SUPPLEMENTARY APPENDIX 7: Recommendation Tables with Strength of Evidence Rating

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

Table A. Recommendations and good practice statements for use of contraception in women with RMD who are at risk for unplanned pregnancy.

In patients with RMD who are at risk for unplanned pregnancy:	Strength of evidence
All women with RMD: • In women with RMD who are of childbearing age, we suggest discussing contraception and plans for pregnancy at an initial or early visit and when initiating treatment with potentially teratogenic medications. • Counseling regarding contraceptive methods for each particular patient should be based on efficacy, safety, and individual values and preferences • In women with RMD for whom use of other, more effective forms of birth control are contraindicated, we suggest using barrier methods of contraception as birth control over other less effective options or no contraception	Good practice statements
Uncomplicated RMD: • In patients with RMD without SLE and without positive aPL: ○ We strongly recommend using hormonal contraceptives or IUDs over other less effective contraceptive options or no contraceptive method (GS1). ○ We conditionally recommend using IUDs or progestin subdermal implant over other hormonal contraceptive options (GS1A).	Not graded* Not graded*
SLE: • In patients with stable (low disease activity) SLE without positive aPL: ○ 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). ○ We conditionally recommend using IUDs and progestin implant over other hormonal contraceptive options (GS2A). ○ We conditionally recommend against using the transdermal estrogen-progestin patch over other hormonal contraceptive options (GS2B). • 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).	Low - moderate Not graded* Not graded* Not graded*
Positive aPL:	

• In women with RMD with positive aPL:
  ○ We strongly recommend against using combined estrogen-progestin contraceptives (GS3).
  ○ We strongly recommend using IUDs (copper or progestin) or a progestin-only pill over other hormonal contraceptive options (GS4).
• In women with RMD, including those who have ever been aPL positive, we strongly recommend using emergency (post-coital) contraception when necessary (GS6).
	Very low
	
	Not graded*
	
	Not graded*

Special RMD situations: • 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). • 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). • For reversible contraception in women with RMD on mycophenolate mofetil or mycophenolic acid, we conditionally recommend use of an IUD (alone) or use of two forms of alternative contraception (GS11)	Not graded* Not graded* Not graded*

Table B. Recommendations for use of assisted reproductive technologies (ART) in women with RMD.

In women with RMD on pregnancy-compatible medications who require assisted reproductive technologies (ART) to achieve pregnancy, oocyte or embryo storage, or surrogacy:	Strength of evidence
Uncomplicated RMD: • We strongly recommend undergoing ART for patients with stable/quiescent disease and negative aPL (GS24).	Very low
SLE: • We strongly recommend deferring ART procedures while SLE or other RMD is moderately or severely active (GS27).	Not graded*
• We conditionally recommend against treating with prophylactic (or prophylactic dosage increase) prednisone during ART procedures in patients with SLE, unless required for control of active disease (GS29).	Not graded*
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: • 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). • 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). • 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 Very low Very low Very low
Special RMD situations: • 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).	

Table C. Recommendations and good practice statements for fertility preservation in patients with RMD during cyclophosphamide therapy.

In patients receiving cyclophosphamide:	Strength of Evidence
Women • In premenopausal women with RMD receiving cyclophosphamide we conditionally recommend treating with monthly GnRH-agonist co-therapy during monthly IV cyclophosphamide therapy (GS31).	Low
Men • In men with RMD receiving cyclophosphamide therapy who have no immediate plans to father a child, we conditionally recommend against treating with testosterone co-therapy (GS35). • In men with RMD receiving cyclophosphamide therapy who have no immediate plans to father a child we suggest - where possible and when future conception is desired - proceeding with sperm cryopreservation, ideally prior to initiating cyclophosphamide therapy.	Very low Good practice statement

Table D. Recommendations and good practice statements for use of hormone replacement therapy (HRT) in postmenopausal women with RMD who have severe vasomotor symptoms and no other contraindications to HRT.

In women with RMD who are eligible for and desire treatment with HRT	Strength of Evidence
Uncomplicated RMD: • In women with RMD without SLE and without positive aPL we suggest treating with HRT according to the guidelines for the general postmenopausal population.	Good practice statement
SLE: • In women with SLE without positive aPL we conditionally recommend treating with HRT over no therapy (GS79).	Moderate
Positive aPL: • In women with positive aPL who do not have APS, we conditionally recommend against treating with HRT (GS80). • In women with obstetric APS (OB-APS) and/or thrombotic APS not currently on anticoagulation, we strongly recommend against treating with HRT (GS81). • In women with thrombotic APS who are on warfarin therapy, we conditionally recommend against treating with HRT (GS82). • 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). • In women with history of APS whose aPL titers have been negative over the last several years, we conditionally recommend against treating with HRT (GS83A)	Low Not graded* Not graded* Not graded* Not graded*

Table E. Recommendations and good practice statements for pregnancy counseling, assessment and management in RMD patients.

In women with RMD who are pregnant or considering pregnancy:	Strength of Evidence
All RMD patients	
• In women with RMD considering pregnancy or who are pregnant we strongly suggest**:**	
○ Counseling patients that maternal and pregnancy outcomes are better when illness is quiescent / low activity before pregnancy (adapted from GS53).	Good practice statement
○ Co-management by a rheumatologist or other physician with relevant expertise throughout pregnancy is preferred (adapted from GS63).	Good practice statement
• In women with RMD who are planning for pregnancy and are taking medication incompatible with pregnancy, we strongly recommend switching to a pregnancy-compatible medication, and observing for a period of time to assess efficacy and tolerability (GS42)	Very low
• In women with RMD who are pregnant with active disease that requires medical therapy, we strongly recommend initiating or continuing a pregnancy-compatible medication (GS54).	Very low
Laboratory testing	
• In women with SLE or SLE-like disease, Sjogren's, systemic sclerosis, and RA who are considering pregnancy or are pregnant, we strongly recommend testing for anti-Ro/SSA and anti-La/SSB one time in early pregnancy, and against repeating the test during pregnancy (GS60, GS62).	Very low
• In women with SLE who are considering pregnancy or are pregnant, we strongly recommend testing for aPL once early in pregnancy, and against repeating the test during pregnancy (GS59, GS61).	Very low
SLE	
• In women with SLE who are considering pregnancy (or are pregnant):	
○ If taking hydroxychloroquine, we strongly recommend continuing HCQ during pregnancy (GS57).	Low to very low
○ If not taking HCQ, we conditionally recommend starting HCQ if there is no contraindication (GS58)	Not graded*
• In women with SLE who are currently pregnant:	
○ We strongly suggest monitoring laboratory tests for disease activity at least once per trimester during pregnancy (GS64)	Good practice statement
○ We conditionally recommend treating with low dose aspirin (GS56)	Very low
Special RMD situations	
• In women who are pregnant with scleroderma renal crisis, we strongly recommend treating with an ACE-inhibitor or angiotensin receptor blocker (ARB) (GS55)	Not graded*

Table F. Recommendations and good practice statements for pregnancy counseling, assessment and management in aPL-positive and APS patients.

In women with positive aPL or APS:	Strength of evidence
Positive aPL only:	
• In pregnant women with positive aPL who do not meet obstetric or thrombotic APS criteria we conditionally recommend:	
○ Treating with prophylactic low dose aspirin during pregnancy (GS45).	Very low
○ Against treating with prophylactic heparin or LMWH combined with low dose aspirin (GS46)	Not graded*
○ Against treating with prophylactic hydroxychloroquine during pregnancy, If the patient does not otherwise require hydroxychloroquine (GS44A).	Not graded*
Obstetric APS:	
• In pregnant women with positive aPL who meet OB-APS criteria and have no history of thrombosis, we strongly recommend treating with *prophylactic* heparin or LMWH and low dose aspirin (GS48).	Moderate
• In pregnant women with positive aPL who meet OB-APS criteria and have failed standard therapy with prophylactic heparin or LMWH and low dose aspirin:	
○ We conditionally recommend against treating with *therapeutic* dose heparin or LMWH combined with low dose aspirin (GS49)	Not graded*
○ We conditionally recommend against treating with IVIG in addition to prophylactic heparin and low dose aspirin (GS50).	Low
○ We strongly recommend against treating with prednisone in addition to heparin or LMWH combined with low dose aspirin (GS51)	Low
• In women who have met OB-APS criteria, we strongly recommend treating with prophylactic, low-dose anticoagulation during the postpartum period (GS84).	Not graded*
Thrombotic APS:	
• In pregnant women with thrombotic APS, we strongly recommend treating with *therapeutic* heparin and low dose aspirin rather than other non-heparin anticoagulation (GS52).	Not graded*
• In pregnant women not otherwise requiring hydroxychloroquine and with obstetric and/or thrombotic APS, we conditionally recommend treating with hydroxychloroquine during pregnancy (GS44B)	Very low

Table G. Recommendations for pregnancy assessment and management in patients with anti-Ro/SSA, anti-La/SSB antibodies.

In women with positive anti-Ro/SSA and/or anti-La/SSB antibodies:	Strength of Evidence
Positive anti-Ro/SSA and/or anti-La/SSB antibodies:	
• In pregnant women with anti-Ro/SSA and/or anti-La/SSB antibodies with no history of an infant with congenital heart block or neonatal lupus (risk of complete heart block ~2%) we conditionally recommend:	
○ Obtaining serial (less frequent than weekly, interval not determined) fetal echocardiography starting at weeks 16-18 through week 26. (GS67)	Low
○ Treating with hydroxychloroquine during pregnancy (GS69)	Low
• In pregnant women with anti-Ro/SSA and/or anti-La/SSB antibodies with history of an infant with congenital heart block or neonatal lupus (risk of complete heart block is 13 -18%) we conditionally recommend:	
○ Obtaining fetal echocardiography every week starting between weeks 16-18 through week 26. (GS68)	Low
○ Treating with hydroxychloroquine during pregnancy (GS70)	Low
Abnormal fetal echocardiogram:	
• In pregnant women with anti-Ro/SSA and/or anti-La/SSB antibodies with abnormal fetal echocardiograms, we conditionally recommend:	
○ If 1st degree heart block, treating with dexamethasone 4 mg PO daily (GS71)	Very low
○ If 2nd degree heart block, treating with dexamethasone 4 mg PO daily (GS72)	Very low
○ If isolated 3rd (complete) degree heart block (without other cardiac inflammation), against treating with dexamethasone (GS73)	Very low

Table H. Recommendations for paternal rheumatology medication use for men with RMD.

Paternal medication use for men with RMD	Strength of evidence
In men with RMD who are planning to father a child, we suggest discussing the use of medications prior to attempting to conceive a pregnancy.	Good practice statement
In men with RMD who are initiating treatment with medications that may affect fertility (e.g. cyclophosphamide), we suggest discussing future pregnancy plans.	Good practice statement
In men with RMD who are planning to father a child within three months:	
• We strongly recommend discontinuing cyclophosphamide (GS133)	Not graded*
• We conditionally recommend discontinuing thalidomide (GS139)	No evidence
• We strongly recommend continuing hydroxychloroquine (GS90).	No evidence
• We strongly recommend continuing azathioprine/ 6-mercaptopurine (GS115)	Not graded*
• We strongly recommend continuing infliximab, etanercept, adalimumab, golimumab, certolizumab (GS143, GS146, GS149, GS152, GS155)	Very low
• We strongly recommend continuing colchicine (GS97)	Not graded*
• We conditionally recommend continuing leflunomide (GS108)	Not graded*
• We conditionally recommend continuing mycophenolate mofetil/ mycophenolic acid (GS119)	Not graded*
• We conditionally recommend continuing classic nonsteroidal anti-inflammatory drugs or Cox2 inhibitors (GS85).	Very low
• We conditionally recommend continuing sulfasalazine (GS94).	Very low
• We conditionally recommend continuing cyclosporine (GS126)	Not graded*
• We conditionally recommend continuing tacrolimus (GS130)	Not graded*
• We conditionally recommend continuing anakinra (GS159)	Very low
• We conditionally recommend continuing rituximab (GS 163)	Very low

Table I. Recommendations for use of conventional rheumatology medications in pregnancy for women with RMD.

Conventional rheumatology medications in pregnancy for women with RMD	Level of evidence
We suggest discussing the use of medications prior to attempting to conceive; we also suggest discussing future pregnancy plans when initiating treatment with medications that may affect fertility such as cyclophosphamide.	Good practice statement
In women with inadvertent exposure to teratogenic medications during pregnancy, we strongly suggest immediate medication discontinuation and referral to a maternal-fetal-medicine specialist or genetics counselor.	Good practice statement
NSAID use: • If having difficulty conceiving, we conditionally recommend discontinuing NSAIDs while trying to conceive if disease control would not be compromised (GS86). • If pregnant, we strongly recommend avoiding NSAIDs in the third trimester (GS87). • If pregnant, we conditionally recommend non-selective NSAIDs over Cox2-specific inhibitors as compatible with pregnancy in the first two trimesters (GS88).	Very low Not graded* Not graded*
In women who are pregnant or planning pregnancy: • We strongly recommend discontinuing methotrexate prior to attempting conception (GS102). • We strongly recommend discontinuing mycophenolate mofetil/mycophenolic acid at least six weeks prior to attempting conception (GS120). • We strongly recommend discontinuing thalidomide prior to attempting conception (GS140). • We strongly recommend discontinuing cyclophosphamide prior to attempting conception (GS134) • In the case of life- or organ- threatening maternal disease in which there are no alternative therapies we conditionally recommend initiating cyclophosphamide in the second or third trimester (GS136). • If an inadvertent pregnancy occurs while using leflunomide, we strongly recommend discontinuing leflunomide and initiating a cholestyramine washout until drug levels are undetectable (GS110). • If treated with leflunomide within 24 months, we strongly recommend demonstrating that blood levels are undetectable, or initiating a cholestyramine washout until drug levels are undetectable, prior to attempting conception (GS109). • We strongly recommend continuing hydroxychloroquine as compatible with pregnancy. (GS91). • We strongly recommend continuing sulfasalazine as compatible with pregnancy (GS95). • We strongly recommend continuing azathioprine/6-mercaptopurine as compatible with pregnancy. (GS116).	Very low Not graded* Not graded* Very low Very low Very low Very low Very low Very low Very low

• We strongly recommend continuing colchicine as compatible with pregnancy (GS98) • We conditionally recommend continuing cyclosporine as compatible with pregnancy (GS127). • We conditionally recommend continuing tacrolimus as compatible with pregnancy. (GS131).	Not graded* Not graded* Not graded*

Table J. Recommendations for use of biologic rheumatology medications in pregnancy for women with RMD.

Biologic and other new medications in pregnancy for women with RMD	Strength of evidence
TNF alpha inhibitor therapy • We strongly recommend continuing certolizumab therapy prior to and during pregnancy (GS156). • We conditionally recommend continuing TNF-inhibitor therapy (infliximab, etanercept, adalimumab, golimumab) prior to and during pregnancy (GS144, GS147, GS150, GS153).	Very low Very low
Rituximab: • We conditionally recommend continuing rituximab through conception (GS164) • We conditionally recommend using rituximab during pregnancy in the setting of severe, life or organ threatening maternal disease (GS165)	Very low Very low
Non-TNFi biologic agents: Including anakinra (GS160), belimumab (GS169), abatacept (GS173), tocilizumab (GS177), secukinumab (GS181), and ustekinumab (GS185) • We conditionally recommend continuing therapy through conception. • We conditionally recommend discontinuing therapy during pregnancy.	No evidence No evidence
Novel, small molecule targeted therapies: Including tofacitinib (GS189), baracitinib (GS 193), and apremilast (GS197), the committee was unable to offer recommendations regarding use during pregnancy due to lack of data.	No evidence

Table K. Recommendations for use of non-fluorinated glucocorticoids during pregnancy and delivery for women with RMD.

Non-fluorinated glucocorticoids during pregnancy and delivery	Strength of Evidence
• We conditionally recommend continuing chronic low dose (<10 mg daily of prednisone or non-fluorinated equivalent) during pregnancy if clinically indicated. (GS201)	Low
• We strongly recommend tapering higher doses of non-fluorinated glucocorticoids to <20 mg daily of prednisone with the addition of a pregnancy-compatible immunosuppressive agent if needed. (GS202)	Low
In women using chronic low dose glucocorticoids during pregnancy:	
• We conditionally do not recommend treating with stress dose corticosteroids at the time of vaginal delivery. (GS206)	No evidence
• We conditionally recommend treating with stress dose glucocorticoids at the time of Cesarean delivery. (GS207)	Low

Table L. Recommendations for use of rheumatology medications during lactation for women with RMD.

Rheumatology medications during lactation for women with RMD	Strength of evidence
Women should be encouraged to breastfeed if desired and possible. Disease control should be maintained with medications compatible with lactation and risks/benefits reviewed with each patient for her particular situation.	Good practice statements
Traditional medications	
• We conditionally recommend that NSAIDs are compatible with breastfeeding (GS89)	Not graded*
• We strongly recommend that hydroxychloroquine is compatible with breastfeeding (GS 92)	Low
• We conditionally recommend that sulfasalazine is compatible with breastfeeding (GS96)	Low
• We conditionally recommend that colchicine is compatible with breastfeeding. (GS99)	Low
Immunosuppressives	
• We strongly recommend against using leflunomide in breastfeeding women (GS113)	No evidence
• We strongly recommend against using mycophenolate mofetil/ mycophenolic acid while breastfeeding (GS124)	No evidence
• We strongly recommend against using cyclophosphamide while breastfeeding (GS137)	Low
• We strongly recommend against using thalidomide while breastfeeding (GS142)	No evidence
• We conditionally recommend against using methotrexate in breastfeeding women (GS106)	Low
• We conditionally recommend that azathioprine and 6 mercaptopurine are compatible with breastfeeding (GS117)	Low
• We conditionally recommend that cyclosporine is compatible with breastfeeding(GS128)	Low
• We conditionally recommend that tacrolimus is compatible with breastfeeding (GS132)	Low
Biologics	
• We strongly recommend that TNF-inhibitors as a class: infliximab, etanercept, adalimumab, golimumab (no-data), certolizumab are compatible with breastfeeding (GS143, GS146, GS149, GS152, GS155)	Low
• We strongly recommend that rituximab is compatible with breastfeeding (GS166)	Low
• We conditionally recommend that anakinra is compatible with breastfeeding (GS161)	No evidence
• We conditionally recommend that belimumab is compatible with breastfeeding (GS170)	Low

• We conditionally recommend that abatacept is compatible with breastfeeding (GS174) • We conditionally recommend that tocilizumab is compatible with breastfeeding (GS178) • We conditionally recommend that secukinumab is compatible with breastfeeding (GS182) • We conditionally recommend that ustekinumab is compatible with breastfeeding (GS186)	No evidence Low No evidence No evidence
Glucocorticoids: • We strongly recommend that prednisone <20mg a day (or non-fluorinated equivalent) is compatible with breastfeeding (GS204) • We strongly recommend that women using prednisone >20mg a day (or non-fluorinated glucocorticoid equivalent) delay breastfeeding or discard breast milk for the four hours following glucocorticoid administration (GS205)	Low Low

***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).**