SUPPLEMENTARY APPENDIX 9: Detailed background and justification for good practice statements and recommendations for contraception, fertility issues and menopause.

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

Contraception:

Contraception is an important aspect of care for reproductive-aged patients with rheumatic and musculoskeletal disease (RMD), especially those with uncontrolled active disease, on teratogenic medications, or with severe disease-related damage. Risks of unplanned pregnancy vary with the individual patient, but may include worsening of disease activity, including organ- or life-threatening maternal outcomes; adverse pregnancy outcomes such as pregnancy loss, severe prematurity, or growth restriction; and major birth defects in offspring. The issue of contraception in RMD patients is especially important because these patients may not consistently use contraception, and when they do, they underuse effective contraception and/or use a less effective method (usually condoms) (1–3).

Reversible contraception includes barrier methods, intrauterine devices (IUDs), and various forms of hormonal contraceptives (including combined estrogen-progestin and progestin-only). "Natural" or fertility awareness methods (that track the menstrual cycle to avoid intercourse at the time of ovulation) are least effective. Permanent contraceptive methods (i.e. bilateral tubal ligation or vasectomy) are not addressed in this guideline but represent very effective options for patients who have completed childbearing. While we do not address elective termination of pregnancy in this

guideline, in serious or life-threatening situations it is be an important option worthy of discussion with the patient and her partner.

Effectiveness of reversible contraceptive methods varies. Counseling should address not only the importance of contraceptive use but should also provide guidance on the safest and most effective methods for each particular patient. Perfect use and typical (or "real world") use effectiveness are closest for methods not directly related to the act of intercourse and are nearly identical for long-acting reversible contraceptives (LARC) such as copper or progestin IUDs and the subdermal progestin implant (4). Recent prospective data from a United States general population cohort study found a contraceptive failure rate of 4.55 pregnancies per 100 participant-years for oral, patch and vaginal ring contraceptives versus 0.27 pregnancies per 100 participant-years for LARC methods (5). Efforts should be made to encourage use of highly effective contraceptive methods (LARC) where appropriate. However, if highly effective and effective (estrogen-progestin or progestin-only) contraceptive methods are contraindicated for medical or personal reasons, barrier contraception (male condom, female condom, diaphragm) is clearly preferable to no contraception. Additionally, barrier methods, unlike LARC, do confer some protection against sexually transmitted diseases.

Uncomplicated RMD:	
In patients with RMD without SLE and without positive aPL:	
• We strongly recommend using hormonal contraceptives or IUDs over other less effective	Not graded*

contraceptive options or no contraceptive method (GS1).	
• We conditionally recommend using IUDs or progestin subdermal implants over other hormonal contraceptive options (GS1A).	Not graded*

GS1. Justification for strong recommendation:

We recommend using effective reversible contraception including estrogen-progestin, progestin only, or an IUD in RMD patients without SLE and without positive aPL. Briefly, positive aPL as defined for guideline recommendations means meeting laboratory criteria for APS, with or without the presence of clinical APS complications (see Appendix 5). The recommendation is strong because these methods are more effective options than are barrier methods, fertility awareness and withdrawal in preventing unplanned pregnancy. Risks of unplanned pregnancy vary with the individual patient but may include worsening of disease activity (including organ- or life-threatening maternal outcomes), adverse pregnancy outcomes (pregnancy loss, severe prematurity or growth restriction), and major birth defects. RMD patients require contraception that is effective, low risk, and associated with a high likelihood of adherence. Hormonal contraceptives fail 9% of the time, IUDs and progestin implants $\leq$1% of the time, and condoms, fertility based methods, and spermicide 18-28% of the time (6).

GS1A. Justification for conditional recommendation:

We recommend using IUDs and the progestin implant in RMD patients without SLE and without positive aPL because these methods are considered first line contraceptives for all appropriate candidates by the American College of Obstetrics and Gynecology

(ACOG), including nulliparous women and adolescents (6). Variability in patients' values and preferences may affect the decision to use IUDs or the progestin implant.

The progestin implant has fewer available data regarding side effects. The implant includes a third generation progestin that has a slightly different side effect profile than do second generation progestins; while no studies suggest an adverse side effect profile with regard to bone loss, thrombosis or lipids, progestin implants are less well studied than are other forms of contraception. No increases in thrombotic risk or bone loss with the progestin (levonorgestrel) IUD have been noted in non-rheumatologic disease populations, including in patients at increased risk for thrombosis (7–9). The recommendation is conditional due to the absence of studies specifically in women with RMD using these methods of contraception. All data are therefore indirect, based on studies of non-RMD women, though they do include women at increased thrombotic risk for other reasons.

SLE: In patients with stable (low disease activity) SLE <u>without</u> positive aPL/APS:	
• We strongly recommend using estrogen-progestin pill or vaginal ring, progestin-only contraceptives, or IUDs over other less effective contraceptive options or no contraceptive method (GS2).	Low - moderate
• We conditionally recommend using IUDs and progestin implant over other hormonal contraceptive options (GS2A).	Not graded*
• We conditionally recommend <u>against</u> using the transdermal estrogen-progestin patch over other hormonal contraceptive options (GS2B).	Not graded*

	Not graded*
In patients with SLE where level of disease activity is moderate or severe (including active nephritis), we strongly recommend using progestin-only (progesterone pill, progestin implant, or DMPA) or IUD contraceptives and avoiding use of combined estrogen-progestin contraception (GS2C).	

GS2. Justification for strong recommendation:

We recommend using estrogen-progestin pill or vaginal ring, progestin-only, contraceptives or IUDs over less effective options or no contraceptive method for patients with SLE and without positive aPL because hormonal contraceptives, including combined estrogen-progestin contraceptives and the IUD, represent effective methods of contraception for most patients with SLE. The strong recommendation for highly effective or effective contraception is due to the high potential risk of unplanned pregnancy in women with SLE, including worsening of disease activity (with organ- or life-threatening maternal consequences), adverse pregnancy outcomes (pregnancy loss, severe prematurity or growth restriction), and major birth defects. SLE patients require contraception that is effective, low risk and associated with a high likelihood of adherence. Hormonal contraceptives fail 9% of the time and IUDs and progestin implants fail <1% of the time as compared to 18-28% for condoms, fertility based methods, and spermicide (6).

Estrogen-progestin contraceptives may be used in patients with SLE with stable, low disease activity and negative aPL antibodies (10,11). Two studies prospectively evaluated the safety of combined estrogen-progestin pills in patients with stable SLE

(one of them a randomized placebo-controlled study) and found no increased risk of flare. Risk of thrombosis was difficult to ascertain since enrollment criteria – specifically aPL status – were different between the two studies and blood clots occurred in both treatment and control arms (10,11). Additionally, no data suggest an increased risk of flare in SLE patients taking progestin-only oral contraceptives, although rates of discontinuation due to gynecologic side effects are high (11,12). In one prospective study of the copper IUD in SLE patients flare rates did not differ from those in patients taking progestin-only or combined estrogen-progestin oral contraceptives (11). Effects of the progestin IUD, progestin implant or depot medroxyprogesterone acetate (DMPA) injections on disease activity in SLE have not been specifically studied; however, progestins in general are not felt to increase disease activity (11–14).

GS2A. Justification for conditional recommendation:
We recommend using IUDs and the progestin implant over other contraception methods in SLE patients without positive aPL because these methods are the most effective forms of contraception and are encouraged as first line contraceptives for all appropriate candidates by the ACOG, including nulliparous women and adolescents (6). Pregnancy rates for these methods are <1%. However, variability in patient's values and preferences may affect their decisions regarding use of IUDs or the progestin implant, and these methods have not been well studied in patients with SLE. The relatively new progestin implant includes a third generation progestin, but no studies suggest an adverse side effect profile with regard to bone loss or risk of thrombosis in the general population. No increases in thrombotic risk or bone loss with the progestin

(levonorgestrel) IUD have been noted in non-rheumatologic disease populations, including patients at increased risk for thrombosis (7–9). The recommendation is conditional due to the very limited direct data in this population. There has only been one prospective study of the copper IUD and none with progestin IUDs or implants in SLE patients (11). Given the lack of direct evidence on the use and safety of the progestin IUD and progestin implant in RMD patients, including SLE patients, and the high effectiveness and convenience of these contraceptives, this is an important area for research.

GS2B. Justification for conditional recommendation:

We recommend avoiding the estrogen-progestin transdermal patch in patients with SLE and without positive aPL due to concerns about potential SLE flare or thrombosis because the patch delivers higher levels of exogenous estrogen compared to methods using oral or transvaginal delivery (15,16). The studies of estrogen-progestin contraception that found no increased risk of lupus flare used 2nd generation oral contraceptives (10,11) and were performed because of longstanding concerns about safety of exogenous estrogen in women with SLE. Since the contraceptives in these studies contained a specific amount and type of estrogen and progestin, the low risk of flare (or thrombosis) seen cannot be generalized to other combined estrogen-progestin contraceptives with a higher estrogen content, different progestin, or different administration method. SLE patients have an increased thrombosis risk compared to the general population even if aPL negative (17). The recommendation is conditional because there are no data on use of the transdermal patch in SLE patients. Potential

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use of alternative forms of estrogen-progestin contraception should be discussed with the patient. Compared to third-generation oral contraceptives, no increase in rate of venous thromboembolism in the general population with use of a transdermal patch has been seen (18).

GS2C. Justification for strong recommendation:

We recommend avoiding use of combined estrogen-progestin contraceptives (oral, or tranvaginal) in women with active SLE and negative aPL. The recommendation is strong because of the clinical concern that administering exogenous estrogen to a patient with active lupus creates an unacceptably high risk of worsening disease. The available controlled studies in lupus are non-informative regarding active SLE because they enrolled women with stable SLE and low disease activity (10,11). Discussion regarding the unknown risks in this situation should precede any initiation of estrogen-containing contraceptives in women with significant SLE disease activity, as the potential risk for organ- or life-threatening outcomes is unknown and other, more effective, contraceptives are available.

Positive aPL: In women with RMD <u>with</u> positive aPL:	
• We strongly recommend <u>against</u> using combined estrogen-progestin contraceptives (GS3).	Very low
• We strongly recommend using IUDs (copper or progestin) or a progestin-only oral contraceptive over other hormonal contraceptive options (GS4).	Not graded*

GS3. Justification for strong recommendation:

We recommend avoiding use of estrogen-containing contraceptives in women with positive aPL/APS. The recommendation is strong because estrogen increases risk of thromboembolism and risk is further increased in the presence of additional risk factors, including positive aPL or genetic prothrombotic factors. While the quality of direct evidence is very low (19), the increased risks include pulmonary embolism, stroke, and death. The overall risk of venous thromboembolism (VTE) in healthy women on current combined estrogen-progestin contraceptives is increased by 3-6x from a baseline annual risk of 1/10,000 women-years. Progestin type also affects thrombosis risk: odds ratios for VTE risk in healthy women with combined estrogen-progestin contraceptive oral contraceptives with similar estrogen content but varying progestin type range from 2.2 to 6.6, depending on type of progestin (20). Although published data are limited, this is not considered to be an area needing future research, as indirect evidence suggests a high risk of potentially life-threatening thrombotic outcomes.

GS4. Justification for strong recommendation:

We recommend using IUDs or the progestin-only pill in women with positive aPL/APS. The recommendation is strong because of the high risk of unplanned pregnancy in this group and the likely safety of these methods for this population. Progestin-only methods are widely accepted as a lower risk option than estrogen-containing contraceptives and depot medroxy-progesterone acetate (DMPA), which may potentially increase thrombotic risk. Professional associations disagree on degree of thrombotic risk with progestin-only methods for patients with positive aPL (21–23).

The risk of venous thromboembolism (VTE) in healthy women using progestin contraceptives is not increased (9). In a large meta-analysis (8 studies, two with patients at high risk for VTE), progestin-only contraceptives were not associated with increased VTE risk compared to non-users, RR = 1.03, (0.76-1.39) (9). Furthermore, use of progestin-only contraceptives does not appear to confer additional risk in women with baseline elevated VTE risk (7,8). If patients are unable or unwilling to use an IUD, then other progestin-only options are recommended.

Progestin-only Oral Contraceptives: Risk of VTE was not elevated with the progestin-only pill (RR = 0.90, 0.57-1.45), nor with the progestin IUD (RR = 0.61, 0.24-1.53) (9). The progestin-only pill was compared to combined estrogen-progestin contraceptive pills in one study of patients with SLE (patients were excluded for a history of thrombosis but not the presence of aPL) (11); there were low and equal numbers of VTE in each of the groups.

Progestin-only Implant: Data are very limited regarding thrombosis risk in patients with the progestin (etonogestrel) subdermal implant, which includes a third-generation progestin. The progestin implant has not been studied specifically in RMD or aPL-positive patients.

IUD: IUDs are most strongly recommended for efficacy and low risk. While the progestin-IUD has not been studied specifically in women with RMD, it is not associated with increased thrombotic risk. The copper IUD may increase menstrual bleeding and cramps in the several months after insertion, while the progestin IUDs often decrease

menstrual bleeding and cramps, a potential benefit for patients on anticoagulation or with menorrhagia.

Depo-medroxyprogesterone (DMPA): Very limited data in non-RMD patients suggest that DMPA may have a higher thrombosis risk than do other progestin-only contraceptives. A subgroup analysis of two studies including DMPA (both with small numbers of patients) suggested increased VTE risk with DMPA, RR = 2.67 (1.29-5.53), similar to that of some oral estrogen-progestin contraceptives (9). For this reason, DMPA is not suggested as a progestin-only contraceptive for long-term use in patients with positive aPL or APS.

When discussing risk of progestin contraceptives in patients with positive aPL or APS, it is critical to weigh the VTE risk during pregnancy against risk associated with use of these contraceptives. Baseline VTE risk in healthy young women (either not using combined hormonal contraceptives, or using progestin-only contraceptives) is 1/10,000 women-years; risk with current combined estrogen-progestin contraceptives is 5/10,000 and risk of VTE in pregnancy is 73/10,000. Although risk of thrombosis in pregnancy for aPL-positive patients is not well-quantified, for patients with a single (genetic) prothrombotic defect VTE risk during pregnancy is 197/10,000, and for those with combined prothrombotic defects, it is 776/10,000 (24).

In women with RMD including those who have ever been aPL positive, we strongly recommend using emergency (post-coital) contraception when necessary (GS6).	Not graded*

GS6. Justification for strong recommendation:

We recommend using emergency (post-coital) contraception in all RMD patients, if desired. The recommendation is strong due to the low risk associated with use with emergency contraception even in high-risk populations, and the benefit of preventing unplanned pregnancy. Options include over-the-counter levonorgestrel, prescription ulipristal, and placement of a copper IUD (preferred for efficacy and long term contraceptive benefit). The latter two methods are prescribed (or placed) by a medical provider, but the levonorgestrel pill is widely available in pharmacies without a prescription. They are intended for one-time or infrequent use, and as a result, the Centers for Disease Control and Prevention (CDC) does not propose any medical contraindications to their use, including thrombophilia, cardiovascular disease, migraine, or breastfeeding (22).

In women with RMD who are on immunosuppressive therapy and desire an IUD, we strongly recommend the IUD (copper or progestin) as an appropriate contraceptive (GS7).	Not graded*

GS7. Justification for strong recommendation:

We recommend that women with RMD who are on immunosuppressive therapy pursue placement of an IUD if desired. IUDs are among the most effective contraceptive options; this benefit provides justification for the strong recommendation for their use in RMD patients on immunosuppressive medications. The extremely low risk of infection after insertion of the IUD should be weighed against the risk of unplanned pregnancy including organ- or life-threatening complications (especially in patients with disease

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that is active and/or severe enough to require immunosuppressive therapy) and against the teratogenic potential of some RMD medications.

The risk of IUD-associated infection in RMD patients on immunosuppressive medications has not been specifically studied. Studies in immunocompromised women infected with HIV show no increased risk of infection after IUD placement (25), and there is no evidence suggesting that use of IUDs increases risk of infection in immunosuppressed patients (26). IUDs are recommended for use in patients with solid organ transplants (27) and are safe and efficacious in adolescents and young adults with solid organ transplants (28). The Sanchez-Guerrero et al. study of contraception in SLE patients included one group using the copper IUD. It is not known if these women were on immunosuppressive therapies, but there were no reported cases of pelvic inflammatory disease in this group over the course of one year of follow-up. Studying the risk of IUD associated infection in RMD patients on immunosuppressive medications represents a key research area for patients with RMD.

In women with RMD and osteoporosis or at increased risk for osteoporosis, we conditionally recommend avoiding use of injectable depot medroxy-progesterone acetate (DMPA) as a long-term contraceptive (GS10).	Not graded*

GS10. Justification for conditional recommendation:

We recommend avoiding use of long-term DMPA in RMD patients with risk of osteoporosis. The recommendation is conditional, based on data that suggest increased risk of bone loss with chronic use of DMPA in the healthy population (up to 7.5% decline

in bone mineral density over 2 years) (29), although no data suggest an increased

fracture risk in healthy women. This indirect evidence suggests it is reasonable to limit

use in a population with low bone density or at increased risk for osteoporosis.

Osteoporosis is a common and concerning issue for RMD patients due to both

corticosteroid use and underlying disease; however, there is no direct evidence in RMD

patients regarding effect of DMPA on bone density. Use of DMPA in women with RMD

requires careful assessment for and discussion of risk factors. ACOG similarly

recommends individualized use in patients with or at increased risk of osteoporosis (6).

For reversible contraception in women with RMD on <u>mycophenolate mofetil</u> or mycophenolic acid, we conditionally recommend use of an IUD (alone) or use of two forms of alternative contraception (GS11)	Not graded*

GS11. Justification for Conditional Recommendation:

The recommendation for use of an IUD or dual contraception for prevention of

pregnancy in patients on mycophenolate mofetil/mycophenolic acid is based on the

finding that these potential drug interactions may reduce the serum concentrations of

estrogen and progesterone. This recommendation has been adapted from the product

label and the Mycophenolate Risk Evaluation and Mitigation (REMS) program, as there

are minimal published clinical data. The concern, while important, is largely theoretical

and degree of risk is difficult to assess; thus, the recommendation is conditional.

The Mycophenolate REMS program suggests use of an IUD alone (copper or progestin

is not specified) or use of estrogen-progestin contraceptives or the progestin implant

together with a barrier form of contraception, as appropriate reversible contraception for

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a patient on a mycophenolate medication (30). While the proposed drug interaction of mycophenolate with oral contraceptives may lower progestin levels, it is unclear whether it can interfere with progestin IUDs (which contain varying amounts of hormone) and potentially decrease efficacy; clinicians should discuss the hypothetical risk of lowered efficacy of the progestin IUD while on mycophenolate medications.

The Mycophenolate REMS program also cites bilateral tubal ligation and vasectomy as appropriate single forms of contraception for patients taking mycophenolate medications. These are not considered here due to our focus on reversible contraception.

Other significant rheumatologic drug interactions with hormonal contraceptives were sought in the systematic literature review. One study evaluated pharmacokinetics and sex hormone levels in patients on oral estrogen-progestin contraceptives treated with a single dose of tocilizumab, and no significant changes in hormone levels were identified (31). No data suggesting risk of other significant rheumatologic medication drug interactions were found that would affect recommendations for use of contraceptives.

Assisted Reproductive Technology:

Fertility is generally unimpaired in RMD patients unless they have been treated with cyclophosphamide or have deferred pregnancy, as fertility in women declines with increasing age.

Common assisted reproductive technology (ART) techniques include ovarian stimulation with or without in vitro fertilization (IVF) and embryo transfer. The least invasive technique is controlled ovarian stimulation with intrauterine insemination (IUI). IVF cycles generally require more aggressive stimulation, with surgical extraction of oocytes, fertilization, and subsequent transfer of embryos. Important risks for RMD patients undergoing ART primarily relate to elevated estrogen levels and include thrombosis as well as flare in SLE patients (32,33). While reports of thrombosis in aPL-positive or APS patients are uncommon, it is important to note that most reported patients undergoing IVF were treated prophylactically with some form of anticoagulation. Recent analyses do not support aPL as a cause of failed IVF or infertility, so, while anticoagulation may be indicated as prophylaxis against maternal thrombosis, it should not be expected to confer improvement in IVF cycle outcome (34).

While uncommon, ovarian hyperstimulation syndrome (OHSS) is an important complication of IVF that results in capillary leak, with pleural effusion and ascites. Severe OHSS increases the risk for arterial and venous thrombosis and renal compromise (35). Underlying thrombophilia increases the risk of severe OHSS (36). As thromboprophylaxis is low risk (37), it has been suggested for patients who develop moderate-to-severe OHSS and for patients with known inherited or acquired thrombophilia (38).

Since protocols can vary, discussion with the reproductive endocrine and infertility (REI) specialist prior to ART regarding the RMD patient's particular risk profile is appropriate.

In addition to prophylactic anticoagulation, patients at increased risk for thrombosis or OHSS may benefit from protocol manipulations by the REI specialist that result in lower peak serum estrogen levels. These include natural cycle IVF or individualized ovarian stimulation regimens using GnRH antagonists, GnRH agonists or aromatase inhibitors (39).

Prophylactic low molecular weight heparin (LMWH) is usually used for thromboprophylaxis, holding it 24-36 hours prior to oocyte retrieval. Aspirin is not commonly used given concern that it could increase bleeding risk at the time of surgical oocyte retrieval. Ideally, patients who will be treated with low-dose aspirin during pregnancy will start this after oocyte retrieval is completed.

Given that the desired outcome of ART is usually pregnancy, ovarian stimulation and IVF should be planned for patients with stable inactive disease on medications compatible with pregnancy. Rheumatologists should assess patients regarding the safety of potential pregnancy as well as the planned procedure before patients pursue ART. Frozen embryo transfer does not generally require ovarian stimulation but often will require use of estrogen to prepare the endometrium for implantation. Embryo and oocyte cryopreservation are good options to preserve fertility in patients who are stable enough to undergo ovarian stimulation but are either not able or not ready to pursue pregnancy at the time of stimulation. A carefully monitored ovarian stimulation/IVF cycle followed by embryo transfer to a surrogate, if available, is an option for some patients

with severe disease-related damage who desire a biological child, are able to undergo

ovarian stimulation and oocyte retrieval, but cannot safely undergo pregnancy.

Uncomplicated RMD: We strongly recommend undergoing ART for patients with stable/quiescent disease and negative aPL (GS24).	Very low

GS24. Justification for strong recommendation:

We recommend RMD patients with stable, quiescent disease pursue ART if desired.

Although the level of direct evidence is very low for RMD patients (40,41), indirect

evidence supports the safety of ART in the general population (35,36). Given that the

risk of ovarian stimulation in these patients is generally thrombosis or, for women with

lupus, flare, the Voting Panel was of the opinion that the risk for patients with stable

quiescent RMD and negative aPL was nearly equal to that of the general population and

so the recommendation in support of this procedure ART in RMD patients who are aPL-

negative is strong. Such risk was thought to be minimal compared to the benefit for

those who desire pregnancy and are unable to conceive naturally, although risks

associated with ART in general and thrombosis and lupus flare in particular should be

discussed in advance with all patients.

SLE: • We strongly recommend <u>deferring</u> ART procedures while SLE or other RMD is moderately or severely active (GS27).	Not graded*
• We conditionally recommend <u>against</u> treating with prophylactic (or prophylactic dosage increase) prednisone	Not graded*

| during ART procedures in patients with SLE, unless required for control of active disease (GS29). | |

GS27. Justification for strong recommendation:

We recommend avoiding ART during periods of disease activity; the recommendation is strong based on evidence regarding higher pregnancy risks with increased RMD disease activity that include organ-or life-threatening maternal outcomes and adverse pregnancy outcomes such as pregnancy loss, severe prematurity or growth restriction. Proceeding with fertility therapy to achieve pregnancy should be planned for a time when pregnancy outcome can be optimized with the lowest possible risk. Even if pregnancy is not planned immediately, i.e. ovarian stimulation for oocyte or embryo cryopreservation, the risk associated with ART should be minimized by having quiescent or stable disease prior to the procedure.

GS29. Justification for conditional recommendation:

We recommend avoiding the use of prophylactic prednisone during ART in SLE patients because no studies have evaluated outcomes of ovarian stimulation with the addition of prophylactic prednisone for prevention of disease flare in SLE. We suggest following carefully and treating for flare if it occurs. However, the recommendation is conditional because many complicating factors may alter this decision. In specific circumstances, low-dose corticosteroids may be added, whether as a standard part of an ART medication protocol (as per the REI) or in a patient who has consistently flared during ovarian stimulation in the past.

Positive aPL: We conditionally recommend undergoing ART for patients with stable/quiescent disease and positive aPL (GS25), including therapy with unfractionated heparin or low molecular weight heparin as detailed below:	Very low
• We conditionally recommend treating with prophylactic dose anticoagulation therapy during ART procedures for patients with positive aPL who have had no clinical manifestations of APS (GS25A).	Very low
• We strongly recommend treating with prophylactic dose anticoagulation therapy during ART procedures for patients who have a history of OB-APS but not thrombotic APS (GS25A2).	Very low
• We strongly recommend treating with *therapeutic* dose rather than prophylactic dose anticoagulation therapy during ART procedures for patients with positive aPL who have a history of thrombotic APS (GS26A).	Very low

GS25. Justification for conditional recommendation:

We recommend patients with positive aPL planning ART be treated with prophylactic

anticoagulation with heparin or low molecular weight heparin (LMWH). The level of

direct evidence supporting prophylactic anticoagulation therapy for aPL-positive patients

during ART procedures is very low (40,41) and represents an important area requiring

further research. As a result, the recommendation here for prophylactic anticoagulation

therapy is conditional. However, the risk of potentially organ- or life-threatening

thrombosis in patients with lupus anticoagulant (LAC) or moderate-high titer aCL or

aβ2GPI (those patients termed aPL-positive for purposes of this guideline) was felt to

outweigh the low risk of short-term use of LMWH. Risks for aPL-positive patients in this

setting include the risk of rising estrogen levels (although not as high as levels achieved during pregnancy, the increase in level is more abrupt) and the risk of a surgical procedure (42). The decision to recommend prophylactic anticoagulation for all aPL-positive patients rests on largely indirect but compelling evidence. First, the risk of OHSS-associatedthrombosis is increased in the presence of prothrombotic risk factors. Further, most reports of aPL-positive women undergoing IVF included treatment with anticoagulation during procedures (40,41). Surgical procedures and pregnancy are major risk factors for increased risk of thrombosis in aPL positive patients, and ovarian stimulation with oocyte retrieval involves potentially high estrogen levels as well as a surgical procedure (42). Finally, two of the four thromboses in the most recent reference in the evidence review were in women who self-discontinued their LMWH after their oocyte retrieval procedures (40).

GS25A. Justification for conditional recommendation

We recommend treating asymptomatic aPL-positive patients with prophylactic anticoagulation during ART procedures because ovarian stimulation may increase the risk of thrombosis even in healthy patients and these aPL-positive patients are at greater risk of thrombosis even without added potential triggers. In the study of SLE and aPL-positive women undergoing IVF reported by Orquevaux et al, 4 of 97 cycles were complicated by thromboses (40). Two of them were in aPL-positive women who stopped their anticoagulant treatment (low molecular weight heparin, after oocyte retrieval, leading to DVT in the first patient and PE in the second patient. In the paper by Guballa et al, most aPL-positive patients were empirically treated with prophylactic

anticoagulation (41). The recommendation is conditional because of the paucity of data, and the inability to predict individual risk. Nonetheless, this is a clinically relevant situation that will likely become more common as more RMD patients pursue ART. The Voting Panel limited discussion and recommendations to patients thought to be at highest risk for thrombosis, that is, those meeting APS laboratory criteria (persistently positive LAC or moderate-high titer aCL or aβ2GPI) (43).

We chose not to comment on prophylactic treatment of low titer aCL or aβ2GPI patients, as risk, while also uncertain, is very likely lower. Decisions regarding potential prophylactic anticoagulation for these patients should rest on an informed discussion between the patient and the physician, relying on assessment of the complete clinical situation including other prothrombotic factors, as well as the patient's values and preferences.

GS25A2. Justification for strong recommendation:
We recommend prophylactic anticoagulation therapy during ART procedures; the recommendation is strong, given the risk of organ- or life-threatening thrombosis in the setting of ovarian stimulation in women with history of obstetric APS (OB APS). If the procedure is successful, prophylactic LMWH will be continued, and low dose aspirin added, for pregnancy prophylaxis therapy.

GS26A. Justification for strong recommendation

We recommend changing to therapeutic heparin for ART procedures in patients on chronic anticoagulation for thrombotic APS; the recommendation is strong based on patient safety issues. These include necessity of continuation of long-term anticoagulation in patients at high risk for recurrent thrombosis, the ability to hold the heparin 24-36 hours prior to oocyte retrieval, and the overall safety of heparin (versus the teratogenicity of warfarin or other unstudied anticoagulants) during an ensuing pregnancy.

We strongly recommend continuing necessary immunosuppressive and/or biologic therapies (with the exception of cyclophosphamide) throughout ovarian stimulation and oocyte retrieval for patients with stable disease on these therapies for the purpose of oocyte or embryo cryopreservation (GS28).	Not graded*

GS28. Justification for strong recommendation:

We recommend continuing rheumatologic medications through ovarian stimulation for oocyte cryopreservation; the recommendation is strong due to the anticipated high risk of uncontrolled disease from withdrawal of effective medication exacerbated by the risks of the procedure itself. No data were found to suggest that oocyte retrieval is contraindicated while patients are on most immunosuppressive or biologic therapies, with the exception of cyclophosphamide, which is known to directly impact maturing follicles.

Fertility preservation:

Regimens containing high cumulative doses of alkylating agents for the treatment of severe manifestations of autoimmune disorders, in particular cyclophosphamide (CYC), are increasingly being replaced by shorter courses of therapy such as the "Euro-lupus" protocol for lupus nephritis (44); induction with mycophenolate mofetil/mycophenolic acid for lupus nephritis (45); or rituximab for ANCA-associated vasculitis (46). Because the risks associated with CYC therapy are largely dose-dependent, this practice change represents a significant reduction in risk of ovarian insufficiency in RMD patients, which is dependent on both cumulative dose and older age at the time of therapy (47). Recent research suggests that no decrease in ovarian reserve, as measured by Anti-Mullerian hormone (AMH) levels, occurs in patients treated with lower dose "Euro-lupus" CYC (48). While these findings are reassuring, it is important to remember that RMD patients may require future courses of CYC due to the waxing and waning nature of disease and CYC exposure has a potential cumulative effect on ovarian reserve, affecting ability to conceive and the numerous health benefits associated with reaching natural, rather than premature, menopause.

The use of gonadotropin releasing hormone agonists (GnRHa) for ovarian protection during CYC therapy in RMD patients was initially proposed on the basis of the strength of evidence supporting its use in the cancer population. The evidence for GnRHa therapy is less robust for RMD patients, with only a handful of randomized clinical trials in different rheumatology populations and heterogeneous outcome measures for

ovarian function. Issues related to the expense of GnRHa therapy, (although significantly less than ART), inconsistent insurance coverage in the out-patient setting, and difficulty coordinating GnRHa administration for the optimal timing of 10-14 days prior to monthly CYC makes GnRHa co-therapy challenging for many rheumatologists. The decision to discuss GnRHa use during CYC therapy should not be made based solely on whether a woman desires future pregnancies; the benefits of intact ovarian function beyond fertility should also be considered including maintenance of bone health.

While initially considered in the scope of this guideline, we were unable to provide recommendations regarding the use of oral estrogen-progestin contraceptives to preserve ovarian reserve during CYC therapy in RMD patients due to the low quality indirect evidence and the concern with starting exogenous estrogen in patients with serious active lupus. Addition of gonadotropin-releasing hormone antagonists (different from GnRHa) was also initially considered, but there was no evidence for the addition of gonadotropin-releasing hormone antagonists in the RMD population, and so no recommendations are offered.

The evidence for fertility preservation using testosterone in men with RMD receiving CYC therapy was very low. Alternatively, sperm cryopreservation in men planning CYC is suggested whenever possible if the patient plans to father children in the future. We acknowledge the difficulty of coordinating sperm banking under situations in which CYC therapy is indicated urgently or semi-urgently. Animal data suggest that CYC causes the

most genetic damage to the post-meiosis spermatids, so the sperm in development

during CYC infusion have the highest degree of genetic damage (49). As a result,

sperm should only be collected prior to CYC or several months after the last infusion,

not in the days or weeks after infusions are started. Urologists recommend waiting a

minimum of three months after CYC therapy is completed (50).

In premenopausal women with RMD receiving cyclophosphamide we conditionally recommend treating with monthly GnRH-agonist co-therapy during monthly IV CYC therapy (GS31).	Low

GS31. Justification for conditional recommendation:

This recommendation for use of GnRHa co-therapy in RMD patients receiving CYC is

based on several small studies in RMD patients. One randomized, double-blind

placebo-controlled dose-escalation study examined return of menstruation following

cessation of CYC therapy in women with childhood-onset SLE who received GnRHa

(51). The evidence was indirect for this outcome, as the study did not report the

outcome of return of menstruation in the placebo group. 16/16 patients who received

GnRHa and CYC had return of menses. A recent study, published after the conclusion

of the systematic literature search, was not included in the evidence review but serves

to further support this conditional recommendation (52). Kaplan-Meier survival

estimates of premature ovarian failure (POF) among 30 premenopausal SLE women

were compared between 16 women co-treated with GnRHa and 14 untreated controls

at a mean of 41 months follow-up. POF, assessed by serum FSH, estradiol levels and

amenorrhea of ≥ 12 months up until age 40, developed in one of the 16 GnRH-a-treated

patients (6%) versus seven of the 14 controls (50%), and significantly more continued

ovarian function was observed in the GnRHa-treated group versus controls (P = 0.030).

The recommendation is conditional because of the low quality of evidence (51,53,54);

most evidence is indirect. The heterogeneity of outcome measures across observational

and randomized clinical trials (return of menses, ability to conceive, LH, AMH levels) is

also a limitation. There were no data addressing ovarian function outcomes for oral

versus shorter or longer IV courses of CYC.However, it may be reasonable -on an

individual basis and reviewing the relative risks and benefits with the patient - to

consider such treatment for patients who must be treated with oral cyclophosphamide.

Such therapy may not be necessary for the lower cumulative CYC dose associated with

the Euro-lupus regimen.

In men with RMD receiving cyclophosphamide therapy who have no immediate plans to father a child, we conditionally recommend <u>against</u> treating with testosterone co-therapy (GS35).	Very low

GS35. Justification for conditional recommendation:

We recommend against treating with testosterone co-therapy in RMD males undergoing

cyclophosphamide therapy; the recommendation is conditional, based on indirect

evidence. Testosterone therapy has not proven efficacious for men undergoing

chemotherapy for malignancy. One study did report the use of testosterone co-therapy

in male patients with SLE who were receiving IV CYC; however, the comparator group

was healthy, age-matched controls who did not receive cyclophosphamide (or testosterone). Sperm quality (including sperm count and sperm motility) was significantly lower in men receiving CYC and testosterone compared to those who did not receive any therapy (55). The recommendation is conditional as the data are limited. Sperm cryopreservation, where possible, is an effective way to preserve male fertility, and should be done prior to administration of CYC.

Menopause:

Current recommendations from other organizations (56–58) suggest limiting use of hormone replacement therapies (HRT) for healthy postmenopausal women, using the lowest dose that alleviates symptoms for the minimal time necessary, generally in the years immediately following onset of menopause. Studies of long term oral HRT therapy have suggested that benefits for prevention of chronic disorders, such as cardiovascular disease, are clearly outweighed by risks of therapy, including stroke and breast cancer (59). HRT therapy is now largely reserved for a relatively small number of peri- or post-menopausal patients with vasomotor or genitourinary symptoms not effectively treated by other non-hormonal therapies.

Risks of HRT differ depending on the type, dose, route of administration, duration of use, and timing of initiation. Treatment should be individualized. For women $\leq$ 60 years, or those within 10 years of menopause onset, benefit-risk balance is most favorable for treatment of severe vasomotor symptoms. For women > 60 years, or more than 10 years after menopause onset, benefit-risk ratio is less favorable due to absolute risks of cardiovascular disease, stroke, and venous thromboembolism (VTE) (57).

Since risk of VTE is increased with HRT use, underlying thrombotic risk, primarily aPL, is an important issue in selection of RMD patients for whom therapy is appropriate. In the Women's Health Initiative study VTE risk increased two-fold in the estrogen-progestin group compared with placebo (HR =2.06, 95% CI 1.6-2.7 (60), confirmed by subsequent systematic review and meta-analysis (61).

Factors affecting VTE risk of oral HRT include type of oral estrogen, type of progestin, and route of administration. Conjugated, but not esterified (plant-derived), estrogens increase VTE risk (62). Relative risk of VTE is higher for women taking oral estrogen-progestin than unopposed estrogen regimens (RR 2.1 versus 1.4) (63). In contrast to oral formulations, transdermal estrogen has little effect on hemostasis and does not increase VTE risk in healthy women (64,65). In a meta-analysis, no excess risk of VTE was observed in women taking transdermal estrogen (OR 1.2, 95% CI 0.1-1.7), even in those with prothrombotic mutations or high body mass index (BMI) (66).

Available data support a high risk of VTE in women with prothrombotic mutations taking oral HRT (67,68); however, no studies have specifically assessed the risk of oral or transdermal HRT in aPL-positive women. In one case-control study of genetic mutations the combination of either factor V Leiden or prothrombin G20210A mutation and oral estrogen gave a 25-fold-increased risk of VTE compared with non-users without mutations (95% CI, 6.9 to 95.0). Risk for women with prothrombotic mutations using transdermal estrogen, however, was similar to that of women with a mutation who were

not using any estrogen (OR, 4.4; 95% CI, 2.0-9.9; and OR, 4.1; 95% CI, 2.3-7.4, respectively) (67).

Overall, available evidence supports the use of HRT when deemed appropriate in RMD patients without aPL, including those with SLE (69). Given the clear lower VTE risk of transdermal as opposed to oral estrogen preparations, it seems reasonable to consider transdermal estrogen as initial therapy for all RMD patients for whom HRT is considered appropriate.

Decisions regarding HRT in patients with lower level aPL that do not meet classification criteria need to be made on a case-by-case basis, with discussion between the patient and the rheumatologist, exploring all risks and benefits and considering any additional relevant risk factors.

Use of hormone replacement therapy (HRT) in postmenopausal women with RMD who have severe vasomotor symptoms, no other contraindications to HRT, and who desire treatment with HRT: **SLE:** In women with SLE without positive aPL we conditionally recommend treating with HRT over no therapy (GS79).	Moderate

GS79. Justification for conditional recommendation:

We recommend treating with HRT if indicated in women with SLE without positive aPL based on moderate quality direct evidence supporting the use of HRT in these women

(69–72). Importantly, patients had stable inactive disease at enrollment in the Safety of

Estrogens in Lupus Erythematosus National Assessment (SELENA) study. The

recommendation is conditional because there is a small increase in risk of mild-

moderate (but not severe) flare in the SELENA study in the HRT group (69). Presence

of disease activity or low level aCL or aβ2GPI should be considered before deciding to

proceed with HRT in patients with SLE. Patients with SLE may be at increased risk for

thrombosis even without positive aPL if they have additional risk factors, such as longer

duration of disease and active nephritis (17).

Positive aPL : In women with positive aPL who do not have APS, we conditionally recommend <u>against</u> treating with HRT (GS80).	Low

GS80. Justification for conditional recommendation:

Patients meeting laboratory criteria for APS have higher risk of thrombosis than do

those with lower titers of aCL or aβ2GPI. Since HRT can increase the risk of VTE, we

recommend against HRT use in patients with RMD who are aPL-positive. The

recommendation is conditional based on a low level of evidence. Cravioto et al.

randomized 106 SLE patients to oral estrogen-progestin HRT or placebo to assess

benefits of HRT on menopausal symptoms; roughly one-third of the participants had

positive aPL (titers unknown) (73). Thrombotic events were not significantly different

between groups over 24 months of follow-up (3 in the HRT group, 1 in the placebo

group).

Although risk of positive aPL in combination with oral HRT has not been quantified, such a study is unlikely to be performed for ethical reasons, as the indirect evidence showing increased VTE risk with other prothrombotic conditions is concerning enough to recommend against using HRT in this population. If HRT were to be considered, after discussion regarding risks and benefits, we would suggest transdermal HRT as it would likely present lower risk of VTE than oral HRT in this population, as in genetic prothrombotic conditions (66).

In women with obstetric APS (OB-APS) and/or thrombotic APS not currently on anticoagulation, we strongly recommend <u>against</u> treating with HRT (GS81).	Not graded*

GS81. Justification for strong recommendation:

We recommend avoiding use of HRT in women who meet laboratory and clinical criteria for OB-APS or thrombotic APS and are not anticoagulated; the recommendation is strong because the Voting Panel considered the risk of thrombosis with HRT to be unacceptably high. Unlike most genetic prothrombotic conditions, the risk of aPL and HRT includes venous thrombosis, arterial thrombosis, and catastrophic APS with potential organ- and life-threatening outcomes. It is unlikely that randomized controlled studies would be performed to answer this question, given the ethical concerns.

In women with thrombotic APS who are on warfarin therapy, we conditionally recommend <u>against</u> treating with HRT (GS82).	Not graded*

GS82. Justification for conditional recommendation:

We recommend against treating women with thromobotic APS with HRT, even if they are on warfarin. Warfarin is recommended therapy for patients with thrombotic APS to reduce the risk of recurrent thrombosis. Given the potential protective benefit against recurrent thrombosis in APS patients on anticoagulant therapy, the recommendation to avoid HRT use in these patients is conditional. There may be situations where the benefits of such HRT are thought to outweigh the risks for a particular patient on warfarin therapy. The physician's and patient's assessments of relative risk and expected benefit in a particular situation should guide such decisions. In this situation we would suggest transdermal HRT, as this would likely present lower risk of VTE in this population (66).

Use of hormone replacement therapy (HRT) in postmenopausal women with RMD who have severe vasomotor symptoms, no other contraindications to HRT, and who desire treatment with HRT: In women with history of positive aPL but not APS, and whose aPL titers have been negative over the last several years, we conditionally recommend treating with HRT (GS83).	Not graded*

GS83. Justification for conditional recommendation:

We recommend treatment with HRT if desired for patients who previously demonstrated asymptomatic positive aPL, but no longer test positive. The recommendation is conditional, as there are no data to help define the risk of thrombosis in these patients.

As a result, it is not clear what the additive risk with HRT would be. This decision, given the lack of evidence supporting safe use of HRT, must be discussed with the patient and the risks and benefits for her particular situation assessed. If HRT were to be considered, we would suggest transdermal HRT as this would likely present lower risk of VTE than oral HRT (66).

In women with history of APS whose aPL titers have been negative over the last several years, we conditionally recommend <u>against</u> treating with HRT (GS83A).	Not graded*

GS83A. Justification for conditional recommendation:

The recommendation to avoid HRT in patients with a known APS history even if current antibodies are negative is based on the Voting Panel's reasoning that the risk of HRT in a patient with previous clinical manifestations, even with current negative aPL, would be unacceptably high and potentially life-threatening. The recommendation is conditional as there are no data that directly address this circumstance. The decision to proceed with HRT in this situation must be discussed with the patient and the risks and benefits for her particular situation assessed. As mentioned, transdermal HRT would likely be preferable given the demonstrated lower risk of thrombosis in multiple studies (66).

*Not graded: Evidence was indirect and derived from additional informal literature reviews of medications and procedures in non-RMD populations, as detailed in Methods (Appendix 1).

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