

SLE patients:

Appendix 4, Table E shows formal recommendations for SLE pregnancy management with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are in online Appendix 8.

We recommend that all women with SLE take hydroxychloroquine (HCQ) during pregnancy if possible. Many studies support maternal and pregnancy benefit of HCQ and low risk for mother and fetus (84,102–111). **If a patient is already taking HCQ, we strongly recommend continuing it during pregnancy; if she is not taking HCQ, we conditionally recommend starting it if there is no contraindication.** Potential contraindications include allergy, adverse side effects or intolerance.

We conditionally recommend treating SLE patients with low dose aspirin (81 or 100 mg daily), beginning in the first trimester. The American College of Obstetricians and Gynecologists (ACOG) and US Protective Health Task Force (USPHTF) recommend low dose aspirin 81 mg daily as prophylaxis in all patients at high risk for preeclampsia. (112,113) (97,114–117).

Treatment with low dose aspirin during pregnancy to prevent or delay the onset of gestational hypertensive disease is recommended for those with SLE or APS because of their increased risk and may be considered for women with other RMD diagnoses depending on individual clinical risk factors. Some investigators have used doses of aspirin up to 150 mg daily, but both ACOG and the U.S. Preventive Services Task Force (USPSTF) note that appropriate comparative studies to show the superiority of doses higher than 100 mg per day are lacking. Low dose aspirin is not thought to complicate anesthesia or delivery (112), however a decision regarding discontinuation prior to delivery should be made by the OB GYN and anesthesiologist according to the patient's specific clinical situation.

Because active disease affects maternal and pregnancy outcome, we strongly suggest, as good practice, monitoring SLE disease activity with clinical history, exam, and laboratory tests at least once per trimester. Abnormalities of CBC, differential, urinalysis and protein/creatinine ratio, anti-DNA, C3, and C4 may indicate possible SLE flare and/or preeclampsia despite absence of clinical symptoms. Frequency of laboratory monitoring and rheumatology follow-up may vary with an individual patient's clinical status and medications.

APL-positive patients:

Pregnancies in patients with positive aPL antibody or APS present specific challenges and may require additional monitoring and therapy. Appendix 4, Table F shows formal recommendations, with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are in online Appendix 8 (page 11-20).

APL is a major risk factor for pregnancy loss and other adverse pregnancy outcomes, especially in SLE patients (118). ACL, aβ2GPI, and LAC should all be tested. Among aPLs, LAC conveys the greatest risk for adverse pregnancy outcome in women with or without SLE: relative risk for adverse pregnancy outcome with LAC was 12.15 (95% CI

2.92–50.54, *p* = 0.0006) (118) in the Predictors of Pregnancy Outcome: Biomarkers in APL syndrome and SLE (PROMISSE) study. Other independent risk factors for aPL-positive women were younger age, history of thrombosis, and SLE.

aPL-positive patients without thrombosis or obstetric complications::

In pregnant women with positive aPL who do not meet obstetric or thrombotic APS criteria, we conditionally recommend treating with prophylactic aspirin, 81 or 100 mg daily, during pregnancy as preeclampsia prophylaxis. Treatment should begin early in pregnancy (before 16 weeks) and continue through delivery.

Obstetric and thrombotic APS patients: **We strongly recommend combined low dose aspirin and prophylactic-dose heparin (usually LMWH), for patients meeting OB APS criteria** (119–126)**.** This is based on evidence of moderate strength. **In women with OB APS, we further strongly recommend treating with prophylactic-dose anticoagulation for 6-12 weeks post-partum** (127)**.**

In pregnant women with thrombotic APS, we strongly recommend treating with low-dose aspirin and therapeutic-dose heparin (usually LMWH) throughout pregnancy and post-partum.

We conditionally recommend against using the combination of prophylactic-dose heparin with low dose aspirin therapy for patients with positive aPL who do not meet OB APS criteria. We appreciate and stress, however, that benefit for individual high-risk circumstances, such as triple-positive aPL or strongly positive LAC results, advanced maternal age or IVF pregnancy, may outweigh risks of this therapy and decisions should be made with discussion between physician and patient weighing potential risks and benefits.

Other therapies for refractory OB APS:

We conditionally recommend against treatments with IVIG or an increased LMWH dose, as these have not been demonstrably helpful in cases of pregnancy loss despite standard therapy with low dose aspirin and prophylactic heparin or LMWH. Prophylactic-dose heparin and aspirin therapy for OB APS improves likelihood of live births, but not necessarily full term. Pregnancy loss occurs, despite treatment, in 25% of OB APS pregnancies. No data support improved outcomes with higher dosage of heparin, and only anecdotal data support IVIG.

We strongly recommend against adding prednisone to prophylactic-dose heparin or LMWH and low dose aspirin for standard therapy failures, since no controlled studies support a benefit. We acknowledge however that this recommendation is based on a lack of compelling data rather than data showing no clear benefit, however, and also that potential risk of this therapy is likely to be strongly affected by daily dose with higher doses imparting greater risk of side effects.

We conditionally recommend the addition of HCQ to prophylactic-dose heparin or LMWH and low dose aspirin therapy for patients with primary APS. Recent small studies of APS pregnancies suggest that HCQ may decrease complications (111).

In pregnant women with positive aPL who do not meet APS criteria nor have another indication for the drug (such as SLE), we conditionally recommend against treating with prophylactic HCQ. As with any unproven treatment, these therapies may be considered in specific circumstances, depending on a patient's values and preferences, and after a discussion about risks and benefits.

Anti-Ro/SSA and/or anti-La/SSB antibodies in pregnancy:

Neonatal lupus (NLE) describes several fetal and infant manifestations caused by or associated with maternal anti-Ro/SSA (commonly) and anti-La/SSB autoantibodies. While isolated anti-La/SSB rarely imposes risk, when combined with anti-Ro/SSA, La/SSB antibodies may increase fetal risk (128). Prospective studies of infants born to

women with anti-Ro/SSA and/or anti-La/SSB antibodies show that about 10% develop an NLE rash, 20% transient cytopenias, and 30% mild transient transaminitis (estimates vary widely between different reports). These complications are short-lived and spontaneously resolve as the child's maternal antibodies disappear (129).

Complete (third degree) heart block (CHB) occurs in about 2% of pregnancies of women with anti-Ro/SSA and/or anti-La/SSB antibodies who have not had a prior NLE infant, and in 13-18% of pregnancies of women with a prior infant who had either cutaneous or cardiac NLE (130). Low titer antibodies are probably not associated with the same risk of CHB as higher titers (131). CHB rarely occurs after week 26. It is irreversible, and management transfers to pediatric cardiologists. About 20% of children with CHB die in utero or in the first year of life; more than half will require a pacemaker (128).

Appendix 4, Table G shows formal recommendations with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are in online Appendix 8.

For pregnant women with anti-Ro/SSA and/or anti-La/SSB antibodies but no history of a prior infant with CHB or NLE we conditionally recommend serial (less frequent than weekly, interval not determined) fetal echocardiography between 16-18 weeks through week 26. For women with a prior infant with CHB or other NLE we conditionally recommend fetal echocardiography <u>weekly</u>, starting at weeks 16-18 and continuing through week 26.

Recommendations regarding monitoring for and treatment of CHB in women with anti-Ro/SSA and/or anti-La/SSB are all conditional. Given the rarity of CHB, large case series are not available; most studies are retrospective and not randomized. An argument against screening includes the risk of identification and treatment of artifacts that do not impact offspring health, thus exposing both fetus and mother to long-term side effects of dexamethasone; this risk must be balanced against the potentially

devastating impact of CHB. All discussions should acknowledge the limited data and consider the patient's values and preferences.

We conditionally recommend treating all women who have anti-Ro/SSA and/or anti-La/SSB antibodies with HCQ during pregnancy. This is based on early and limited data and the low risk profile of HCQ. Retrospective studies demonstrate that pregnant women with a prior child with cardiac NLE who take HCQ have a lower risk of the current fetus developing CHB (132).

For pregnant women with anti-Ro/SSA and/or anti-La/SSB antibodies and fetal echocardiograms showing first or second-degree heart block, we conditionally recommend treatment with 4 mg of oral dexamethasone daily. If CHB (without other cardiac inflammation) is present, we conditionally recommend against treating with dexamethasone.

Fluorinated corticosteroids, such as dexamethasone and betamethasone, cross the placenta; low to moderate-dose non-fluorinated corticosteroids, such as prednisone and prednisolone, are largely metabolized before they reach the fetus. Whether dexamethasone given for fetal first- or second-degree heart block changes outcome is controversial. Treatment should be limited to several weeks, depending on response, because of the risk of irreversible fetal and maternal toxicity. Whether dexamethasone improves long-term survival for a fetus with CHB is controversial (133,134), but recent analyses do not support its use (135).

Paternal medication use:

Appendix 4, Table H shows best practice statements and recommendations, with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are in online Appendix 9. Table 2 summarizes recommendations for paternal medication use.

Medication issues differ for men with RMD who are planning to father a pregnancy and for those whose sexual partner is pregnant. Pre-conception, the concerns are potential effects on male fertility and medication-associated teratogenicity. Few data address these potential effects of RMD medications in men. A decision to stop a medication must be weighed against the impact it may have on paternal disease activity.

When the man's partner is pregnant, the concern is whether his medication is present in seminal fluid and can transfer through vaginal mucosa, cross the placenta, and be teratogenic. In fact, post-conception exposure of the embryo or fetus is likely minimal, as seminal concentrations of medications and volumes transferred are small (136). There are no reports of post-conception teratogenesis attributable to medications used by a man with RMD. When his sexual partner is pregnant, reassurance regarding low risk is generally warranted for treated men.

Absent adequate data regarding paternal exposure for most medications used for RMD, we developed recommendation statements when (a) at least some data on paternal exposure were available; (b) accumulated clinical experience of paternal exposure guided the recommendation; or (c) there were no data on paternal exposure, but maternal exposure demonstrates teratogenicity. We did not present recommendations for new medications with no available class level or drug-specific data.

We strongly recommend against use of CYC and thalidomide in men prior to attempting conception. Paternal use of CYC may impair spermatogenesis or be mutagenic for DNA (137) and should be discontinued 3 months prior to attempting conception. Thalidomide is detectable in seminal fluid and is strongly teratogenic when given to pregnant women (138,139) and should be discontinued at least 1 month prior to attempting conception.

The remaining medications are recommended either strongly or conditionally for continuation during peri- and post-conception periods. **We strongly recommend continuation of HCQ, , azathioprine, 6-mercaptopurine, colchicine, and TNF**

inhibitors (140–142)**. Based on a smaller body of evidence, we conditionally recommend continuing methotrexate (MTX), MMF, leflunomide, sulfasalazine, calcineurin inhibitors, and non-steroidal anti-inflammatory drugs (NSAIDs)** (142–149)**. Although sulfasalazine may affect sperm count and quality, no data suggest teratogenicity** (146,150)**; we conditionally recommend continuation**. If conception does not occur, semen analysis should be considered. Although the drug label suggests discontinuation of MTX before attempting pregnancy, **we conditionally recommend continuation of MTX based on data that show no evidence for mutagenesis or teratogenicity** (143–145). **We also conditionally recommend continuation of anakinra and rituximab based on limited data** (151,152)**.**

Maternal medication use:

Appendix 4, Tables I (conventional rheumatology medications), J (biologic rheumatology medications), and K (glucocorticoids) show formal best practice statements and recommendations with strength of supporting evidence.

Detailed justifications for strong and conditional recommendations are in online Appendix 9 (page 13). Table 3 summarizes recommendations for maternal medication use.

As standard good practice, we suggest discussing medications well before the patient attempts to conceive; we also suggest discussing pregnancy plans prior to initiating treatment with medications that may affect gonadal function, such as CYC. There are no data regarding specific timing for medication discussion, which will vary according to the individual clinical situation, but in general we suggest adequate time to allow for appropriate medication changes and demonstration of tolerability and disease stability, usually a minimum of several months.

MTX, MMF, CYC, and thalidomide are known teratogens. We strongly recommend discontinuation of these within 3 months prior to conception (153–156). Data regarding timing of discontinuation are conflicting and do not permit more specific

recommendations. However, discontinuation within one menstrual cycle would represent the minimum, and 3 months the most common, period for discontinuation. In addition to concerns about teratogenicity, adequate time for observation of disease stability off medication is considered optimal.

For leflunomide, we strongly recommend cholestyramine washout if there are detectable serum levels of metabolite prior to or as soon as pregnancy is confirmed. Once metabolite serum levels are non-detectable, the risks of pregnancy loss and birth defects are not elevated (157,158). **CYC is conditionally recommended for use in life-threatening conditions in the second and third trimesters** (86)**. When potential teratogenic medications are discontinued prior to pregnancy, we strongly recommend a period of observation off medication or transition to pregnancy-compatible medications to ensure disease stability** (as discussed above). **In women with inadvertent exposure to teratogenic medications we strongly suggest immediate referral to a MFM, pregnancy medication specialist, or genetics counselor as standard good practice.**

Medications commonly used for RMD and strongly recommended as compatible for use throughout pregnancy include HCQ, azathioprine/6-MP, colchicine, and sulfasalazine (104,106,159–161)**. Calcineurin inhibitors (tacrolimus and cyclosporine) and NSAIDs are conditionally recommended as compatible for use during pregnancy** (154)**. We conditionally recommend discontinuation of NSAIDs pre-conception if the patient is having difficulty conceiving (and if disease control would not be compromised**), **due to the possibility of NSAID-induced unruptured follicle syndrome, a cause of sub-fertility** (162)**. We strongly recommend avoiding NSAIDs in the third trimester because of the risk of premature closure of the ductus arteriosus** (163). **We conditionally recommend non-selective NSAIDs over Cox2-specific inhibitors in the first two trimesters due to lack of data for Cox2-specific inhibitors.**

Non-fluorinated glucocorticoids should be used when needed, but substitution of steroid-sparing pregnancy-compatible immunosuppressive therapy is desirable when high dose or prolonged use is required. **We conditionally recommend continuing low dose glucocorticoid (≤10 mg daily of prednisone or non-fluorinated equivalent) during pregnancy if clinically indicated, and strongly recommend tapering higher doses of non-fluorinated glucocorticoids to <20mg daily of prednisone, adding a pregnancy-compatible glucocorticoid-sparing agent if necessary. Although data are minimal regarding women using chronic low dose glucocorticoid during pregnancy, we conditionally recommend against routine administration of stress dose glucocorticoids at the time of vaginal delivery, but conditionally do recommend such treatment for surgical (Cesarean) delivery.**

We conditionally recommend continuing TNF-inhibitor therapy with infliximab, etanercept, adalimumab, and golimumab prior to and during pregnancy (164,165). The TNF-inhibitor certolizumab does not contain an Fc chain and thus has minimal placental transfer (166)**. We strongly recommend continuation of certolizumab therapy prior to and during pregnancy.**

Placental transfer and fetal exposure for most biologic therapies vary with gestational stage. The majority of RMD biologic therapies contain an Fc IgG1 construct that does not cross into the fetal circulation in significant concentrations until the second trimester (167). Use of the TNF-inhibitors that include an IgG1 Fc construct during the third trimester (infliximab, etanercept, adalimumab, and golimumab) results in high levels of placental transfer and significant drug levels in the neonate. A modest amount of evidence suggests that these TNF-inhibitors cause no adverse effects, especially in the first trimester. There was extensive voter panel discussion regarding if, and when, these medications be discontinued prior to delivery. If the patient's disease is under good control, the voting panel agreed that these medications may be discontinued in the third trimester. While there is a paucity of safety data, if the patient's disease is active, continuing TNF-inhibitors through delivery can be considered, understanding that the neonate will have significant serum levels of drug for a period of time.

There are limited data on the compatibility of other biologics with pregnancy. Given that these agents likely do not cross the placenta until the second trimester, the panel conditionally recommends that non-TNF inhibitor IgG-based molecules are compatible in the peri-conception period but should be discontinued during pregnancy (that is, once a pregnancy test is positive). **For anakinra, belimumab, abatacept, tocilizumab, secukinumab, and ustekinumab we conditionally recommend continuing therapy while a woman is trying to conceive but discontinuing once she is found to be pregnant.** If disease cannot be controlled with medications considered compatible with pregnancy, the physician and patient should discuss and weigh the possible risks from these medications with the risks of uncontrolled disease during pregnancy.

We conditionally recommend continuing rituximab while trying to conceive, and conditionally recommend continuing rituximab during pregnancy if severe, life or organ threatening maternal disease so warrants. Dosing in the 2nd half of pregnancy puts the fetus at high risk for having minimal B cells at delivery (168)**.**

No evidence regarding use or safety during pregnancy is available for the new small molecule agents, tofacitinib, baricitinib, and apremilast. The voting panel elected not to offer recommendations for these drugs. It should be noted however that small molecules are likely to pass through the placenta.

Medication use during breastfeeding

The benefits of breastfeeding are numerous (169–175); exclusive breastfeeding is recommended by the AAP for the first 6 months and continued breastfeeding until one year (9). Because women with RMD may suffer disease flare post-partum and require treatment, balancing benefits of disease control with risk of infant exposure through breast milk is important.

Infant serum levels depend on multiple variables and are a function of drug concentration in breast milk, quantity of breast milk ingested, and drug absorption

through the infant's gastrointestinal tract. Premature infants or those with gastrointestinal disorders may absorb medication differently. Rheumatologists should collaborate with pediatricians when making recommendations (176). Levels of drug in breast milk are routinely expressed as the relative infant dose (RID) (infant dose mg/kg/day divided by maternal dose mg/kg/day) and are available in reference publications; a value of less than 10% is considered safe.

Appendix 4, Table L shows formal best practice statements and recommendations for use of medications during breastfeeding with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are in online Appendix 9.

We suggest as standard good practice that women be encouraged to breastfeed if they so desire and are able to do so. In addition, we suggest that disease control be maintained with lactation-compatible medications and that individualized risks and benefits be reviewed with each patient.

Fortunately, many RMD medications may be initiated or continued during lactation. **We strongly recommend as compatible with breastfeeding: HCQ, colchicine, sulfasalazine, rituximab, and all TNF-inhibitors** (177–181)**. We also strongly recommend prednisone <20mg a day (or equivalent non-fluorinated glucocorticoid) as compatible with breastfeeding, but strongly recommend that for doses of prednisone ≥20mg a day (or equivalent) women delay breastfeeding or discard breast milk accumulated in the four hours following glucocorticoid administration.**

Medications conditionally recommended as compatible with breastfeeding include azathioprine/6-MP, calcineurin inhibitors, NSAIDs and the non-TNF-inhibitor biologic agents (anakinra, rituximab, belimumab, abatacept, tocilizumab, sekukinumab, and ustekinumab) (182–184)**.**

We strongly recommend against use of CYC, leflunomide, MMF, and thalidomide during breastfeeding. We conditionally recommend against using MTX while breastfeeding. Despite minimal passage of MTX into breast milk, especially with once weekly dosing, this medication may accumulate in neonatal tissues (185,186).

The voting panel declined to vote on the compatibility of new small-molecule agents regarding use during breastfeeding due to absence of data; in theory, however, these medications may transfer into breast milk because of their low molecular weights.

Discussion:

Patients' reproductive health concerns are relevant to all practicing rheumatologists. Issues regarding contraception, fertility, pregnancy, lactation, and the offspring's health affect almost every patient across all RMD diagnoses. The importance of this area is highlighted by recent publications that have addressed key elements of reproductive health for some or all RMD patients. The European League Against Rheumatism (EULAR) published recommendations for women's health issues in patients with SLE and APS(187), and both EULAR (with points to consider) and the British Society for Rheumatology (BSR)/ British Health Professionals in Rheumatology (BHPR) (with guideline recommendations) addressed use of medications before, during and after RMD pregnancy(188–190). Here, we address broad reproductive health concerns as well as medication use surrounding pregnancy for all RMD patients with special attention, when indicated, for patients with specific disorders such as SLE or APS.

Even with the wide spectrum of reproductive issues addressed here (Table 4), this project has important limitations. This Guideline was developed, and the literature review conducted, in the adult population. An important future step will be to consider these issues among adolescents, as counseling and care for these patients may differ.

Another important limitation is the inability to include recommendations for uncommon but important clinical situations. Although our mandate was broad, our task was to derive and support our recommendations with available evidence, but many uncommon clinical scenarios have little published data. One such situation that reflects an ongoing research need is the challenge of

reproductive health issues specific to transgender individuals, especially regarding hormonal therapies.

A relatively rare but important scenario is the therapeutic termination of pregnancy in patients with life-threatening disease damage or flare. Pregnancy in patients with pre-existing severe organ damage carries profound maternal risk. Pulmonary arterial hypertension (PAH) is associated with a particularly high risk of maternal mortality, estimated at up to 20% even with aggressive therapy (191). Other high-risk scenarios include severe renal insufficiency, cardiomyopathy, or valvular dysfunction. Severe autoimmune disease flare occurring during pregnancy – including diffuse alveolar hemorrhage, active nephritis or vasculitis, or central nervous system inflammation – also carries high risk for maternal morbidity and mortality (192–195). In these and other high-risk situations, the option of therapeutic termination of pregnancy may be lifesaving and should be discussed with the patient (196). Decisions regarding pregnancy termination in the setting of teratogenic medication exposure will depend on the specific medication, timing of exposure, and the patient's assessment of the available data; counseling by expert professionals such as MFM or genetics specialists regarding degree of risk based on specific circumstances is suggested in these cases.

We provide data-derived recommendations for common clinical reproductive health decisions including recent advances in this area and emphasize the need for early involvement of the rheumatologist in reproductive health discussions, for instance, the importance of effective contraception for RMD patients. Almost half of pregnancies in the US are unplanned (197). In RMD patients unplanned pregnancies carry greater risk than do planned pregnancies in periods of quiet disease on compatible medications. Considering pregnancy or not, patients should know maternal and fetal risks, including fetal exposure to teratogenic medications and their safest and most effective contraception options.

Asking a patient about desire for pregnancy early and periodically (not only during perceived periods of change) and acknowledging her personal risk factors will ensure open dialogue. New information supports a shift from the paradigm of discontinuing all RMD medications except prednisone, since pregnancy-compatible steroid-sparing DMARDs and biologics pose fewer short- and long-term risks

to mother and infant. With adequate planning, treatment and monitoring, most women with RMD can have successful pregnancies. New data indicate compatibility of many rheumatology medications with both lactation and with paternal use. The rheumatologist's familiarity with drug safety during these periods is important to maintain disease control and minimize mother and infant risk.

Fertility and post-menopausal issues are not uncommon in RMD patients. Recommendations regarding ART reflect a growing demand among patients with RMD for fertility therapies. Oocyte freezing is now widely available (198). Attention to disease activity and aPL status and discussion with REI will optimize safety. For patients undergoing CYC therapy, the greatest challenge is to consider preservation of gonadal function and to initiate protective treatment protocols. HRT is another issue of importance for postmenopausal RMD patients. Severe vasomotor symptoms may be debilitating and if affected patients do not have aPL, HRT may improve quality of life.

The strength of evidence on reproductive health topics in RMD patients is moderate at best, and usually low, very low or nonexistent for many topics of interest. Identification of areas with weak evidence highlights research priorities. One need is to establish the long-term safety profile of highly effective contraceptives in RMD patients with and without aPL. Although low dose aspirin for preeclampsia prophylaxis in SLE and aPL patients is a low risk intervention, effectiveness is not known. Management of OB APS is one area with moderately strong evidence, but treatment for women with recurring adverse outcomes despite standard therapy is needed. Much in the field of neonatal lupus prevention, screening, and management requires further study. There are very limited data on RMD medication effects on male fertility and teratogenicity. Because women with RMD who plan to conceive, are pregnant, or are lactating are usually excluded from clinical trials, large scale data about drug use in these populations are also lacking. Pregnancy registries collect these data but suffer reporting bias and may not reflect the racial and ethnic make-up of all patients. Given the difficulties of collecting clinical data, research that focuses on better understanding of placental and breast physiology, as well as drug and antibody transport, may also help inform decision-making.

With the development of this Guideline, the ACR recognizes the importance of rheumatology clinicians not only in managing disease activity but also in understanding the interactions of RMDs and their therapies in the context of reproductive health. This

guideline's most important goal is to provide substance and direction for discussion between clinicians and patients. A second goal is to encourage development of close working relationships among rheumatologists, OB-GYN, MFM, REI specialists, and other involved clinicians. We present this guideline as a resource to share, discuss, and disseminate across specialties and patient groups.

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Figure 1. Recommendations and good practice statements for use of contraception in women with RMD. GPS = Good practice statement; aPL = anti-phospholipid antibodies (persistent, moderate/high titer anticardiolipin or anti-beta2 Glycoprotein I antibody or persistent positive lupus anticoagulant); IUD = Intrauterine device (copper or progestin); DMPA = depot medroxyprogesterone acetate.

Figure 2. Recommendations for use of assisted reproductive technology (ART) in women with RMD. CYC = Cyclophosphamide; aPL = antiphospholipid antibody (persistent, moderate/high titer anticardiolipin or anti-beta2 Glycoprotein I antibody or persistent positive lupus anticoagulant); APS = antiphospholipid syndrome (obstetric and/or thrombotic); OB APS (Obstetric APS) = Patients with laboratory criteria for APS and prior consistent pregnancy complications (3 consecutive losses prior to 10 weeks

gestation, fetal loss after 10 weeks gestation, or delivery < 34wks due to preeclampsia, intrauterine growth restriction, or fetal distress) and no history of thrombosis; Thrombotic APS = Patients with laboratory criteria for APS and a prior thrombotic event (arterial or venous), regardless of whether they have had obstetric complications; ART = assistive reproductive technology; LMWH = low molecular weight heparin; UH = unfractionated heparin.

Figure 3. Recommendations and good practice statements for HRT use in postmenopausal women with RMD. GPS = Good practice statement; aPL = anti-phospholipid antibody (persistent with moderate-high titer); APS = Obstetric and/or thrombotic antiphospholipid antibody syndrome; HRT = Hormone replacement therapy; SLE = systemic lupus erythematosus.

Figure 4. Recommendations and good practice statements for pregnancy counseling, assessment and management in RMD women. GPS = Good practice statement; aPL = antiphospholipid antibody (persistent, moderate-high titer); APS = antiphospholipid antibody syndrome; HCQ = hydroxychloroquine; NLE = neonatal lupus.

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Table 1: Safety and efficacy of various contraceptive methods in women with rheumatic and musculoskeletal disease (RMD)

Method	**Safety in women with RMD:**	**1 year failure rate***
HIGHLY EFFECTIVE (LARC)		
Copper IUD	Safe in all women with RMD May *increase* menstrual bleeding	<1%
Progestin IUD	Safe in all women with RMD May *decrease* menstrual bleeding	
Progestin implant	Limited data, but likely safe in all women with RMD	
EFFECTIVE		
Progestin-only pill (daily)	Safe in all women with RMD. Higher rate of breakthrough bleeding than combined contraceptives Must take same time every day for efficacy	6-9%
DMPA (q12wk IM injection)	Safe in most women with RMD ***Exceptions***: aPL positive ; high risk for osteoporosis	
Combined estrogen & progesterone pill (daily)	Safe in most women with RMD ***Exceptions***: aPL positive; very active SLE	
Transdermal patch (weekly)	Safe in most women with RMD Serum estrogen levels are higher than with pill or vaginal ring ***Exceptions***: aPL positive; very active SLE	
Vaginal ring (monthly)	Safe in most women with RMD ***Exceptions***: aPL positive; very active SLE	
LESS EFFECTIVE		
Diaphragm	Safe in all women with RMD.	12%

Condom	Safe in all women with RMD. **Only form to prevent STD**	18%
Fertility awareness - based methods**	Safe in all women with RMD. Limited efficacy, especially if irregular menses	24%
Spermicide	Safe in all women with RMD. Use with condoms or diaphragm to improve efficacy	28%

*Percent of women who will become pregnant within the first year of typical use

**Fertility awareness-based methods are methods based on the timing of the menstrual cycle

LARC: Long-acting reversible contraception

IUD: Intrauterine device

DMPA: Depot medroxyprogsterone acetate

Table 2. Paternal Medications.

Recommendations regarding medication use for men with RMD who are planning to father a child.

Strongly Recommend Continuing	Conditionally Recommend Continuing	Strongly Recommend Discontinuing	Conditionally Recommend Discontinuing	Unable to make a recommendation due to limited data
• Azathioprine/6-MP • Colchicine • Hydroxychloroquine • TNF-inhibitors (all)	• Anakinra • Cox-2 Inhibitors • Cyclosporine • Leflunomide • Methotrexate • Mycophenolate mofetil • Mycophenolic acid • NSAIDs • Rituximab • Sulfasalazine *(Semen analysis if delayed conception)* • Tacrolimus	• Cyclophosphamide *discontinue 12 weeks prior to attempted conception*	• Thalidomide *discontinue 4 weeks prior to attempted conception*	• Abatacept • Apremilast • Baracitanib • Belimumab • Secukinumab • Tocilizumab • Tofacitinib • Ustekinumab

Table 3. Maternal Medication Use.

Medication	Pre-conception	During pregnancy	Breastfeeding
CONVENTIONAL MEDICATIONS:			
Hydroxychloroquine	++	++	++
Sulfasalazine	++	++	++
Colchicine	++	++	++
Azathioprine, 6-MP	++	++	+ *Low transfer*
Prednisone	+ *Taper to <20mg/day by adding pregnancy-compatible immunosuppressants*	+ *Taper to <20mg/day by adding pregnancy-compatible immunosuppressants*	+ *After a dose >20mg, delay breastfeeding for 4 hours*
Cyclosporine, Tacrolimus	+ *Monitor blood pressure*	+ *Monitor blood pressure*	+ *Low transfer*
NSAIDS *(COX 2 inhibitors not preferred)*	+ *Discontinue if the woman is having difficulty conceiving*	+ *Continue 1st and 2nd trimesters; Discontinue 3rd trimester*	+ *Ibuprofen preferred*
TNF-INHIBITORS:	***TNF-INHIBITORS ARE CONSIDERED COMPATIBLE WITH PREGNANCY***		
Certolizumab	++	++	++
Infliximab Etanercept Adalimumab Golimumab	+ *Continue through conception*	+ *Continue in 1st & 2nd trimesters; discontinue in 3rd trimester several half-lives prior to delivery*	++

RITUXIMAB:			
Rituximab	+ *Discontinue at conception*	+ *Life / organ-threatening disease*	++

OTHER BIOLOGICS: ***LIMITED SAFETY DATA. LIMITED TRANSFER EARLY PREGNANCY BUT HIGH TRANSFER IN 2ND HALF OF PREGNANCY.***

Anakinra Belimumab Abatacept Tocilizumab Secukinumab Ustekinumab	+ *Discontinue at conception*	× *Discontinue during pregnancy*	+ *Expect minimal transfer due to large molecular size but no available data*

NOT COMPATIBLE WITH PREGNANCY:

Methotrexate	×× *Stop 1-3 months prior to conception*	×× *Stop and give folic acid 5mg/day*	× *Limited data suggest low transfer*
Leflunomide	×× *Cholestyramine washout if detectable levels*	×× *Stop and give cholestyramine washout*	××
Mycophenolate mofetil & Mycophenolic acid	×× *Stop >6wks prior to conception to assess disease stability*	××	××
Cyclophosphamide	××	+	××

	Stop 3 months prior to conception	*Life / organ threatening disease in the 2nd and 3rd trimesters*	
Thalidomide	×× *Stop 1-3 months prior to conception*	××	××
Tofacitinib Apremilast Baracitanib	***Unable to determine due to lack of data.*** ***Small molecular size suggests transfer across the placenta and into breastmilk***		

Overview of medication use before and during pregnancy, and during breastfeeding:

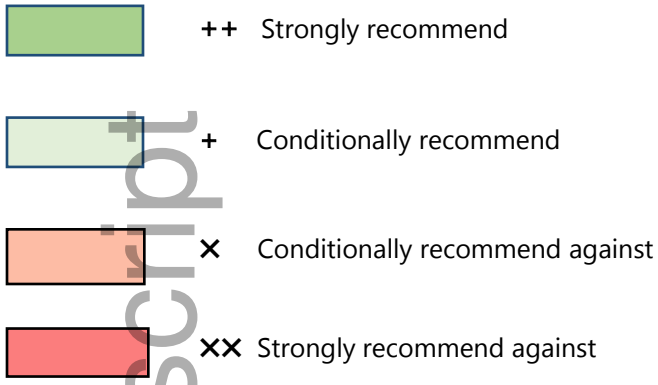

Table 4. Reproductive health care in patients with RMD: Concise recommendation summary*

Topic	Recommendation	Strength
Contraception		
All RMD	Contraception / pregnancy discussion early and regularly; Choose contraception based on safety, efficacy and patient preference	GPS
	Use barrier methods if unable to use other methods	GPS
	Use emergency contraception if necessary [6]	Strong
	Women on immunosuppressive medications: use IUDs if desired [7]	Strong
	Women at risk for osteoporosis: AVOID DMPA [10]	Conditional
	Women on MMF: Use an IUD or two other methods together [11]	Conditional
	RMD without SLE or aPL: Use highly effective or effective methods [1]	Strong
	Highly effective preferred to effective methods [1A]	Conditional
SLE	*SLE with negative aPL and low/stable disease activity*: Use highly effective or effective methods [2]	Strong
	Highly effective preferred to effective methods [2A]	Conditional
	AVOID transdermal estrogen-progestin patch [2B]	Conditional
	SLE with negative aPL and moderate-high disease activity: Use progestin-only contraceptives or IUDs [2C]	Strong
aPL positive	Do NOT use combined estrogen-progestin contraceptives [3]: Use IUDs or progestin-only pill [4]	Strong
ART		
All RMD	*Stable disease and negative aPL:* proceed with ART:	
	IVF if pregnancy compatible medications [24]	Strong
	Oocyte cryopreservation: continue medications except CYC [28]	Strong
	Active disease: defer ART until disease stable/quiescent [27]	Strong
SLE	*Active SLE:* defer ART until disease stable/quiescent [27]	Strong
	Do NOT treat with prophylactic prednisone [29]	Conditional
aPL positive	*No prior thromboses or OB APS*: prophylactic heparin or LMWH [25A]	Conditional

	No prior thromboses but history of OB APS: prophylactic heparin or LMWH [25A2] *Prior thromboses*: therapeutic heparin or LMWH [26A]	Strong Strong
Fertility preservation	Women: Use GnRH(a) therapy during IV CYC [31] Men: Sperm cryopreservation pre-CYC; do not use GnRH(a) therapy [35]	Conditional GPS/ Conditional
Menopause/HRT		
All RMD	*RMD without SLE or aPL*: treat with HRT if indicated**	GPS
SLE	*SLE and negative aPL*: treat with HRT if indicated** [79]	Conditional
aPL positive	*If no prior thrombosis or OB APS:* do NOT treat with HRT [80] If current titers negative, treat with HRT if indicated** [83]	Conditional Conditional
	If prior thrombosis or OB APS and not on anticoagulation: do NOT treat with HRT [81] If current titers negative, do NOT treat with HRT [83A]	Strong Conditional
	If prior thrombosis or OB APS and on anticoagulation: do NOT treat with HRT [82]	Conditional
Pregnancy		
General RMD	Counseling: Outcomes improved with pregnancy planning, stable disease, compatible medications and co-management with rheumatology and OB-GYN / MFM Pre-pregnancy: change to pregnancy-compatible medication and observe for stability [42] *If active disease during pregnancy*: initiate pregnancy-compatible medication [54]	GPS Strong Strong
	If SLE or SLE-like disease, Sjogren's, systemic sclerosis or RA: test once (early) for anti-Ro/SSA and La/SSB [60, 62]	Strong
	If scleroderma and renal crisis during pregnancy, treat with ACE-I or ARB for life-threatening disease [55]	Strong
SLE	*SLE or SLE-like disease*: test once (early) for aPL (aCL, aβ2GPI,LAC) [59, 61]	Strong
	Continue HCQ during pregnancy [57]	Strong
	If not taking HCQ, start HCQ during pregnancy if no contraindications [58]	Conditional
	Monitor laboratory tests at least once per trimester	GPS
	Treat with low dose aspirin starting in first trimester [56]	Conditional

Positive aPL	*Positive aPL only:*	
	If no prior thrombosis or OB APS: treat with low dose aspirin starting in first trimester [45]	Conditional
	Do NOT treat with combination prophylactic heparin or LMWH / low dose aspirin therapy [46]	Conditional
	Do NOT treat with HCQ [44A]	Conditional
	OB-APS:	
	If no thrombosis but meet OB-APS criteria: treat with combination prophylactic heparin or LMWH /low dose aspirin therapy [48]	Strong
	Do NOT treat with combination therapeutic heparin or LMWH / low dose aspirin therapy [49]	Conditional
	Do NOT treat with addition of IVIG [50]	Conditional
	Do NOT treat with addition of prednisone [51]	Strong
	Treat with addition of HCQ for combination heparin / low dose aspirin therapy failure [44B]	Conditional
	Treat with prophylactic anticoagulation during post-partum period [84]	Strong
	Thrombotic APS:	
	If prior thrombosis (+/- OB-APS criteria): treat with therapeutic heparin or LMWH / low dose aspirin therapy [52]	Strong
	Treat with addition of HCQ for therapeutic heparin or LMWH / low dose aspirin therapy failure [44B]	Conditional
Positive anti-Ro/SSA +/- anti-La/SSB	Treat with HCQ during pregnancy [69, 70]	Conditional
	If no prior history of neonatal lupus: serial (interval uncertain) fetal echocardiograms in weeks 16-26 [67]	Conditional
	If prior history of neonatal lupus: weekly fetal echocardiograms in weeks 16-26 [68]	Conditional
	Abnormal fetal echocardiogram:	
	If 1st or 2nd degree heart block: treat with dexamethasone 4 mg daily [71,71]	Conditional
	If isolated 3rd degree heart block (and no other cardiac inflammation): do NOT treat with dexamethasone [73]	Conditional
Paternal medications		
	If planning to father a child, discuss medication use including CYC	GPS

	Discontinue CYC and thalidomide [133, 139]	Strong / Conditional
	Continue HCQ, AZA, infliximab, etanercept, adalimumab, golimumab, certolizumab and colchicine [90, 115, 143, 146, 149, 152, 155, 97]	Strong
	Continue leflunomide, MMF, NSAIDs, sulfasalazine, cyclosporine, tacrolimus, anakinra, rituximab [108, 119, 85, 94, 126, 130, 159, 163]	Conditional
Maternal medications		
	If planning pregnancy: discuss medication use including CYC	GPS
	If pregnant and exposed to teratogenic medications: discontinue immediately, pursue counseling	GPS
	NSAIDs: discontinue if difficulty conceiving [86] Avoid in third trimester [87] Use non-selective rather than Cox-2 specific [88]	Conditional Strong Conditional
	Discontinue MTX, MMF, thalidomide, CYC prior to conception [102, 120, 140, 134] Use CYC for life-threatening disease only in 2nd / 3rd trimester pregnancy [136]	Strong Conditional
	Discontinue leflunomide 24 months prior to conception or check serum metabolite levels and treat with cholestyramine washout [109, 110]	Strong
	Continue HCQ, sulfasalazine, AZA, colchicine [91,95,116, 98] Continue cyclosporine and tacrolimus [127, 131] Continue certolizumab [156] Continue infliximab, etanercept, adalimumab, golimumab [144,147, 150,153]	Strong Conditional Strong Conditional
	Stop when pregnancy confirmed: rituximab, belimumab, anakinra, abatacept, tocilizumab, secukinumab, ustekinumab [164, 169, 160, 173, 177, 181, 185] Use rituximab for organ- or life-threatening disease during pregnancy [165]	Conditional Conditional
	No recommendations due to lack of data for tofacitinib, baracitinib, apremilast [189, 193,197]	
	Continue chronic low dose prednisone [201] and taper high dose prednisone with addition of pregnancy-	Conditional

	compatible drug if needed [202]	Strong
	Stress dose steroid at delivery: do NOT treat for vaginal delivery, do treat for Cesarean delivery [206, 207]	Conditional
Medications in lactation		
	Encourage breastfeeding and maintain disease control with compatible medications if possible	GPS
	Compatible medications: HCQ, infliximab, etanercept, adalimumab, golimumab, certolizumab, rituximab [92, 143, 146, 149, 152, 155] NSAIDs, sulfasalazine, colchicine, AZA, cyclosporine, tacrolimus anakinra, belimumab, abatacept, tocilizumab, sekukinumab, ustekinumab [89, 96, 99, 117, 128, 132, 161, 170, 174, 178, 182, 186] Prednisone or non-fluorinated steroid equivalent: < 20 mg [204]; ≥ 20 mg daily, discard milk for 4 hours following medication [205]	 Strong Conditional Strong Strong
	Do NOT treat with leflunomide, MMF, CYC, thalidomide [113, 124, 137, 142] Do NOT treat with MTX [106]	Strong Conditional

Recommendation numbers are denoted as numbers in square brackets, allow for cross referencing of recommendations with other tables/appendices, and reference the order in the original list

GPS: Good practice statement

RMD: Rheumatic and musculoskeletal disease
SLE: systemic lupus erythematosus
RA: Rheumatoid arthritis
aPL: antiphospholipid antibody, meeting laboratory APS criteria (Appendix 5)
aCL: anticardiolipin antibody
aβ2GPI: anti-beta2 Glycoprotein I antibody
LAC: Lupus anticoagulant
OB APS: Meeting laboratory APS criteria and clinical obstetric criteria (Appendix 5)

OB-GYN: Obstetrics-gynecology

MFM: Maternal fetal medicine

ART: Assisted reproductive technology

IVF: In vitro fertilization

Highly effective contraceptives: Long-acting reversible contraceptives including progestin or copper IUD and progestin implant

IUD: intrauterine device

Effective contraceptives: Estrogen-progestin contraceptives (oral, patch or vaginal ring) and progestin-only (oral, DMPA)

DMPA: Depo-medroxyprogesterone acetate

LMWH: low molecular weight heparin

ACE-I: Angiotensin converting enzyme inhibitors

ARB: Angiotensin II receptor blockers

NSAIDs: Non-steroidal anti-inflammatory drugs

CYC: cyclophosphamide

HCQ: Hydroxychloroquine

MMF: Mycophenolate mofetil (and mycophenolic acid)

MTX: Methotrexate

AZA: Azathioprine (and 5-fluorouracil)

* For more detailed / complete recommendations, see text or Appendix 4.

**General indication for HRT therapy: Current recommendations suggest limiting HRT use in healthy postmenopausal women and using the lowest dose that alleviates symptoms for the minimal time necessary. Benefit-risk balance is most favorable for severe vasomotor symptoms in women $\leq$ 60 years old or within 10 years of menopause onset. (The 2017 hormone therapy position statement of The North American Menopause Society. Menopause. 2017;24:728–53.)

Discuss contraception and pregnancy planning at initial or early visit with women of reproductive age and counsel regarding efficacy and safety [GPS]. Recommend barrier methods if more effective methods are contraindicated [GPS]. Recommend emergency (post-coital) contraception when necessary [6].