SUPPLEMENTARY APPENDIX 11: Detailed background and justification for good practice statements and recommendations for pregnancy assessment, counseling and management

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

General pregnancy in rheumatic and musculoskeletal disease (RMD) patients:

Most information regarding pregnancy management in RMD comes from observational studies, primarily in patients with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS), as well as obstetrical guidelines that focus on high-risk patients but not necessarily those with RMD. Very few controlled trials exist. Data about pregnancies in rare rheumatic diseases, such as Takayasu arteritis or Behçet's syndrome, come from small case series. For these reasons, many recommendations are conditional, supported by collective experience of Voting Panel members who also relied on obstetric experience parallel to, but not directly about, RMD patients.

Many studies support the importance of quiescent rheumatic disease prior to pregnancy. Direct observational studies discuss management of SLE patients (1–10), and additional observational studies with indirect evidence (11,12,21,22,13–20) include SLE, rheumatoid arthritis (RA), and ANCA-associated vasculitis. Most did not stratify patients or include control populations. In addition, studies published after the literature review was completed continue to support the good practice statements. A recent study from the Organization of Teratology Information Specialists (OTIS) comparing 657 women with RA, 170 with JIA, and 564 with no autoimmune disease documented an

increased risk for preterm delivery in women with RA who had active disease early in pregnancy (23).

We believe co-management with obstetrics specialists by the rheumatologist throughout pregnancy is critical to ensuring optimal pregnancy outcome for mother and child. Rheumatologists are familiar with nuances of systemic autoimmune diseases and often have a long history of caring for the individual who is newly pregnant. Hematologists, nephrologists and other specialists offer additional relevant expertise. Coordinated care and frequent communication with the obstetrician-gynecologist and other specialists is desirable.

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

GS42. Justification for strong recommendation:

The recommendation to change to pregnancy-compatible medications when planning pregnancy is based on the potential life-altering outcomes for offspring that are associated with use of teratogenic medications. This recommendation is strong because major birth defects from rheumatology medications impact offspring and parents, are potentially preventable since alternatives are available for most teratogenic rheumatology medications, and presence of uncontrolled illness worsens both maternal and pregnancy prognoses (4,24). A small observational study showed generally

acceptable fetal and maternal outcomes among 18 women with lupus nephritis whose maintenance medication was changed from mycophenolate to azathioprine (AZA) (25). Because any change of medication risks flare of illness, an observation period is necessary to assure disease stability during the ensuing pregnancy. The duration of time needed for observation is medication and patient dependent. Most studies find AZA, hydroxychloroquine (HCQ), and low-dose prednisone safe for both mother and fetus regarding pregnancy complications, fetal development, and maternal health. Discontinuing medications, including those compatible with pregnancy, may risk flare and poor pregnancy outcome. A prospective observational study of 257 pregnancies of women with SLE showed similar rates of miscarriage, stillbirth, pregnancy loss, and congenital abnormalities among women taking, not taking, or discontinuing HCQ, but worse lupus activity among women who discontinued the drug (26).

In a limited number of situations, it may be reasonable for patients to taper off teratogenic medication in anticipation of pregnancy without substitution of alternative compatible medication; for example, patients with quiescent lupus tapering off maintenance mycophenolate after an appropriate course of therapy for nephritis. The decision to taper, rather than substitute, medication should be made by the rheumatologist and the patient based on the patient's particular clinical situation and history, and will likely be an uncommon occurrence. If tapering off, patients should be observed off the medication for a period of time to assure continued quiescent disease before attempting pregnancy.

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

GS54. Justification for strong recommendation:

We recommend initiating or continuing pregnancy-compatible medications to control maternal disease activity during pregnancy, based on the demonstration that flare of maternal illness threatens both mother and child, confirmed in numerous studies (4,24,26–32). Although no controlled studies test the hypothesis, prematurely discontinuing a pregnancy-compatible medication is likely to risk flare for most systemic rheumatic illnesses. Supporting indirect data regarding pregnancy are available for SLE, APS, RA, juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS,) in which almost all studies indicate worse pregnancy outcome if the mother has active disease (4,27–30,33). The recommendation to initiate or continue pregnancy compatible medication for active disease during pregnancy is strong, although level of direct evidence is very low, because multiple studies indirectly support the concept that the healthier the mother, the better the fetal outcome. Inadequate treatment of RMD flares risks death or serious morbidity for mother and fetus. If pregnancy risk of a medication that cannot be discontinued is unknown, patients should be encouraged to enroll in an FDA or other pregnancy registry so that knowledge about use of this medication in pregnancy will be gained.

	Very low /

In women with SLE, 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, against repeating the test during pregnancy (GS60, GS62).	Not graded*

GS60 and GS62. Justification for strong recommendation:

We recommend checking anti-Ro/SSA and anti-La/SSB antibodies in women without a history of known positive antibodies based on evidence that these antibodies are predictors of development of the serious complication of complete congenital heart block and less severe manifestations of rash and cytopenias (34). This recommendation is strong despite the unknown effectiveness of fetal echocardiogram monitoring and prophylactic treatments in preventing or reversing congenital heart block in the fetus because knowledge of anti-Ro/SSA and anti-La/SSB status permits close monitoring and early recognition of all neonatal lupus complications, including cytopenias or neonatal rash that might otherwise be attributed to other etiologies or provoke unnecessary intensive and invasive clinical investigation in the neonate. The one-time blood test poses little risk or expense to the patient. In addition, knowledge of antibody status improves the rheumatologist's ability to counsel the patient regarding pregnancy risk and potential for adverse outcome, and improves the patient's ability to make her own risk/benefit assessment regarding pursuing pregnancy.

No data were found to support significant fluctuation of anti-Ro/SSA or anti-La/SSB antibodies during pregnancy. In general, these antibodies are not reported to vary significantly over the short term in non-pregnant patients. Once the test is positive and a

decision is made to pursue monitoring, it is unlikely that a subsequent negative test would change monitoring plans.

In women with SLE who are considering pregnancy or are pregnant, we strongly recommend testing for aPL one time early in pregnancy, and against repeating the test during pregnancy (GS59, GS61).	Very low / Not graded*

GS59 and GS61. Justification for strong recommendation:

We recommend checking antiphospholipid antibody (aPL) in SLE patients (without a known history of positive aPL) considering pregnancy or early in pregnancy based on evidence that aPL is an unequivocal predictor of adverse pregnancy outcome in patients with SLE (35). The recommendation is strong because knowledge of aPL status permits close monitoring, early recognition and targeted treatment of pregnancy complications, and testing poses little risk or expense to the patient. Furthermore, knowledge of aPL status improves the physician's ability to more accurately counsel the patient regarding her risk of pregnancy and potential for adverse outcome, improving her ability to make a better individualized risk/benefit assessment.

Standard clinical tests for aPL include anticardiolipin (aCL) IgG and IgM, anti-beta 2 Glycoprotein I (aβ2GPI) IgG and IgM, and lupus anticoagulant (LAC). LAC is identified by abnormal screening results with dRVVT or PTT-LA and confirmed by mixing tests with normal plasma and by either dilution or addition of phospholipid. In general, LAC confers greatest risk and best predicts fetal outcome for women with aPL (35,36).

Equivocally positive tests for LAC, or LAC determined by tests other than dRVVT or PTT-LA, have not been definitively shown to predict pregnancy outcome. High, but not low, titers of IgG or IgM aCL or aβ2GP1 may also be predictive; some authors consider "triple positive" patients, *i.e.* those with LAC, aCL and aβ2GP1, to be at highest risk (37). Individual studies, but no consensus evidence, support risk assessment by other tests for aPL, such as antibody to domain 1 of β2GP1, anti-phosphatidylserine, or any antibody of IgA isotype. However, these are not presently considered standard clinical testing (38).

In patients with stable SLE who are aPL-negative and do not have other additional risk factors such as hypertension, pregnancy outcome is close to that of the general population, with adverse pregnancy outcome rate of 7.8% (39). Although not studied, in theory, extensive fetal monitoring with NST, Dopplers, and serial ultrasounds may not be necessary for an aPL-negative SLE patient with a low-risk profile.

APL titer does not rapidly change during the course of a pregnancy (40) and there is no evidence to indicate that changes in titer affect outcome. Although the classification criteria laboratory definition requires that it be present on two occasions at least twelve weeks apart, if aPL is being checked for the first time, presence of underlying SLE makes it unlikely that a positive aPL is infection or drug-induced. Any concern regarding this possibility should prompt a repeat test in 12 weeks to confirm persistence.

In women with SLE who are considering pregnancy (or are pregnant):	

• If taking hydroxychloroquine (HCQ), we strongly recommend continuing HCQ during pregnancy (GS57).	Low to very low
• If not taking HCQ, we conditionally recommend starting HCQ (GS58).	Not graded*

GS57. Justification for strong recommendation:

We recommend continuing HCQ during pregnancy in patients with SLE based on data suggesting improved maternal and fetal outcomes with continued use. Observational studies find rates of SLE flare to be significantly lower in patients taking HCQ relative to those not taking HCQ (OR=0.58; 95% CI: 0.37 to 0.91) (26,41,42). A prospective observational study of 257 pregnancies of women with SLE shows similar rates of miscarriage, stillbirth, pregnancy loss, and congenital abnormalities among women taking, not taking, or discontinuing HCQ, but worse lupus activity among women who discontinued the drug (26). Other observational studies show lower prednisone dose, longer pregnancy duration (43), and better fetal outcomes (42) in HCQ users. HCQ reduced the risk of both pregnancy and post-partum flare in another observational study (44).

The recommendation to continue HCQ is strong because, while level of direct evidence is low to very low, many studies indirectly support multiple benefits; in addition, the risk of HCQ use in pregnancy is very low for both mother and fetus (14,26,49,41–48).

GS58. Justification for conditional recommendation:

We recommend initiating HCQ during pregnancy in patients with SLE not currently taking this medication; the recommendation is conditional because, while the data detailed above support the benefits of HCQ for patients with SLE during pregnancy, one must balance the risk of introducing a new medication in pregnancy against the demonstrated benefits of HCQ. The drug should not be introduced if the patient is known (or thought to be) allergic to HCQ or if she has had prior severe side effects; the nature and severity of previous side effects should be discussed with the patient and risks/ benefits weighed.

In women with SLE who are currently pregnant: • We conditionally recommend treating with low dose aspirin (GS56)	Very low

GS56. Justification for conditional recommendation:

We recommend use of low dose aspirin (81 or 100 mg daily) to prevent preeclampsia in patients with SLE. Although no prospective studies specifically assess the effect of low dose aspirin therapy on preeclampsia risk in SLE, studies in other high-risk obstetric populations suggest benefit. The estimated benefit of treatment with low dose aspirin in high-risk patients is modest (relative risk of preeclampsia in treated high risk women is 0.76-0.90) (50) but the risk and cost of therapy are quite low. SLE patients have an increased risk of preeclampsia (39). Available studies in the evidence report, all observational and uncontrolled (9,51–53), primarily discuss use of low dose aspirin in women at high risk of preeclampsia due to lupus nephritis or aPL antibody. Two of

these indirect observational studies did not have comparison groups. All patients in the first study (52) received low dose aspirin, while most patients in the second study (9) did not receive low dose aspirin. Preeclampsia developed in 8.4% of the low dose aspirin-treated group versus 19.4% in the untreated patient cohort, with RR=0.43. However, the quality of evidence for these comparisons is very low given that two different studies were combined. The recommendation for treatment of SLE patients with low dose aspirin during pregnancy is conditional; while the quality of evidence is very low, the risk of such treatment is minimal and the potential benefit is a reduced risk of preeclampsia.

ACOG (American College of Obstetrics & Gynecology) and USPHTF (US Protective Health Task Force) recommendations are to use low dose aspirin in all patients at high risk for preeclampsia; their criteria for high risk include presence of autoimmune disease (SLE and APS) (50,54). Treatment should begin early in pregnancy (ideally before 16 weeks) and continue through to delivery as it is not thought to complicate anesthesia or delivery (50).

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*

GS55. Justification for strong recommendation:

We recommend initiating angiotensin converting enzyme inhibitor (ACE-inhibitor) therapy in the setting of scleroderma renal crisis during pregnancy to prevent maternal

and fetal death. Data are derived only from case reports. In non-pregnant patients ACE-inhibitor therapy can be renal protective and life-saving for this condition (55). ACE-inhibitors and especially angiotensin II receptor blockers (ARBs) are typically contraindicated in the second and third trimester as they can be associated with permanent fetal renal damage and severe oligohydramnios in one-third of exposed infants (56). Captopril, with its shorter half-life, may pose the least risk of the available ACE-inhibitors, and the benefits likely outweigh the risk of not treating confirmed scleroderma renal crisis. This recommendation is strong because of the life-threatening nature of this complication. Scleroderma renal crisis in pregnancy carries a high probability of renal failure and/or death for both mother and child. Scleroderma renal crisis is rare in pregnancy and may be confused with preeclampsia; a high level of suspicion should be maintained for such patients.

Antiphosphoipid antibody (aPL) and pregnacy:

APL is a major risk factor for pregnancy loss and other adverse pregnancy outcomes, especially when present in the setting of SLE (35). These recommendations refer to patients meeting APS laboratory crtieria (see Appendix 5). Lower titers of aCL or aβ2GPI that do not meet APS laboratory criteria are not addressed here, and so clinical judgment is important in assessing their significance. Testing of alternative (noncriteria) aPL antibodies is generally not recommended due to lack of standarization and absence of strong supporting data.

LAC has been identified as the most important risk factor for adverse pregnancy outcome in aPL-positive women (with or without SLE): in the Predictors of Pregnancy Outcome: Biomarkers in Antiphospholipid Antibody Syndrome and Systemic Lupus Erythematosus (PROMISSE) study, relative risk (RR) for adverse pregnancy outcome with LAC was 12.15, 95% CI 2.92–50.54,*p*= 0.0006) (35). Other independent risk factors for aPL positive women were younger age, history of thrombosis, and presence of SLE.

Note that recommendations here regarding positive aPL, OB APS and thrombotic APS refer to current APS Classification Criteria (38), however, APS criteria are undergoing revision. When published, these new criteria should be utilized to provide reference definitions for both laboratory and clinical criteria in this guideline.

Positive aPL only: In pregnant women with positive aPL who <u>do not</u> meet obstetric or thrombotic APS criteria we conditionally recommend:	
• Treating with prophylactic low dose aspirin during pregnancy (GS45).	Very low
• <u>Against</u> treating with prophylactic heparin or low molecular weight heparin (LMWH) together with low dose aspirin (GS46)	Not graded*
• <u>Against</u> treating with prophylactic hydroxychloroquine during pregnancy, if the patient does not otherwise require hydroxychloroquine (GS44A).	Not graded*

GS45. Justification for conditional recommendation:

We recommend treating asymptomatic aPL-positive women with low dose aspirin during pregnancy to reduce the likelihood of development of preeclampsia. APL-positive patients have been demonstrated to have an increased risk for preeclampsia (35,39) and are considered to be high-risk for this complication. In women with positive aPL who did not meet clinical or laboratory criteria for APS, treating with low-dose aspirin during pregnancy versus not treating has been addressed by one retrospective observational cohort study (57). Low-dose aspirin was used in 104 pregnancies and 35 pregnancies were not treated; there was no statistical difference between the groups in pregnancy loss or pre-term delivery; preeclampsia was not reported. The recommendation to treat asymptomatic aPL-positive women with low dose aspirin during pregnancy is conditional as the evidence is very low level or indirect. It is based on ACOG recommendations for low dose aspirin to prevent preeclampsia (50) in high risk patients, and not as prophylactic therapy to prevent pregnancy loss (which available data do not support). Low dose aspirin carries very little risk and is thought to be protective, at least at a modest level, for patients at increased risk for preeclampsia.

GS46. **Justification for conditional recommendation:**

We do not recommend routine treatment of aPL-positive women not meeting OB APS criteria with combination therapy of prophylactic heparin or low molecular weight heparin (LMWH) and low dose aspirin during pregnancy. Treatment incurs both cost and risk. Risks of heparin include bleeding, decreased bone density and heparin-induced thrombocytopenia. The probabilities of developing these complications are low

overall, and are lower with LMWH than unfractionated heparin (UFH). There is no direct evidence concerning treatment in this population, however, and so this recommendation is conditional.

We recognize that in some situations the risk of not treating may outweigh the low risk of therapy, and discussion between the patient, the maternal fetal medicine (MFM) specialist and the rheumatologist may determine that treatment is indicated even when OB APS criteria are not met. Examples include patients who are older or have had difficulty conceiving (requiring ART); those with triple positive or strongly positive LAC, (especially with underlying SLE); and/or those who have had 1 or 2 prior early pregnancy losses with strongly positive titers (APS criteria require $\geq$3 early losses). Low titer aCL or aβ2GPI antibody not meeting APS laboratory criteria with no clinical events does not impart significant pregnancy risk and does not generally justify treatment.

GS44A. Justification for conditional recommendation:

We do not recommend HCQ treatment for asymptomatic aPL-positive women not otherwise requiring this therapy. Benefits of HCQ for pregnancies in SLE patients are clear; these patients are encouraged to continue HCQ whether they are aPL-positive or negative. For aPL-positive patients without SLE who do not meet criteria for obstetric or thrombotic APS, no data are found, and we conditionally recommend against use of HCQ in this setting. Such patients may benefit from treatment with low dose aspirin for preeclampsia prophylaxis, however. A retrospective observational study of 194 pregnant patients with primary APS showed higher live birth rates in women taking

HCQ, particularly those taking 400 mg daily before onset of pregnancy (49). Based on this very preliminary evidence, we conditionally recommend addition of HCQ in certain circumstances, such as failure of standard treatment, for the patient with primary OB and/or thrombotic APS, in conjunction with standard therapy, and after careful discussion of relative risks and benefits, following which the decision should be jointly made (see GS44B).

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 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 <u>against</u> treating with *therapeutic* dose heparinor LMWH and low dose aspirin (GS49)	Not graded*
• We conditionally recommend <u>against</u> treating with IVIG in addition to prophylactic heparin or LMWH and low dose aspirin (GS50).	Low
• We strongly recommend <u>against</u> treating with prednisone in addition to heparin or LMWHand 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*

GS48. Justification for strong recommendation:

We recommend prophylactic treatment with heparin or LMWH and low dose aspirin for patients who meet criteria for OB APS; the recommendation for treatment is strong because, though not definitive, the best available data support efficacy. Level of evidence is moderate. Prophylactic dosing for unfractionated heparin is generally 5000 units BID, and for enoxaparin 40 mg daily. In women with positive aPL meeting criteria for OB APS, treating with low-dose heparin plus low dose aspirin during pregnancy was addressed by three direct randomized controlled trials and five direct observational studies (58–65). Overall, the outcomes provided by direct randomized controlled trials show favorable effect of low-dose low molecular weight heparin (LMWH) plus low dose aspirin for pregnancy failures. Most adverse pregnancy outcomes, including pregnancy loss, across direct observational studies also favored LMWH plus low dose aspirin use. A recent study, published after the systematic literature review was completed, was the first to address the risk of bleeding with antithrombotic therapy specifically in SLE and APS patients and provided reassuring data regarding risk. The authors examined the safety of antithrombotic therapy in 264 pregnancies in APS patients from two cohorts (of whom 46% of patients had had prior thrombosis and 23% had SLE). Major bleeding occurred in only 3% of all pregnancies and was associated with emergency Caesarean section, but not with specific use of aspirin or prophylactic or therapeutic doses of heparin (66).

GS49. Justification for conditional recommendation:

We recommend against treating patients with OB APS with therapeutic levels of heparin or LMWH. Therapeutic dosingis generally indicated for current or prior thromboses only,

and risks of therapeutic dose heparin treatment are assumed to be greater than for prophylactic dose heparin (67). The recommendation to avoid use of therapeutic heparin or LMWH dosing for patients with OB APS in the absence of thrombotic APS is conditional, because no studies have addressed efficacy of this therapy.

GS50. Justification for conditional recommendation:

We do not recommend routine use of intravenous immunoglobulin (IVIG) for patients failing standard OB APS therapy. Studies supporting the use of IVIG for patients who meet obstetric APS criteria are small and highly selected, and level of evidence is low. The recommendation to avoid adding IVIG for OB APS patients who have failed heparin and low dose aspirin is conditional, since data are conflicting. The only direct randomized controlled trial failed to show benefit in pregnancy outcome (68), while several observational studies suggested possible benefit (69–74). Although overall risk of IVIG is relatively low, IVIG is expensive, and side effects and administration procedures can be burdensome. Deguchi and colleagues retrospectively compared IVIG, LMWH and low dose aspirin therapy in 16 APS patients to LMWH plus low dose aspirin therapy in 54 APS patients and found IVIG combination therapy outcomes to be favorable compared to LMWH plus low dose aspirin (70). A decision regarding use of IVIG should take into account the lack of direct evidence indicating benefit as well as the expected costs and risks. Some patients and physicians may wish to proceed with IVIG therapy regardless, given the current lack of other options for failure of standard OB APS therapy.

GS51. Justification for strong recommendation:

We do not recommend use of prednisone treatment for patients with OB APS who fail standard therapy. The recommendation against treatment with prednisone for OB APS patients is strong because there are no data that clearly support this practice. Studies of the use of prednisone for patients who meet OB APS criteria – and have no other indications for corticosteroid treatment - are small, highly selected, and uncontrolled (70,72,74). Despite the low cost and relatively limited risk of low dose prednisone, no data support a recommendation to treat. While some studies show favorable results for prednisone (in combination with other therapies) regarding pregnancy loss and growth restriction (74); others (70) find prednisone to be a risk factor for hypertension, thrombocytopenia, and preterm delivery.

GS84. Justification for strong recommendation:

We recommend prophylactic low-dose anticoagulation in women with OB APS post-partum to prevent development of thromboembolism during this high risk period. While no direct data support this recommendation specifically for OB APS, obstetric recommendations for women with increased thrombophilic risk (75) and standard practice for postoperative care for APS patients (76) strongly favor continued anticoagulation for 6 to 12 weeks. This is a strong recommendation because the risk of thrombosis in all women is increased postpartum (77) and is assumed to be at least as high, if not higher, in women with OB APS. The risk of prophylactic anticoagulation is minimal, so the benefit/harm ratio of treating is high. Post-partum thromboses such as

pulmonary embolism or stroke are life threatening, justifying the strength of this recommendation.

Thrombotic APS: In pregnant women with thrombotic APS, we strongly recommend treating with therapeutic heparin or LMWH 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

GS52. Justification for strong recommendation:

We recommend treating pregnant patients with thrombotic APS with therapeutic LMWH based on the safety of heparin and LMWH in pregnancy when compared to warfarin or other anticoagulants. Warfarin is generally replaced with unfractionated heparin or LMWH due to the potential teratogenicity of the oral drug. LMWH, in therapeutic doses, together with low dose aspirin are of proven efficacy and safety in preventing thromboses in patients with thrombotic APS. Because pregnancy is an additional risk factor for thrombosis in women with APS (78) therapeutic dosing of heparin or LMWH is critical and so this recommendation is strong. The safety and efficacy of alternative anticoagulant agents in APS pregnancy are unclear. In nonpregnant patients, the first randomized controlled clinical trial comparing rivaroxaban to warfarin in thrombotic APS

demonstrated rivaroxaban to be inferior to warfarin in preventing arterial thromboses (79).

GS44B. Justification for conditional recommendations:

We recommend considering addition of HCQ to traditional therapy for pregnant women with OB APS and/or thrombotic APS (GS44B) but not for asymptomatic aPL-positive women (GS44A, above). Benefits of HCQ for pregnancies in SLE patients are clear; these patients are encouraged to continue HCQ whether they are aPL-positive or negative. A retrospective observational study of 194 pregnant patients with primary APS showed higher live birth rates in women taking HCQ, particularly those taking 400 mg daily before onset of pregnancy(49). Based on this very preliminary evidence, we conditionally recommend addition of HCQ in certain circumstances, such as failure of standard treatment, for the patient with primary OB and/or thrombotic APS, in conjunction with standard therapy, and after careful discussion of relative risks and benefits, following which the decision should be jointly made.

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

Neonatal lupus denotes several fetal and infant manifestations caused by maternal autoantibodies. The anti-Ro/SSA antibody is the most common antibody involved in neonatal lupus; anti-La/SSB antibodies, when present with anti-Ro/SSA antibodies, may increase the risk for complications. Isolated anti-La/SSB antibodies rarely impose a significant risk (80). Prospective studies of infants born to anti-Ro/SSA and/or anti-La/SSB antibody-positive women demonstrate an estimated 10% of infants with the

classic rash, 20% with transient cytopenias, and 30% with mild transient transaminitis, (estimates vary widely between different reports). Each of these complications is relatively short-lived and resolves as the maternal antibodies dissipate (81).

Complete (third degree) heart block occurs in an estimated 2% of pregnancies in women with anti-Ro/SSA and/or anti-La/SSB antibodies without a prior infant born with neonatal lupus and an estimated 18% of pregnancies in women with a prior infant born with either cutaneous or cardiac neonatal lupus (34). Complete heart block is irreversible; management generally transfers to the pediatric cardiology team. An estimated 20% of those affected will die in utero or in the first year of life, and over half of these offspring will require a pacemaker (80).

Due to the potentially devastating impact of complete heart block, we conditionally recommend prophylactic treatment with HCQ to lower risk (although it is acknowledged that an ongoing prospective open label study in women who have had a previous child with CHB will further support or refute this recommendation), screening with fetal echocardiograms, and treating with dexamethasone for early first or second degree heart block. Given the rarity of complete heart block, the data to support these efforts are limited. The consequences of excessive screening include identifying and treating artifacts that would not have a long-term impact on the health of the offspring. Additionally, long-term treatment with dexamethasone could have consequences for the fetus and the mother.

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:	Level of evidence
• Obtaining serial fetal echocardiography (less frequently than weekly) 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

GS67 and GS68. Justification for conditional recommendations:

These recommendations regarding screening are the result of a comprehensive review of available data and an intense Voter Panel discussion regarding risks and benefits for patients. They are conditional based on the disparate nature of the data regarding utility and optimal timing of fetal echocardiogram screening. The goal of the fetal echocardiogram is to identify early, potentially reversible inflammatory cardiac changes for which treatment might prevent complete heart block which, once complete, is not reversible. The utility of the fetal echocardiogram rests on the ability to identify a prolonged PR interval of first degree block or second degree block, both being harbingers of complete block; controversy remains as to what value of first degree block predicts progression (82). Extra-nodal disease, such as endocardial fibroelastosis, may also be a harbinger of conduction disease and, even in isolation, a prognosticator of morbidity and mortality.

The optimal schedule for fetal echocardiograms has not been established through scientific study (3,14,90–97,82–89). We recommend starting between 16 and 18 weeks gestation, just prior to the most common time of detection (about 20 weeks), and also the time at which the fetal echocardiogram can show sufficient detail for an accurate report. We recommend ending fetal echocardiogram surveillance at about week 26, as it is rare for a fetus to develop cardiac changes beyond this point. Complete fetal heart block can occur within 24 hours and may occur between scheduled fetal echocardiograms. Recent data published after the completion of this systematic literature review suggests that home fetal Doppler monitoring may identify congenital heart block within 8 hours. This new modality shows promise, since it is possible that early treatment may lead to return to normal sinus rhythm (98).

The patient discussion panel argued strongly that the benefits of potentially identifying first or second degree block, and thereby preventing progression to complete block, as well as the reassurance of normal fetal cardiac function, outweighs the potential cost, burden of regular visits, and associated stress of having the fetal echocardiograms.

For anti-Ro/SSA and/or anti-La/SSB antibody positive women without a prior history of an infant with neonatal lupus, the risk of complete heart block is low (2%). Therefore, the number needed to screen through fetal echo is large compared to the expected frequency of heart block. Given the relative rarity of the condition, every other week

fetal echocardiograms may be more appropriate than weekly, but this remains controversial.

The risk for heart block in anti-Ro/SSA and/or anti-La/SSB antibody positive women with a prior infant having neonatal lupus (cutaneous or cardiac) is 13-18% (80). Given this significantly higher risk, weekly fetal echocardiograms are warranted. The Voting Panel discussed these recommendations extensively. Due to the unknown benefit of weekly fetal echocardiograms (since there are no strong data supporting improved outcomes) as well as the time and expense associated with this testing, panel members varied in their opinions. One member of the panel dissented, citing the lack of data and the time, expense, and emotional burden of weekly testing and one patient voting panel member agreed with this view. Others thought that, although the likelihood of detecting and successfully treating an early heart block was low, the time and expense were worth the possibility of preventing the need for a lifelong pacemaker. Until newer data and/or technology change current practices, physicians should review the available data with patients and make a decision together regarding timing of fetal echocardiograms. Other factors may impact the decision. The titer of antibody likely matters, as low titer antibodies are probably not associated with the same risk of congenital heart block as are higher titers (84,89). A challenge is that commercial laboratories may not titer antibodies at all or, if they do, methodology is not uniform across different laboratories, and so no clear threshold titer for highest risk has been determined. If patient or financial concerns limit the accessibility of fetal echocardiograms, the highest likelihood of developing, and thus detecting, an abnormality would likely be at 19-20 weeks.

Finally, fetal echocardiograms may rarely show evidence of other cardiac inflammation affecting cardiac function that might respond to fluorinated corticosteroid therapy, further justifying the screening regimen.

GS69 and GS70. Justification for conditional recommendations:

We recommend treating anti-Ro/SSA and/or anti-La/SSB positive women with prophylactic HCQ during pregnancy to reduce the risk of neonatal lupus. The recommendation is conditional because the quality of evidence is low. When compared to women with anti-Ro/SSA and/or anti-La/SSB antibodies not taking HCQ during pregnancy, retrospective studies demonstrate that women with a history of a child with cardiac neonatal lupus taking HCQ have a lower risk of the infant developing complete heart block. The benefit is statistically significant in an international study that combined three prospectively collected databases of women with a prior infant with neonatal lupus: in 21.2% of subsequent pregnancies in women without HCQ and 7.5% of pregnancies in women taking HCQ, the child had cardiac neonatal lupus (adjusted OR 0.23 in favor of HCQ, 95% CI, 0.06-0.92) (93). For cohorts of women with and without prior affected infants, the difference in heart block rates has also been large, but not statistically significant, because of limited power (1/18 with HCQ vs. 6/22 without HCQ, p=0.10) (99), (1/14 with HCQ vs. 7/19 without HCQ, p=0.09) (91), (1/73 with HCQ vs. 12/195 without HCQ, p=0.07) (87).

HCQ is considered compatible with pregnancy; data do not suggest increased risk for congenital anomalies, pregnancy loss, or other adverse fetal outcomes. Due to its

prolonged half-life and the long lead-time required to see clinical benefit in rheumatology patients, HCQ should be started prior to or very early in pregnancy to confer benefit. Again, given the much higher risk of complete heart block in infants of women with a prior child with neonatal lupus and limited data suggesting benefit in women with a prior infant having cardiac neonatal lupus, HCQ preventive therapy is more strongly encouraged in this group. Fortunately, a prospective study is nearing completion.

Abnormal fetal echocardiogram: In pregnant women with anti-Ro/SSA and/or anti-La/SSB antibodies with abnormal fetal echocardiograms, we conditionally recommend:	Level of evidence
• If first degree heart block, treating with dexamethasone 4 mg PO daily (GS71)	Very low
• If second degree heart block, treating with dexamethasone 4 mg PO daily (GS72)	Very low
• If isolated third (complete) degree heart block (without other cardiac inflammation), <u>against</u> treating with dexamethasone (GS73)	Very low

GS71. Justification for conditional recommendation:

We recommend a limited course of dexamethasone for first degree heart block detected on fetal echocardiogram. The recommendation is conditional because data are conflicting and degree of benefit is uncertain. The long-term trajectory and impact of first degree heart block is currently unknown, so impact of treatment with dexamethasone

remains controversial (82,89,100): some cases reverse spontaneously while others are a precursor to complete heart block. Jaeggi et al. included 165 fetuses of 142 anti-Ro/SSA-positive women with or without anti-La/SSB antibody: 15 fetuses had atrio-ventricular conduction prolongation, none received glucocorticoid therapy and none progressed to complete heart block (82). Friedman et al. found advanced block and cardiomyopathy could occur within 1 week of a normal echocardiogram without initial first-degree block (89).

Prognosis may depend on the measured PR interval and the precise definition for PR prolongation. For this reason, we conditionally recommend that a brief course of dexamethasone 4 mg daily is warranted to assess the impact on first degree block. Optimal duration of glucocorticoid therapy is not known and likely should be limited from one to several weeks given the maternal and fetal risks of prolonged therapy. If complete heart block is identified after treatment has been started, we recommend cessation of steroids, as complete heart block is not reversible.

Fluorinated corticosteroids such as dexamethasone or betamethasone treat fetal cardiac inflammation because they cross the placenta significantly more than non-fluorinated steroids like prednisone. The long-term impact of dexamethasone on the fetus is not fully understood, and prolonged use during pregnancy places the fetus at increased risk for adrenal insufficiency at delivery. In addition, continued use of corticosteroid can impact the mother’s health, increasing risk for diabetes, hypertension, osteoporosis and osteonecrosis.

GS72. Justification for conditional recommendation:

We recommend a limited course of dexamethasone for second degree heart block detected on fetal echocardiogram. Data regarding efficacy of dexamethasone for second degree heart block are varied and interpretation is difficult, leading to a conditional recommendation for treatment (11,89,101–105). A recent analysis of 5 studies including 71 fetuses found that progression to complete heart block when first or second degree block was identified by fetal echocardiogram occurred in 52% of those treated with corticosteroids and 73% of those not treated (101). These data are drawn from non-randomized studies, making comparison challenging, but better data are not currently available. For this reason, we conditionally recommend dexamethasone 4mg a day if second degree block is identified on fetal echocardiogram. Treatment should begin immediately, as progression happens rapidly. Due to the potential toxicity of dexamethasone (described above), treatment should be limited to several weeks and tapered when possible. If complete heart block is identified after treatment has been started, we recommend cessation oftreatment, as complete heart block is irreversible.

GS73. Justification of conditional recommendation:

We do not recommend dexamethasone treatment of complete heart block on fetal echocardiogram. Complete heart block does not reverse with corticosteroid therapy. Whether dexamethasone improves long-term survival for a fetus with complete heart block is controversial; historic cohorts suggest benefit and more recent cohorts demonstrate no benefit (86,89). Recent analyses do not support the use of

dexamethasone in cases of isolated third degree block (11). Given the increased maternal and fetal risks from dexamethasone, the fragility of the health of a fetus with complete heart block and the limited potential for benefit, we conditionally recommend against treatment.

Recommendation cannot be made at this time for the rare case of endocardial fibroelastosis (EFE) in a fetus with heart block. The Voting Panel discussed this extensively and agreed that if EFE is noted in association with poor cardiac function, (i.e. there are clear functional consequences) one would consider treatment. However, the echocardiogram may show a mild abnormality that does not affect function and does not progress, so the group was unwilling to recommend treatment broadly.

No recommendations are offered regarding use of IVIG as preventive therapy for neonatal lupus-related heart block. Two prospective studies of IVIG to prevent heart block failed to show benefit (they used replacement doses of 400mg/kg rather than anti-inflammatory doses of 1g/kg), so this is not recommended as prophylactic therapy (88,94). Benefit from IVIG for complete or incomplete block has not been clearly demonstrated.

*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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