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2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases

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Objective. To develop an evidence-based guideline on contraception, assisted reproductive technologies (ART), fertility preservation with gonadotoxic therapy, use of menopausal hormone replacement therapy (HRT), pregnancy assessment and management, and medication use in patients with rheumatic and musculoskeletal disease (RMD).

Methods. We conducted a systematic review of evidence relating to contraception, ART, fertility preservation, HRT, pregnancy and lactation, and medication use in RMD populations, using Grading of Recommendations Assessment, Development and Evaluation 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 were agreed upon when indirect evidence was sufficiently compelling that a formal vote was unnecessary.

Results. This American College of Rheumatology guideline provides 12 ungraded good practice statements 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, those positive for antiphospholipid antibody, and/or those positive for anti-Ro/SSA and/or anti-La/SSB antibodies. Recommendations and good practice statements 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 receiving pregnancy-compatible medications, and ongoing physician-patient discussion with obstetrics/gynecology collaboration for all reproductive health issues, given the overall low level of available evidence that relates specifically to RMD.

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 in patients with rheumatic and musculoskeletal diseases (RMD) differs from that in healthy 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 (ART), fertility preservation, and hormone replacement therapy (HRT), and they must collaborate with specialists in the fields of obstetrics-gynecology, maternal-fetal medicine, and reproductive endocrinology and infertility.

Pregnancy in women with RMD may lead to serious maternal or fetal adverse outcomes; accordingly, contraception, tailored to the individual patient 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. The ability to become pregnant may itself be an independent concern for some patients, so minimizing risk of gonadal insufficiency is important. RMD patients with subfertility value advice from their rheumatologists about oocyte preservation and in vitro fertilization (IVF).

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

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. There has been little attention to aspects of reproductive health care other than pregnancy in patients with RMD, and the American College of Rheumatology (ACR) recognizes the imperative for guidance in reproductive health issues for these patients.

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METHODS

These recommendations follow the ACR guideline development process, using a systematic literature review and Grading of Recommendations Assessment, Development and Evaluation methodology (for details, see Supplementary Appendices 1, 2, and 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). When no direct data on RMD patients were available from the systematic literature review, discussion and voting were supplemented with indirect data collected in additional, less formal literature reviews (Supplementary Appendix 4, http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) performed by Core Team members (Supplementary Appendix 5, http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract); these data were not part of the systematic literature review and are listed as "not graded" in evidence tables. Results of the systematic literature review were compiled in an Evidence Report (Supplementary Appendix 6, http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract).

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 a lack of data, limited data, or conflicting data that lead to uncertainty. Finally, *good practice statements* are those for which indirect evidence is sufficiently compelling that a formal vote is unnecessary. They are presented as "suggestions" rather than formal recommendations. Recommendation numbers are denoted in Supplementary Appendix 7 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) as numbers in parentheses, allowing for cross-referencing of recommendations with tables/appendices, and referencing the order in the original list (i.e., may not be consecutive in the supplementary appendix.)

RESULTS/RECOMMENDATIONS

The detailed tables of recommendations appear in Supplementary Appendix 7 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). Concise recommendations within this appendix and throughout the article are grouped into categories of contraception,

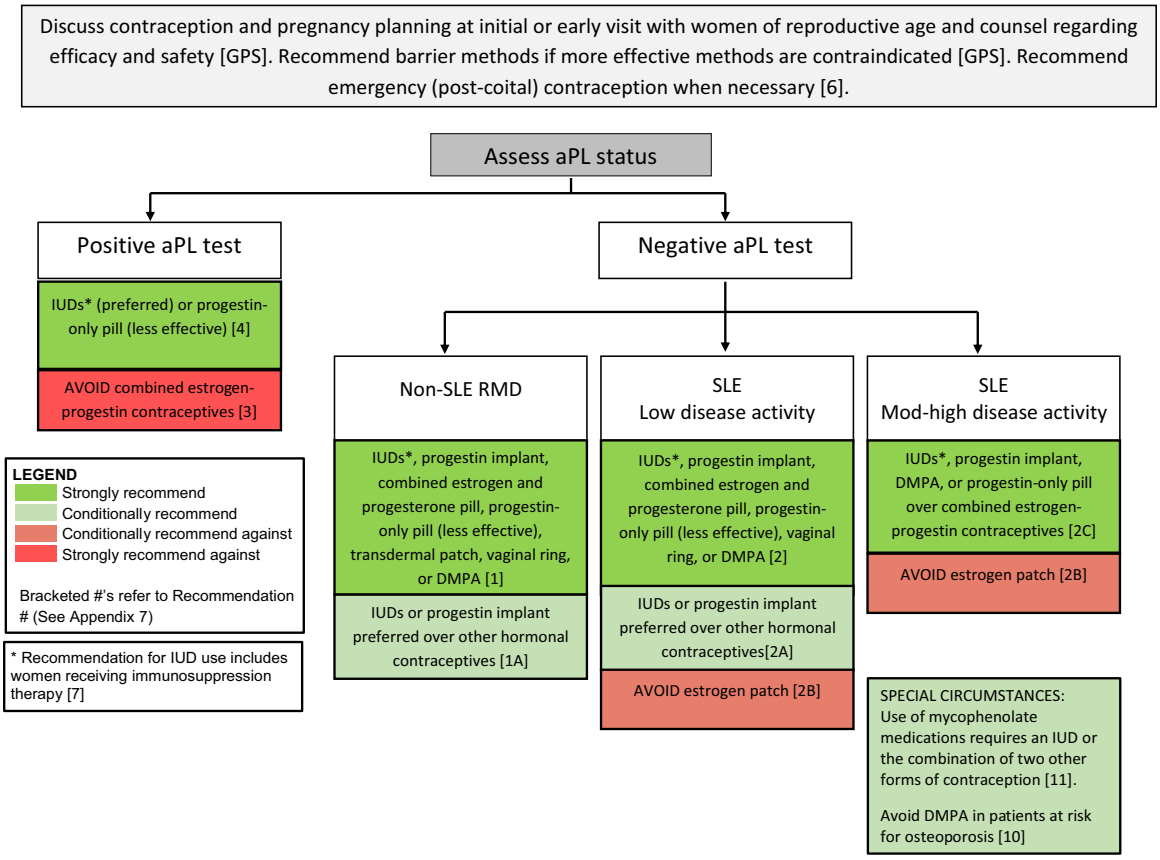

Figure 1. Recommendations and good practice statements (GPS) for use of contraception in women with rheumatic and musculoskeletal disease (RMD). aPL = antiphospholipid antibody (persistent moderate [Mod]–to-high–titer anticardiolipin or anti–β_2-glycoprotein I antibody or persistent positive lupus anticoagulant); IUDs = intrauterine devices (copper or progestin); SLE = systemic lupus erythematosus; DMPA = depot medroxyprogesterone acetate.

ART, fertility preservation with gonadotoxic therapy, use of menopausal HRT, pregnancy assessment and management, and medication use (compatibilities for paternal, maternal, and breastfeeding use are reported).

Most recommendations are general; when 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 anti-La/SSB antibodies). In general, testing for aPL should be performed 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 (2 positive test results at least 12 weeks apart) moderate-high–titer anticardiolipin antibody (aCL) (≥40 units or ≥99th percentile), moderate-high–titer anti–β_2-glycoprotein I (anti-β_2GPI) (≥40 units or ≥99th percentile), or positive lupus anticoagulant (LAC).

Detailed definitions of aPL and antiphospholipid syndrome (APS) are presented in Supplementary Appendix 8 (available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). Briefly, included within the positive aPL group are patients with asymptomatic aPL who have no history of thrombosis or pregnancy morbidity (i.e., meet laboratory but not clinical APS criteria), patients with obstetric APS (OB APS), and patients with thrombotic APS. OB APS refers to patients who meet laboratory criteria for APS and have experienced prior pregnancy complications consistent with APS (with other causes ruled out). These include 3 consecutive losses prior to 10 weeks' gestation, a fetal loss at or after 10 weeks' gestation, or delivery at <34 weeks due to preeclampsia, intrauterine growth restriction, or fetal distress. Thrombotic APS refers to patients who meet laboratory criteria for APS and have experienced a prior thrombotic event (arterial or venous), regardless of whether they have had obstetric complications. The aPL definitions in the guideline include both patients with and patients without other underlying autoimmune disease, unless specifically stated.

Patients with lower-titer aCL and/or anti-β_2GPI (or non-criteria aPL) who 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

Supplementary Appendix 7, Table A (on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) presents formal recommendations regarding contraception; strength of evidence and justifications for strong and conditional recommendations are shown in Supplementary Appendix 9 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). Figure 1 details the contraception decision-making

Table 1. Safety and efficacy of various contraceptive methods in women with 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	<1
Progestin implant	Limited data, but likely safe in all women with RMD	<1
Effective		
Progestin-only pill (daily)	Safe in all women with RMD; higher rate of breakthrough bleeding than with combined contraceptives; must take same time every day for efficacy	5–8
DMPA (IM injection every 12 weeks)	Safe in most women with RMD; exceptions: positive aPL, at high risk for OP	3
Combined estrogen and progesterone pill (daily)	Safe in most women with RMD; exceptions: positive aPL, very active SLE	5–8
Transdermal patch (weekly)	Safe in most women with RMD; exceptions: positive aPL, SLE; serum estrogen levels higher than with pill or vaginal ring	5–8
Vaginal ring (monthly)	Safe in most women with RMD; exceptions: positive aPL, very active SLE	5–8
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 menses are irregular	24
Spermicide	Safe in all women with RMD; use with condoms or diaphragm to improve efficacy	28

* RMD = rheumatic and musculoskeletal disease; LARC = long-acting reversible contraception; IUD = intrauterine device; DMPA = depot medroxyprogesterone acetate; IM = intramuscular; aPL = antiphospholipid antibody; OP = osteoporosis; SLE = systemic lupus erythematosus; STD = sexually transmitted disease.
† Percent of women who will become pregnant within the first year of typical use.
‡ Methods based on the timing of the menstrual cycle.

process, and Table 1 provides efficacy data and comments on available contraceptives.

RMD patients typically underutilize effective contraception (11–13). The most important reason for effective contraception in 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 1-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-age 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 (www.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 (copper or progestin intrauterine devices [IUDs]) and subdermal progestin implants), ideal use and "real-world" use effectiveness are similar, with pregnancy rates of <1% per year ("highly effective"). Combined estrogen-progestin methods, depot medroxyprogesterone acetate (DMPA) injections, and progestin-only pills yield pregnancy rates of 3–8% per year ("effective") (15,16). 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 long-acting reversible contraceptives 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 (see Special RMD Situations below and Supplementary Appendix 10, on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). "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 (i.e., women who may become pregnant).

In fertile women with RMD who have neither SLE nor positive aPL, we strongly recommend use of effective contraceptives (i.e., hormonal contraceptives or IUDs) over less effective options or no contraception; among effective methods, we conditionally recommend the highly effective IUDs or subdermal progestin implant (long-acting reversible contraceptives) 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 have 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 showed no increased risk of flare related to estrogen-progestin pills (19,20), and there are no data suggesting increased SLE flare risk with progestin-only pills or copper IUDs (20,21).

In SLE patients with stable or low disease activity who are not positive for aPL, we strongly recommend use of effective contraceptives (i.e., hormonal contraceptives or IUDs) over less effective options or no contraception, and we conditionally recommend the highly effective IUDs or subdermal progestin 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 regarding 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.

Antiphospholipid antibody–positive patients. Presence of aPL, with or without history of clinical complications, is a contraindication to use of estrogen-containing contraceptives due the potential further increase in thrombosis risk.

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 in women with positive aPL.

In aPL-positive patients, we do not recommend DMPA due to concern regarding thrombogenicity. We do not comment on the relatively new progestin implant due to lack of data.

The risk of venous thromboembolism (VTE) in healthy women taking combined estrogen-progestin contraceptives is 36 times 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 in patients for whom estrogens are contraindicated but who still need effective contraception (18,25,26). The specific progestin and its 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 or the progestin IUD is not increased, with relative risks (RRs) of 0.90 (95% confidence interval [95% CI] 0.57–1.45) and 0.61 (95% CI 0.24–1.53), respectively (27). Furthermore, thrombosis frequency does not increase when progestin (levonorgestrel) IUDs are used in non-RMD patients with increased (non–aPL-associated) thrombosis risk (27–29). VTE data on the newer progestin (etonogestrel) subdermal implant are inadequate to permit recommendations (the prior progestin implant containing levonorgestrel is no longer available in the US). Very limited data on non-RMD patients suggest that injectable DMPA imparts a higher VTE risk than do other progestin-only contraceptives (RR 2.67 [95% CI1.29–5.53]), similar to that with 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 (30), a potential benefit for patients receiving anticoagulation therapy.

We suggest the progestin-only pill (which is an effective, but not highly effective, contraceptive) as a low-risk alternative for patients who are 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 >10 times that seen with estrogen-progestin contraceptive use. Pregnancy-related thrombosis risk in 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) if there are multiple prothrombotic mutations.

Other special RMD situations. Factors other than diagnosis of SLE or presence of aPL may influence the choice of contraception in women with RMD. These include use of medications and presence or risk of osteoporosis. Immunosuppressive therapy does not preclude use of any contraceptive method, but there is concern that mycophenolate-containing medications may interfere with hormonal contraceptive efficacy.

Since IUDs are the most effective contraceptive options, we strongly recommend the IUD (copper or progestin) for women with RMD who are receiving immunosuppressive therapy, despite hypothetical infection risk.

IUD-associated infection risk in RMD patients receiving immunosuppressive therapy 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). In one arm of an SLE contraceptive trial a copper IUD was used; although the number of patients receiving immunosuppressive agents was not reported, there were no cases of pelvic inflammatory disease (20).

In women with RMD who are 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 that bone mineral density declines by up to 7.5% over 2 years of use in a healthy population (35).

Although there are no published data suggesting increased fracture risk, the American College of Obstetricians and Gynecologists recommends caution regarding DMPA use in 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 2 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 Strategy 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

Supplementary Appendix 7, Table B (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) presents the ART recommendations with strength of supporting evidence; detailed justifications for strong and conditional recommendations are shown in Supplementary Appendix 9 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). Figure 2 details the ART decision-making process.

While fertility is typically normal in women with RMD (who have not been treated with cyclophosphamide [CYC]), it decreases with age, and ART may be needed by some RMD patients. ART techniques include ovarian stimulation, which elevates estrogen levels, 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 reproductive endocrinology and infertility specialist regarding adjustments to the ovarian stimulation protocol in order to minimize the risk to the patient. Women with these underlying conditions who undergo fertility therapy should do so only in centers where the appropriate expertise is readily available.

We strongly recommend proceeding with ART if needed in women with uncomplicated RMD who are receiving pregnancy-compatible medications, whose disease is stable/quiescent, and who are negative for aPL.

Compared to the benefit of a successful pregnancy, the risk of ART for subfertile patients with RMD is low; nonetheless,

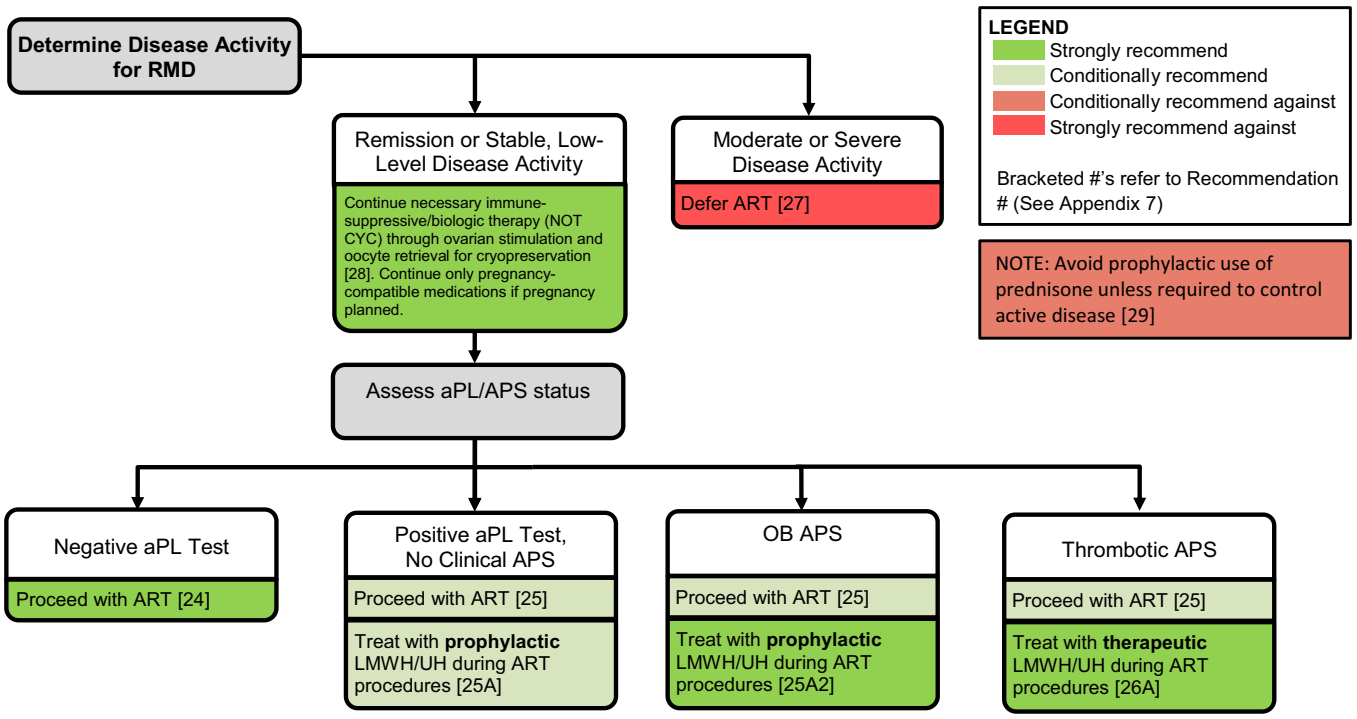

Figure 2. Recommendations for use of assisted reproductive technology (ART) in women with rheumatic and musculoskeletal disease (RMD). CYC = cyclophosphamide; aPL = antiphospholipid antibody (persistent moderate-to-high–titer anticardiolipin or anti–β_2-glycoprotein I antibody or persistent positive lupus anticoagulant); APS = antiphospholipid syndrome (obstetric and/or thrombotic); obstetric APS (OB APS) = patients meeting laboratory criteria for APS and having prior consistent pregnancy complications (≥3 consecutive losses prior to 10 weeks' gestation, fetal loss at or after 10 weeks' gestation, or delivery at <34 weeks due to preeclampsia, intrauterine growth restriction, or fetal distress) and with no history of thrombosis; thrombotic APS = patients meeting laboratory criteria for APS and having a prior thrombotic event (arterial or venous), regardless of whether they have had obstetric complications; LMWH = low molecular weight heparin; UH = unfractionated heparin.

risks associated with ART, especially thrombosis and lupus flare (39,40), should be discussed with patients. The level of evidence specific to RMD patients is very low (41,42), but evidence supports the safety of ART in a general population (43,44).

SLE patients. Data on IVF cycles in RMD patients are limited; however, the intended outcome of IVF, pregnancy, may be adversely affected by the presence of active RMD. In addition, there is concern that flare in SLE patients might be worsened in the setting of elevated estrogen levels.

We strongly recommend deferring ART procedures in patients with 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, 6 months of stable inactive or low-level disease is most often suggested, but individual clinical factors may influence this decision. In 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 monitoring the patient carefully and treating for flare if it occurs.

No studies have evaluated prescription of prophylactic prednisone to prevent SLE flare during ART.

Antiphospholipid antibody–positive patients. Patients who are positive for aPL are at increased risk for thrombosis. Most reports of aPL-positive patients undergoing IVF describe the use of empiric prophylactic anticoagulation due to concern regarding further increased risk of potentially life-threatening thrombosis from elevated estrogen levels during ovarian stimulation.

In subfertile patients with RMD who desire pregnancy, have stable/quiescent disease, and have asymptomatic positive aPL, OB APS, or treated thrombotic APS, we conditionally recommend ART with anticoagulation, as described below.

We conditionally recommend prophylactic anticoagulation therapy with heparin or low molecular weight heparin in 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 of bleeding or other complications of unfractionated heparin or low molecular weight heparin (LMWH).

We strongly recommend prophylactic anticoagulation with heparin or LMWH in women with OB APS, and we strongly recommend therapeutic anticoagulation in women with thrombotic APS, during ART procedures.

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, 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 of severe ovarian hyperstimulation syndrome (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 ovarian hyperstimulation syndrome, 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, 2 of 4 reported thromboses occurred in women who, on their own decision, 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, withheld 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 reproductive endocrinology and infertility specialist. The treatment is often continued until estrogen levels return to near-physiologic levels if no pregnancy occurs. Patients with OB APS 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 receiving regular anticoagulation therapy with vitamin K antagonists for thrombotic APS should transition to therapeutic-dose LMWH for ART (usually enoxaparin 1 mg/kg subcutaneously every 12 hours), with this treatment withheld for retrieval and resumed subsequently, to continue throughout pregnancy. Since ovarian stimulation protocols vary, discussion with the reproductive endocrinology and infertility specialist is appropriate. In addition to anticoagulation, patients at risk for thrombosis or ovarian hyperstimulation syndrome 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 whose condition is stable enough for them to undergo ovarian stimulation but who 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 biologic child and 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 CYC, which directly impacts maturing follicles) in treated patients whose condition is stable, when the purpose of ovarian stimulation is oocyte retrieval for oocyte or embryo cryopreservation.

This includes continuation of mycophenolate or methotrexate (MTX). There is an anticipated risk of uncontrolled disease from withdrawal of effective medication. However, there are no published data that directly address oocyte retrieval during treatment with most immunosuppressive or biologic therapies other than CYC.

Fertility preservation with cyclophosphamide

Supplementary Appendix 7, Table C (on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) presents the formal recommendations regarding fertility preservation with CYC treatment and strength of supporting evidence. Detailed justifications for strong and conditional recommendations are shown in Supplementary Appendix 9 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract).

Fertility preservation in women with RMD treated with CYC. Although CYC is used less frequently than in the past due to availability of alternative treatments, it remains a mainstay of therapy for severe or life-threatening RMD. Ovarian insufficiency is a potential long-term complication of monthly intravenous CYC therapy. Hormonal co-therapy during the course of CYC is suggested to reduce risk of ovarian insufficiency.

To prevent inducing primary ovarian insufficiency in premenopausal women with RMD receiving monthly intravenous CYC, we conditionally recommend monthly gonadotropin-releasing hormone agonist co-therapy.

Ovarian insufficiency risk with CYC treatment depends on patient age and cumulative monthly CYC dose (48); measures of ovarian function remained stable during treatment according to the Euro-Lupus protocol (49). The recommendation of gonadotropin-releasing hormone agonist therapy for ovarian protection during monthly CYC therapy is based on evidence supporting benefit in early breast cancer (50,51); evidence more specific to RMD patients is less robust but positive, with limited clinical trials of gonadotropin-releasing hormone agonist (usually leuprolide acetate) that included patients with SLE and other RMD populations and used a number of different outcome measures (52–56).

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

Fertility preservation in men with RMD treated with CYC. CYC may cause infertility and long-term gonadal damage in treated men. Options for fertility preservation should be presented to male patients in whom CYC therapy is required.

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 CYC-treated men 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 postmeiosis spermatids and sperm developing during therapy have the highest degree of genetic damage (58), sperm should be collected prior to CYC treatment. If sperm is collected after CYC treatment, urologists recommend waiting a minimum of 3 months after completion of therapy (59).

Menopause and hormone replacement therapy

Supplementary Appendix 7, Table D (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) presents formal recommendations regarding menopause and HRT with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are shown in Supplementary Appendix 9 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). Figure 3 details the HRT decision-making process. In this guideline, 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 minimum time necessary. Studies of long-term HRT show that risks, including stroke and breast cancer, outweigh benefits (63). Risks of HRT

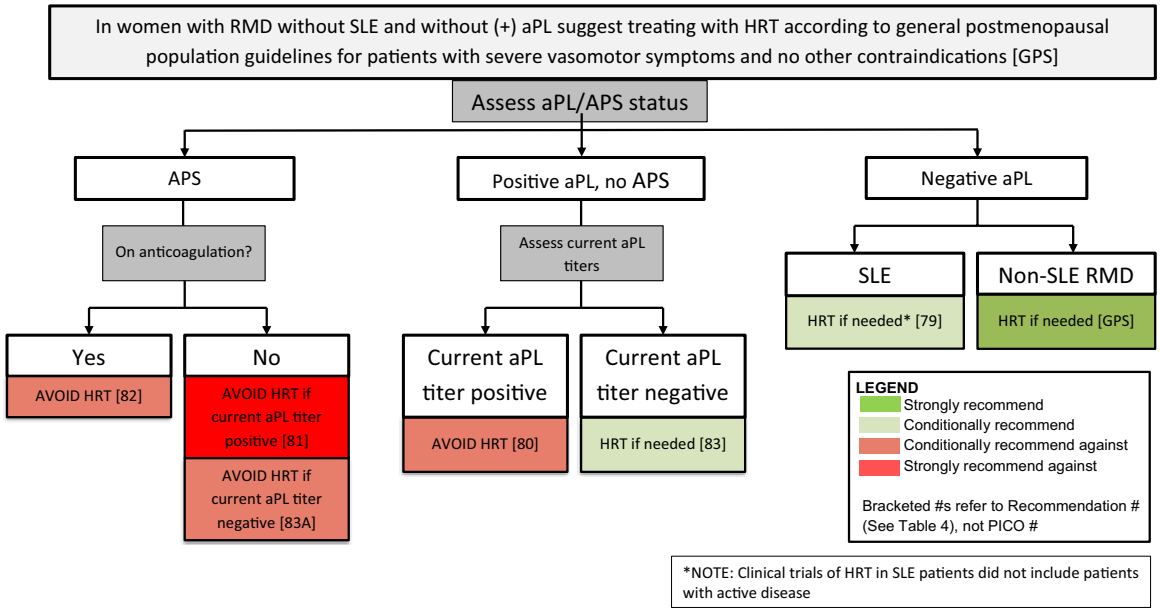

Figure 3. Recommendations and good practice statements (GPS) for hormone replacement therapy (HRT) use in postmenopausal women with rheumatic and musculoskeletal disease (RMD). SLE = systemic lupus erythematosus; aPL = antiphospholipid antibody (persistent moderate-to-high–titer anticardiolipin or anti–β_2-glycoprotein I antibody or persistent positive lupus anticoagulant); APS = antiphospholipid syndrome (obstetric and/or thrombotic); PICO = population, intervention, comparator, outcomes.

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, 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 desire treatment with HRT.

SLE patients. Use of HRT in symptomatic postmenopausal SLE patients may raise concerns regarding increased risk of flare and/or thrombosis; however, HRT use in aPL-negative women with quiescent SLE may be considered.

In SLE patients without positive aPL who desire HRT due to severe vasomotor symptoms and have no contraindications, we conditionally recommend HRT treatment.

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 have directly addressed use of HRT in patients with moderate-to-high disease activity. The recommendation is conditional because there was a small increase in risk of mild-to-moderate (but not severe) lupus flares with use of oral HRT in the Safety of Estrogens in Lupus Erythematosus National Assessment study (65), and because the studies did not include women with active disease.

aPL-positive patients. Estrogen use in aPL-positive patients should be avoided due to the potential increased risk of thrombosis. Data are limited, however, for many clinical situations, and specific recommendations vary in strength for this reason.

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 conditionally recommend *against* HRT use in patients with APS who are receiving anticoagulation treatment and in patients with APS who are currently negative for aPL.

We conditionally recommend consideration of HRT, if desired, in women who have a history of positive aPL but are currently testing negative for aPL and have 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 with oral estrogen-progestin increased 2-fold over placebo (70), and oral HRT in patients with factor V Leiden or prothrombin G20210A mutations increases VTE risk 25-fold compared to mutation-free women not receiving HRT (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, have specifically assessed thrombosis risk with 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 have addressed risk of flare in SLE but not thrombosis, and some studies excluded patients with prior thrombosis (65,67). In one study 106 SLE patients, regardless of aPL status but excluding those with recent thrombosis, were randomized to receive oral estrogen-progestin HRT or placebo. Approximately one-third of the patients in each group had some degree of positivity for aPL (level unreported) (78). During 24 months of follow-up 3 thrombotic events occurred in the HRT group and 1 in the placebo group, a nonsignificant 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 with 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 assessment, counseling, and management

Obstetrics-gynecology or maternal-fetal medicine specialists necessarily assume primary medical management of pregnancy in 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 obstetric 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 worsen 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 obstetrics-gynecology or maternal-fetal medicine physicians working together.

Most information regarding pregnancy management in RMD comes from observational studies, primarily in patients with SLE and APS. There have been very few controlled trials. 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. Supplementary Appendix 7, Table E (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) presents formal recommendations regarding pregnancy in patients with RMD with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are shown in Supplementary Appendix 11 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). Figure 4 details the pregnancy management process in patients with RMD. Supplementary Appendix 10 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) provides assessment and management suggestions for specific RMDs.

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 specialists in obstetrics-gynecology, maternal-fetal medicine, neonatology, 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 high risk of maternal morbidity and mortality.

In women with RMD planning pregnancy who are receiving medication that is 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 with pregnancy-compatible medications. Timing will vary depending on individual clinical factors; in clinical practice this is usually a minimum of several months.

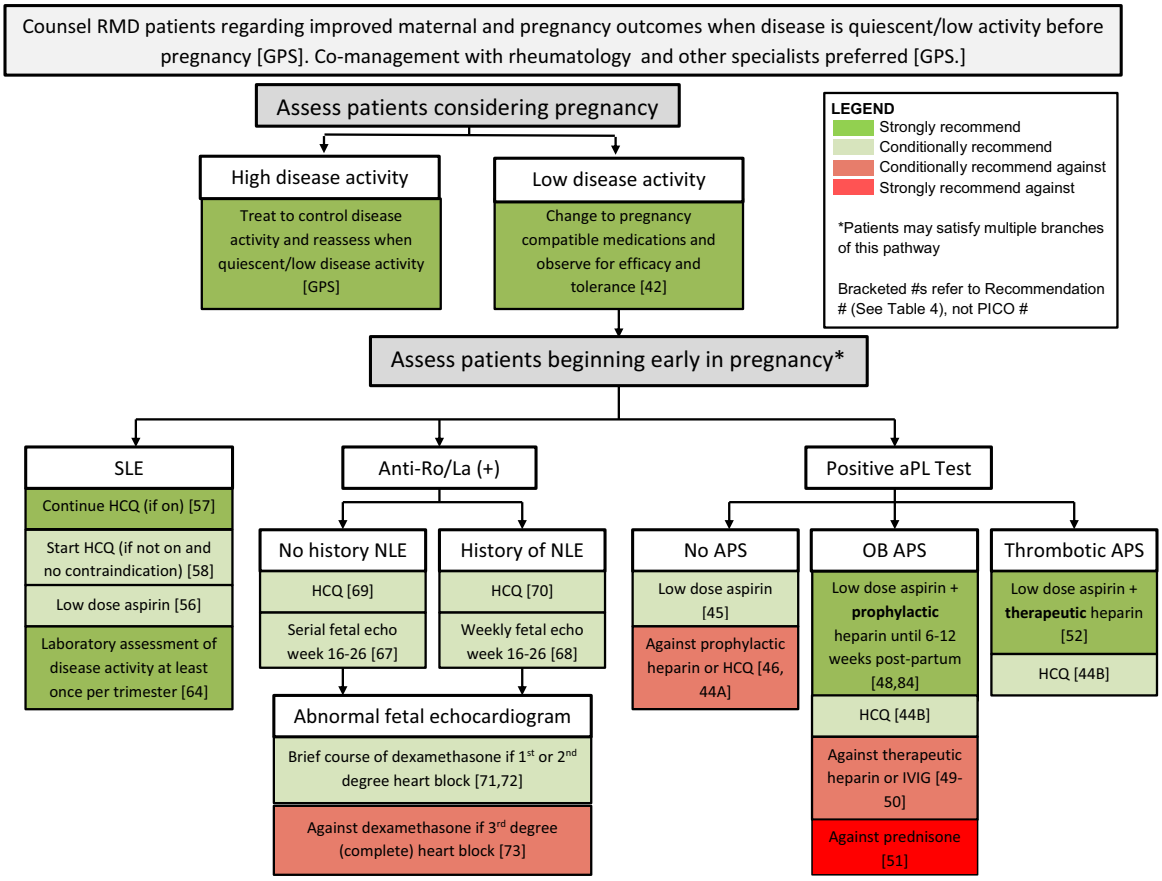

Figure 4. Recommendations and good practice statements (GPS) for pregnancy counseling, assessment, and management in women with rheumatic and musculoskeletal disease (RMD). SLE = systemic lupus erythematosus; HCQ = hydroxychloroquine; NLE = neonatal lupus erythematosus; aPL = antiphospholipid antibody (persistent moderate-to-high–titer anticardiolipin or anti–β_2-glycoprotein I antibody or persistent positive lupus anticoagulant); APS = antiphospholipid syndrome (obstetric and/or thrombotic); obstetric APS (OB APS) = patients meeting laboratory criteria for APS and having prior consistent pregnancy complications (≥3 consecutive losses prior to 10 weeks' gestation, fetal loss at or after 10 weeks' gestation, or delivery at <34 weeks due to preeclampsia, intrauterine growth restriction, or fetal distress) and with no history of thrombosis; thrombotic APS = patients meeting laboratory criteria for APS and having a prior thrombotic event (arterial or venous), regardless of whether they have had obstetric complications; IVIG = intravenous immunoglobulin; PICO = population, intervention, comparator, outcomes.

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 continuous high-dose glucocorticoid treatment 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 status improves counseling regarding pregnancy and fetal risk.

We strongly recommend testing for anti-Ro/SSA and anti-La/SSB once before or early in pregnancy in women with SLE or SLE-like disorders, Sjögren's syndrome, systemic sclerosis, and rheumatoid arthritis. Given the relative persistence and unchanged titers of these antibodies, we strongly recommend *against* repeating the test during pregnancy.

Patients with scleroderma renal crisis. Most disease-specific recommendations for RMD pregnancy management focus on presence of underlying SLE or positive aPL. One aspect of disease in systemic sclerosis, however, is of particular importance during pregnancy: the development of scleroderma renal crisis. While effective medications are usually contraindicated during pregnancy due to risk of adverse fetal effects, they should be considered in this unusual and life-threatening circumstance.

We strongly recommend use of angiotensin-converting enzyme 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. Angiotensin-converting enzyme inhibitors can be renal-protective and life saving (100); however, they are contraindicated in the second and third trimesters of pregnancy because of potential oligohydramnios or permanent fetal renal damage (101), and should be considered only for active scleroderma renal crisis.

SLE patients. Supplementary Appendix 7, Table E (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) presents formal recommendations for SLE pregnancy management, with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are shown in Supplementary Appendix 11 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract).

In women with SLE who are considering pregnancy or are pregnant, we strongly recommend testing for LAC, aCL, and anti-β_2GPI antibodies once before or early in pregnancy, and *against* repeating these tests during pregnancy.

We recommend that all women with SLE take hydroxychloroquine (HCQ) during pregnancy if possible. 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.

Many studies support maternal and pregnancy benefit of HCQ and low risk for mother and fetus (84,102–111). 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 and US Protective Health Task Force recommend aspirin 81 mg daily as prophylaxis in all patients at high risk for preeclampsia (97,112–117). 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 the American College of Obstetricians and Gynecologists and the U.S. Preventive Services Task Force note that there is a lack of appropriate comparative studies to show the superiority of doses >100 mg per day. 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 obstetrician-gynecologist 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, examination, and laboratory tests at least once per trimester.

Abnormalities in the complete blood cell count, differential cell count, urinalysis results and urinary protein:creatinine ratio, or anti-DNA, C3, or C4 levels 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.

Antiphospholipid antibody–positive patients. Pregnancies in patients with positive aPL or APS present specific challenges and may require additional monitoring and therapy. Supplementary Appendix 7, Table F (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) presents formal recommendations, with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are shown in Supplementary Appendix 11 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract).

Antiphospholipid antibody is a major risk factor for pregnancy loss and other adverse pregnancy outcomes, especially in SLE patients (118). Anti-β_2GPI, aCL, and LAC should all be tested. Among aPLs, LAC conveys the greatest risk for adverse pregnancy outcome in women with or without SLE: the RR for adverse pregnancy outcome with LAC was 12.15 (95% CI 2.92–50.54, $P = 0.0006$) in the PROMISSE (Predictors of Pregnancy Outcome: Biomarkers in APL syndrome and SLE) study (118). Other independent risk factors in aPL-positive women were younger age, history of thrombosis, and SLE.

Antiphospholipid antibody–positive patients without thrombosis or obstetric complications. Asymptomatic aPL-positive patients (those without pregnancy complications or history of thrombosis) are not generally treated with prophylactic therapy to prevent pregnancy loss. However, presence of aPL regardless of clinical history is considered a risk factor for development of preeclampsia.

In pregnant women with positive aPL who do not meet criteria for obstetric or thrombotic APS, 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.

Patients with obstetric and thrombotic APS. Pregnancy increases the risk of thrombosis due to both hemostatic and anatomic factors. Patients who meet criteria for APS—whether obstetric or thrombotic—should receive therapy with heparin (usually LMWH) to improve pregnancy outcome and/or reduce risk of thrombosis.

We strongly recommend combined low-dose aspirin and prophylactic-dose heparin (usually LMWH) for patients meeting criteria for OB APS (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 and low-dose aspirin therapy for patients with positive aPL who do not meet criteria for OB APS.

We appreciate and stress, however, that benefit in 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. Despite improved outcomes with standard therapy with low-dose aspirin and prophylactic heparin/LMWH, additional treatments are needed for patients who do not respond to standard therapy. Intravenous immunoglobuin, low-dose prednisone, increased dose of heparin/LMWH, and HCQ have all been suggested as additional or alternative treatments.

We conditionally recommend *against* treatment with intravenous immunoglobulin 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 birth, but not necessarily full-term birth. Pregnancy loss occurs, despite treatment, in 25% of OB APS pregnancies. There are no data demonstrating improved outcomes with a higher dose of heparin, and only anecdotal data support the use of intravenous immunoglobulin.

We strongly recommend *against* adding prednisone to prophylactic-dose heparin or LMWH and low-dose aspirin in patients in whom standard therapy has been unsuccessful, since there are no controlled studies demonstrating a benefit.

We acknowledge, however, that this recommendation is based on a lack of compelling data rather than data showing no clear benefit, and also that potential risk with this therapy is likely to be strongly affected by daily dosage, 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 criteria for APS and do not have another indication for the drug (such as SLE), we conditionally recommend *against* treating with prophylactic HCQ.

As with any unproven treatment, this therapy 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 erythematosus (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 ~10% develop an NLE rash, 20% transient cytopenias, and 30% mild transient transaminitis (estimates vary widely between 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 ~2% of pregnancies of women with anti-Ro/SSA and/or anti-La/SSB antibodies who have not had a prior infant with NLE, 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. Approximately 20% of children with CHB die in utero or in the first year of life; more than half will need a pacemaker (128).

Supplementary Appendix 7, Table G (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) presents formal recommendations regarding pregnancy in women with anti-Ro/SSA and/or anti-La/SSB antibodies, with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are shown in Supplementary Appendix 11 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract).

In pregnant women with anti-Ro/SSA and/or anti-La/SSB antibodies but no history of an infant with CHB or NLE, we conditionally recommend serial fetal echocardiography (less frequent than weekly; interval not determined) starting between 16 and 18 weeks and continuing

through week 26. For women with a prior infant with CHB or other NLE we conditionally recommend fetal echocardiography weekly, starting at week 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 are positive for 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 in pregnant women with a prior child with cardiac NLE who take HCQ, there is 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 first- or second-degree heart block shown on echocardiography, we conditionally recommend treatment with oral dexamethasone 4 mg daily. If CHB (without other cardiac inflammation) is present, we conditionally recommend *against* treating with dexamethasone.

Fluorinated glucocorticoids, such as dexamethasone and betamethasone, cross the placenta; low-to-moderate–dose nonfluorinated glucocorticoids, 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 a matter of controversy. 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).

Medication use

Paternal medication use. Supplementary Appendix 7, Table H (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) presents best practice statements and recommendations regarding paternal medication use in men with RMD, with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are shown in Supplementary Appendix 12 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). Table 2 summarizes recommendations for paternal medication use.

Medication issues differ between men with RMD who are planning to father a pregnancy and those whose sexual partner is pregnant. Pre-conception, the concerns are potential effects on male fertility and medication-associated teratogenicity. There are few published data addressing these potential effects of medications for RMD. 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,

Table 2. Recommendations regarding medication use for men with rheumatic and musculoskeletal disease 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-mercaptopurine Colchicine Hydroxychloroquine Tumor necrosis factor inhibitors (all)	Anakinra Cyclooxygenase 2 inhibitors Cyclosporine Leflunomide Methotrexate Mycophenolate mofetil Mycophenolic acid Nonsteroidal anti-inflammatory drugs 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 Baricitinib Belimumab Secukinumab Tocilizumab Tofacitinib Ustekinumab

Table 3. Maternal medication use: overview of medication use before and during pregnancy, and during breastfeeding

Medication	Pre-conception	During pregnancy	Breastfeeding
Conventional medications			
Hydroxychloroquine	++	++	++
Sulfasalazine	++	++	++
Colchicine	++	++	++
Azathioprine, 6-mercaptopurine	++	++	+ Low transfer
Prednisone	+ Taper to <20 mg/day by adding pregnancy-compatible immunosuppressants	+ Taper to <20 mg/day by adding pregnancy-compatible immunosuppressants	+ After a dose of >20 mg, delay breastfeeding for 4 hours
Cyclosporine, tacrolimus	+ Monitor blood pressure	+ Monitor blood pressure	+ Low transfer
Nonsteroidal antiinflammatory drugs (cyclooxygenase 2 inhibitors not preferred)	+ Discontinue if the woman is having difficulty conceiving	+ Continue in first and second trimesters; discontinue in third trimester	+ Ibuprofen preferred
Tumor necrosis factor inhibitors (tumor necrosis factor inhibitors are considered compatible with pregnancy)			
Certolizumab	++	++	++
Infliximab, etanercept, adalimumab, golimumab	+ Continue through conception	+ Continue in first and second trimesters; discontinue in third trimester several half-lives prior to delivery	++
Rituximab	+ Discontinue at conception	+ Life-/organ-threatening disease	++
Other biologics (limited safety data; limited transfer in early pregnancy but high transfer in second 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 5 mg/day	× Limited data suggest low transfer
Leflunomide	×× Cholestyramine washout if detectable levels	×× Stop and give cholestyramine washout	××
Mycophenolate mofetil and mycophenolic acid	×× Stop >6 weeks prior to conception to assess disease stability	××	××
Cyclophosphamide	×× Stop 3 months prior to conception	+ Life-/organ-threatening disease in second and third trimesters	××
Thalidomide	×× Stop 1–3 months prior to conception	××	××
Tofacitinib, apremilast, baricitinib	Unable to determine due to lack of data; small molecular size suggests transfer across the placenta and into breast milk		

++ Strongly recommend

\+ Conditionally recommend

× Conditionally recommend against

×× Strongly recommend against

as seminal concentrations of medications and volumes transferred are small (136). There are no reports of post-conception teratogenesis attributable to medications taken by a man with RMD. When a man's sexual partner is pregnant, reassurance regarding low risk associated with his RMD treatment is generally warranted.

In the absence of adequate data regarding paternal exposure for most medications used for RMD, we developed recommendation statements when 1) at least some data on paternal exposure were available, 2) accumulated clinical experience of paternal exposure could guide the recommendation, or 3) there were no data on paternal exposure, but maternal exposure demonstrates teratogenicity. We do 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.

In men with RMD who are planning to father a pregnancy, we strongly recommend continuation of HCQ, azathioprine, 6-mercaptopurine, colchicine, and tumor necrosis factor inhibitors (140–142).

In men with RMD who are planning to father a pregnancy, we conditionally recommend, based on a smaller body of evidence, continuing treatment with MTX, MMF, leflunomide, sulfasalazine, calcineurin inhibitors, and nonsteroidal antiinflammatory drugs (NSAIDs) (142–149).

Although the drug label suggests discontinuation of MTX before attempting pregnancy, data show no evidence for mutagenesis or teratogenicity (143–145).

Although sulfasalazine may affect sperm count and quality, there are no data suggesting teratogenicity (146,150), and we conditionally recommend its continuation. If conception does not occur, semen analysis should be considered.

We conditionally recommend continuation of anakinra and rituximab based on limited data (151,152).

Maternal medication use. Supplementary Appendix 7, Tables I (conventional rheumatology medications), J (biologic rheumatology medications), and K (glucocorticoids) (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) present formal best practice statements and recommendations regarding maternal medication use in patients with RMD, with strength of supporting evidence. Detailed justifications for strong and conditional recommendations are shown in Supplementary Appendix 12 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). 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 published 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 1 menstrual cycle would represent the minimum, and 3 months the most common, period for discontinuation. In addition to concerns about teratogenicity, it is optimal to allow adequate time for observation of disease stability without medication.

For women treated with 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 is not detectable in the serum, the risks of pregnancy loss and birth defects are not elevated (157,158).

We conditionally recommend treatment with CYC for life-threatening conditions in the second or third trimester (86).

When potentially teratogenic medications are discontinued prior to pregnancy, we strongly recommend a period of observation without 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 maternal-fetal medicine specialist, pregnancy medication specialist, or genetics counselor as standard good practice.

We strongly recommend HCQ, azathioprine/6-mercaptopurine, colchicine, and sulfasalazine, medications commonly used for RMD, as compatible for use throughout pregnancy (104,106,159–161).

We conditionally recommend calcineurin inhibitors (tacrolimus and cyclosporine) and NSAIDs 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 subfertility (162).

We strongly recommend *against* use of NSAIDs in the third trimester because of the risk of premature closure of the ductus arteriosus (163).

We conditionally recommend nonselective NSAIDs over cyclooxygenase 2–specific inhibitors in the first 2 trimesters, due to lack of data on cyclooxygenase 2–specific inhibitors.

Nonfluorinated 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 treatment (≤10 mg daily of prednisone or nonfluorinated equivalent) during pregnancy if clinically indicated. We strongly recommend tapering higher doses of nonfluorinated glucocorticoids to <20 mg daily of prednisone, adding a pregnancy-compatible glucocorticoid-sparing agent if necessary. Although there are only minimal data regarding prolonged treatment with low-dose glucocorticoids 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 tumor necrosis factor inhibitor therapy with infliximab, etanercept, adalimumab, or golimumab prior to and during pregnancy (164,165). The tumor necrosis factor 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 tumor necrosis factor (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 Voting Panel discussion regarding if, and when, these medications should be discontinued prior to delivery. The Voting Panel agreed that if the patient's disease is under good control, these medications may be discontinued in the third trimester. While there is a paucity of safety data, continuing TNF inhibitors through delivery if the patient's disease is active can be considered, with the 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 periconception period but should be discontinued during pregnancy (i.e. at the time of the first positive pregnancy test result).

We conditionally recommend continuing treatment with anakinra, belimumab, abatacept, tocilizumab, secukinumab, and ustekinumab 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 versus the risks of uncontrolled disease during pregnancy.

We conditionally recommend continuing treatment with rituximab while a woman is trying to conceive, and we conditionally recommend continuing rituximab during pregnancy if severe life- or organ-threatening maternal disease so warrants.

Dosing in the second half of pregnancy puts the fetus at high risk of having minimal B cells at delivery (168).

There is no available evidence regarding use or safety of the new small-molecule agents, tofacitinib, baricitinib, and apremilast, during pregnancy. The Voting Panel elected not to offer recommendations regarding 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); the American Academy of Pediatrics recommends exclusive breastfeeding for the first 6 months and continued breastfeeding until 1 year (9). Because women with RMD may experience disease flare post partum and require treatment, it is important to balance benefits of disease control with risk of infant exposure through breast milk.

Infant serum levels of drugs ingested by the mother 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

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 receiving immunosuppressive medications: Use IUD if desired [7]	Strong
	Women at risk for osteoporosis: *Avoid* DMPA [10]	Conditional
	Women receiving MMF: Use IUD or 2 other methods together [11]	Conditional
	RMD without SLE or aPL: Use highly effective or effective methods† [1]	Strong
	Highly effective methods 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 methods preferred to effective methods [2A]	Conditional
	Avoid transdermal estrogen-progestin patch [2B]	Conditional
	SLE with negative aPL and moderate-to-high disease activity: Use progestin-only contraceptives or IUD [2C]	Strong
Positive aPL	Do *not* use combined estrogen-progestin contraceptives [3]; use IUD or progestin-only pill [4]	Strong
Assisted reproductive technology		
All RMD	Stable disease and negative aPL: Proceed with assisted reproductive technology:	
	IVF if pregnancy-compatible medications [24]	Strong
	Oocyte cryopreservation: Continue medications except CYC [28]	Strong
	Active disease: Defer assisted reproductive technology until disease is stable/quiescent [27]	Strong
SLE	Active SLE: Defer assisted reproductive technology until disease is stable/quiescent [27]	Strong
	Do *not* treat with prophylactic prednisone [29]	Conditional
Positive aPL	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]	Strong
	Prior thromboses: Therapeutic heparin or LMWH [26A]	Strong
Fertility preservation	Women: Use gonadotropin-releasing hormone agonist therapy during IV CYC treatment [31]	Conditional
	Men: Sperm cryopreservation pre–CYC treatment	GPS
	Do *not* use gonadotropin-releasing hormone agonist therapy [35]	Conditional
Menopause/hormone replacement therapy		
All RMD	RMD without SLE or aPL: Treat with hormone replacement therapy if indicated‡	GPS
SLE	SLE and negative aPL: Treat with hormone replacement therapy if indicated‡ [79]	Conditional
Positive aPL	If no prior thrombosis or OB APS: Do *not* treat with hormone replacement therapy [80]	Conditional
	If current titers negative, treat with hormone replacement therapy if indicated‡ [83]	Conditional
	If prior thrombosis or OB APS and not receiving anticoagulation treatment: Do *not* treat with hormone replacement therapy [81]	Strong
	If current titers negative, do *not* treat with hormone replacement therapy [83A]	Conditional
	If prior thrombosis or OB APS and receiving anticoagulation treatment: Do *not* treat with hormone replacement therapy [82]	Conditional
Pregnancy		
All RMD	Counseling: Outcomes improved with pregnancy planning, stable disease, compatible medications, and co-management by rheumatology and obstetrics-gynecology/maternal-fetal medicine	GPS
	Pre-pregnancy: Change to pregnancy-compatible medication and observe for stability [42]	Strong
	If active disease during pregnancy: Initiate pregnancy-compatible medication [54]	Strong
	If SLE or SLE-like disease, SS, SSc, or RA: Test once (early) for anti-Ro/SSA and anti-La/SSB [60, 62]	Strong
	If SSc and renal crisis during pregnancy: Treat with ACE inhibitor or ARB for life-threatening disease [55]	Strong

(Continued)

Table 4. (*Cont'd*)

Topic	Recommendation	Strength
SLE	SLE or SLE-like disease: Test once (early) for aPL (aCL, anti-β_2GPI, 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 values 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 [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 [48]	Strong
	Do *not* treat with combination therapeutic heparin or LMWH/low-dose aspirin [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 failure [44B]	Conditional
	Treat with prophylactic anticoagulation during post partum period [84]	Strong
	Thrombotic APS: If prior thrombosis (meeting or not meeting OB APS criteria), treat with therapeutic heparin or LMWH/low-dose aspirin [52]	Strong
	Treat with addition of HCQ for therapeutic heparin or LMWH/low-dose aspirin therapy failure [44B]	Conditional
Positive anti-Ro/SSA with or without anti-La/SSB	Treat with HCQ during pregnancy [69, 70]	Conditional
	If no prior history of neonatal lupus: Serial (interval uncertain) fetal echocardiography in weeks 16–26 [67]	Conditional
	If prior history of neonatal lupus: Weekly fetal echocardiography in weeks 16–26 [68]	Conditional
	Abnormal fetal echocardiography: If first- or second-degree heart block, treat with dexamethasone 4 mg daily [71, 72]	Conditional
	If isolated third-degree heart block (and no other cardiac inflammation), do *not* treat with dexamethasone [73]	Conditional
Medication		
Paternal medication	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, 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 medication	If planning pregnancy: Discuss medication use including CYC	GPS
	If pregnant and exposed to teratogenic medications: Discontinue immediately, pursue counseling	GPS
	Discontinue NSAIDs if difficulty conceiving [86]	Conditional
	Avoid NSAIDs in third trimester [87]	Strong
	Use nonselective rather than COX-2–specific NSAIDs [88]	Conditional
	Discontinue MTX, MMF, thalidomide, CYC prior to conception [102, 120, 140, 134]	Strong
	Use CYC for life-threatening disease only in second and third trimester [136]	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]	Strong
	Continue cyclosporine and tacrolimus [127, 131]	Conditional
	Continue certolizumab [156]	Strong
	Continue infliximab, etanercept, adalimumab, golimumab [144, 147, 150, 153]	Conditional
	Stop when pregnancy confirmed: rituximab, belimumab, anakinra, abatacept, tocilizumab, secukinumab, ustekinumab [164, 169, 160, 173, 177, 181, 185]	Conditional
	Use rituximab for organ- or life-threatening disease during pregnancy [165]	Conditional
	No recommendations for tofacitinib, baricitinib, apremilast due to lack of data [189, 193, 197]	
	Continue regular low-dose prednisone [201]	Conditional

(Continued)

Table 4. (*Cont'd*)

Topic	Recommendation	Strength
	Taper high-dose prednisone with addition of pregnancy-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
Breastfeeding	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]	Strong
	NSAIDs, sulfasalazine, colchicine, AZA, cyclosporine, tacrolimus, anakinra, belimumab, abatacept, tocilizumab, secukinumab, ustekinumab [89, 96, 99, 117, 128, 132, 161, 170, 174, 178, 182, 186]	Conditional
	Prednisone or nonfluorinated steroid equivalent <20 mg daily [204]	Strong
	For prednisone ≥20 mg daily, discard breast milk obtained within 4 hours following medication [205]	Strong
	Do *not* treat with leflunomide, MMF, CYC, thalidomide [113, 124, 137, 142]	Strong
	Do *not* treat with MTX [106]	Conditional

* Recommendation numbers, shown in brackets, allow for cross-referencing with supplementary appendices. For more detailed/complete recommendations, see text or Supplementary Appendix 7 (on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract). RMD = rheumatic and musculoskeletal disease; GPS = good practice statement; MMF = mycophenolate mofetil (and mycophenolic acid); SLE = systemic lupus erythematosus; aPL = antiphospholipid antibody, meeting laboratory criteria for antiphospholipid syndrome (APS) (Supplementary Appendix 8, http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract); IVF = in vitro fertilization; CYC = cyclophosphamide; OB APS = APS meeting laboratory criteria and clinical obstetric criteria (Supplementary Appendix 8); LMWH = low molecular weight heparin; IV = intravenous; SS = Sjögren's syndrome; SSc = systemic sclerosis; RA = rheumatoid arthritis; ACE inhibitor = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; aCL = anticardiolipin antibody; anti-β_2GPI = anti–β_2-glycoprotein I; LAC = lupus anticoagulant; HCQ = hydroxychloroquine; IVIG = IV immunoglobulin; AZA = azathioprine (and 5-fluorouracil); NSAIDs = nonsteroidal antiinflammatory drugs; COX-2 = cyclooxygenase 2; MTX = methotrexate.
† Highly effective contraceptives are long-acting reversible contraceptives including progestin or copper intrauterine device (IUD) and progestin implant. Effective contraceptives are estrogen-progestin contraceptives (oral, patch, or vaginal ring) and progestin-only (oral, depot medroxyprogesterone acetate [DMPA]).
‡ General indication for hormone replacement therapy: Current recommendations suggest limiting hormone replacement therapy use in healthy postmenopausal women and using the lowest dose that alleviates symptoms for the minimum time necessary. Benefit-risk balance is most favorable for severe vasomotor symptoms in women ≤60 years old or within 10 years of menopause onset (ref. 61).

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 (infant dose mg/kg/day divided by maternal dose mg/kg/day) and are available in reference publications; a value of <10% is considered safe.

Supplementary Appendix 7, Table L (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract) presents 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 shown in Supplementary Appendix 12 (http://onlinelibrary.wiley.com/doi/10.1002/art.41191/abstract).

We suggest as standard good practice that women with RMD 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 treatment with HCQ, colchicine, sulfasalazine, rituximab, and all TNF inhibitors as compatible with breastfeeding (177–181).

We also recommend prednisone <20 mg daily (or equivalent nonfluorinated glucocorticoid) as compatible with breastfeeding, but strongly recommend that with doses of prednisone ≥20 mg a day (or equivalent), women delay breastfeeding or discard breast milk accumulated in the 4 hours following glucocorticoid administration.

We conditionally recommend treatment with azathioprine/6-mercaptopurine, calcineurin inhibitors, NSAIDs and the non–TNF inhibitor biologic agents (anakinra, rituximab, belimumab, abatacept, tocilizumab, secukinumab, and ustekinumab) as compatible with breastfeeding (182–184).

We strongly recommend *against* use of CYC, leflunomide, MMF, and thalidomide while breastfeeding. We conditionally recommend *against* use of 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 for 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 regarding women's health issues in patients with SLE and APS (187), and both EULAR (with points to consider) and the British Society for Rheumatology/British Health Professionals in Rheumatology (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 preexisting severe organ damage carries profound maternal risk. Pulmonary arterial hypertension 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 (55,192–194). In these and other high-risk situations, the option of therapeutic termination of pregnancy may be lifesaving and should be discussed with the patient (195). 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 maternal-fetal medicine 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 involving patients with RMD, for instance, the importance of effective contraception. Almost half of pregnancies in the US are unplanned (196). In RMD patients unplanned pregnancies carry greater risk than do planned pregnancies in periods of low disease activity treated with compatible medications. Whether 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 dialog. New information supports a shift from the paradigm of discontinuing all RMD medications except prednisone, since pregnancy-compatible steroid-sparing disease-modifying antirheumatic drugs and biologic agents 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. Recent data indicate compatibility of many rheumatology medications both with 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 postmenopausal 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 (197). Attention to disease activity and aPL status and discussion with reproductive endocrinology and infertility specialists 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, its 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 prevention, screening, and management of NLE requires further study. There are very limited data on RMD medication effects on fertility and teratogenicity in men with RMD. Because women with RMD who plan to conceive, are pregnant, or are lactating are usually excluded from clinical trials, large-scale data about medication 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 the patient population. 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 help inform decision-making.

With the development of this guideline, the ACR recognizes the key role of clinical rheumatologists not only in managing disease activity but also in understanding the interactions of RMDs and their therapies in the context of reproductive health. The most important goal of this guideline 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, specialists in obstetrics-gynecology, maternal-fetal medicine, and reproductive endocrinology and infertility, 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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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Sammaritano had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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