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American College of Rheumatology (ACR)
Reproductive Health in Rheumatic Diseases Guideline

Project Plan – November 2017

PARTICIPANTS

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**Participant no longer a member of the Voting Panel, but participated in the September 2017 scoping meeting.*

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ORGANIZATIONAL LEADERSHIP AND SUPPORT

This project of the American College of Rheumatology (ACR) has the broad objective of developing an evidence-based clinical practice guideline related to the management of reproductive health issues for rheumatic disease patients.

BACKGROUND

Women and men with autoimmune and inflammatory disease often face reproductive health issues related to their disease or therapy. Since reproductive-aged women are disproportionally impacted by rheumatologic disorders, family planning issues including contraception and pre-conception counseling, fertility, pregnancy management, and postpartum management including breastfeeding are an important part of disease management.

Ideally women with autoimmune and inflammatory disease should have planned pregnancies at times of low disease activity or when they are not using teratogenic medications. Moreover, patients with severe active disease or disease related damage may be counseled to avoid pregnancy. Finally, some patients, male or female, may decide to not have children or may have completed their families. In spite of the need for careful family planning, effective contraceptive methods tend to be underutilized by reproductive-aged women with rheumatic disease. Choice of safe and effective contraception will vary depending on the patient's disease, autoantibody status, stage of life, and personal feelings, and will rely on the rheumatologist's awareness of the impact of the patient's rheumatic disease on contraceptive options.

Fertility is an area of concern for many patients with autoimmune and inflammatory disorders. Women with systemic lupus erythematosus (SLE) and rheumatoid arthritis have smaller families than do control groups, and relevant factors may include disease effects, medication exposure, and patient preference. Age is another significant fertility factor – many patients are counseled to wait for quiescent disease to conceive and then may find they have limited ovarian reserve. Oocyte cryopreservation is a relatively recent advance that may play an important role for patients who are deferring pregnancy. Although high cumulative doses of cyclophosphamide are less commonly used than in the past, this is still considered definitive therapy for organ threatening and refractory disease in SLE, systemic vasculitis and other disorders. The GnRH-agonist leuprolide acetate, administered prior to intravenous cyclophosphamide pulse therapy in women with SLE, appears to offer some protective effect on ovarian reserve, although it remains unclear whether formal recommendations for use are appropriate. Reproductive medicine treatments and technology have revolutionized the issue of infertility for all women, but concerns regarding disease flare and thrombosis may limit their utilization in rheumatic disease patients.

Furthermore, assisted reproductive technologies do not address the myriad of long term health issues beyond fertility that result from primary ovarian insufficiency including bone, cardiovascular, sexual, and mental health of these patients. Therefore explicit recommendations for patients, especially those with SLE or antiphospholipid antibody syndrome, are needed.

Pregnancy, while perhaps the best-studied reproductive issue, remains an area of uncertainty for many rheumatologists and patients. Adverse pregnancy outcomes, including pregnancy loss, preterm delivery, and small-for-gestational-age infants, are more common in patients with certain rheumatic disorders. Hypertensive disorders of pregnancy, including preeclampsia, are also more common. A balance between maintaining adequate disease control and ensuring safety for the fetus can be difficult to achieve. Factors that may limit the rheumatologist's ability to counsel and manage patients include lack of clinical trial data in pregnancy, limited understanding of drug metabolism, transfer, and risks of teratogenicity of medications during pregnancy, and difficulty assessing the impact of poorly controlled disease on pregnancy outcome.

Although benefits of breastfeeding are well established, those benefits must be balanced against the potential impact of rheumatic disease medications in women who are lactating. Breastfeeding while receiving therapy ultimately is determined by individual choice, but patients require up-to-date information in order to weigh the potential risk of a medication used to control disease during lactation versus the benefits of breastfeeding. Data in this area, although limited, are evolving, especially in the case of certain commonly used medications such as TNF-inhibitors.

In recent years, short- and long-term issues for offspring of rheumatic disease patients, including concerns of neonatal infection risk related to immunosuppressive exposure and longer-term issues related to developmental delays (whether related to maternal disease, presence of maternal autoantibody, or antepartum medication use) has become of greater concern.

Safety of hormone replacement therapy for severe vasomotor symptoms and prevention of bone loss in menopausal rheumatic disease patients is a final and important reproductive health question.

OBJECTIVES

The objective of this project is to develop recommendations related to the management of reproductive health issues for rheumatic disease patients. Specifically, we aim to focus on the following areas:

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1. **Pre-pregnancy:**
    a. Contraception safety and efficacy
    b. Fertility preservation in the setting of cyclophosphamide therapy
    c. Assisted reproductive technology safety and management
    d. Counseling in anticipation of pregnancy
2. **Pregnancy:**
    a. Pregnancy management including management of antiphospholipid antibody-positive patients
    b. Management and monitoring of the anti-Ro/La+ mother
    c. Safety of paternal medication exposure
    d. Medication safety during pregnancy
    e. Corticosteroid safety in pregnancy
3. **Post-pregnancy:**
    a. Medication safety during lactation
    b. Long-term issues in the offspring
    c. Menopause and use of hormone replacement therapy

METHODS

Identification of Studies

Literature search strategies, based on PICO questions (Population/patients, Intervention, Comparator, and Outcomes; *see Appendix A*) will be developed by the principal investigators, systematic literature review leader, and a research librarian, with input from the Core Team. The search strategies will be peer reviewed by another medical librarian using Peer Review of Electronic Search Strategies (PRESS) (1). Searches will be performed in OVID Medline (1946 +), Embase (1974 +), the Cochrane Library, and PubMed (mid-1960s +).

The search strategies will be developed using the controlled vocabulary or thesauri language for each database: Medical Subject Headings (MeSH) for OVID Medline, PubMed and Cochrane Library; and Emtree terms for Embase. Text words will also be used in OVID Medline, PubMed, and Embase, and keyword/title/abstract words in the Cochrane Library.

Search Limits

Only English language articles will be retrieved.

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Grey Literature

The websites of appropriate agencies, such as the Agency for Healthcare Research and Quality (AHRQ), will be searched for peer-reviewed reports not indexed by electronic databases.

Literature Search Update

Literature searches will be updated just before the voting panel meeting to ensure completeness.

Inclusion/Exclusion Criteria

See PICO questions (*Appendix A*), which outline the defined patient population, interventions, comparators and outcomes.

Management of Studies and Data

References and abstracts will be imported into bibliographic management software (Reference Manager) (2), duplicates removed, and exported to Distiller SR, a web-based systematic review manager (3). Screening and data abstraction forms will be created in Distiller SR. Search results will be divided among reviewers, and two reviewers will screen each title/abstract, with disagreements at the title/abstract screening stage defaulting to inclusion for full manuscript review. Following the same dual review process, disagreements at the full manuscript screening stage will be discussed and adjudicated by the literature review leadership, if necessary.

Phases

1. A search for randomized controlled trials and observational studies about contraception, fertility, pregnancy, lactation, medications, offspring outcomes and menopause will be performed to determine existing studies covering outcomes of interest. Subsequently, identified studies will be assessed using the RevMan (4) and GRADE Pro tools (5).
2. Chosen studies will be assessed for risk of bias using modified versions of the Cochrane Risk of Bias tool (6) and the Newcastle-Ottawa Scale (7).
3. Additionally, recently published systematic reviews covering outcomes of interest will also be sought and used for reference cross-checking and, when current and rigorous, may constitute the best source of evidence.

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GRADE Methodology

GRADE methodology (8) will be used in this project to grade available evidence and facilitate development of recommendations. The certainty in the evidence (also known as 'quality' of evidence) will be graded as high, moderate, low or very low. The strength of recommendations will be graded as strong or conditional. The strength of recommendations will not depend solely on the certainty in the evidence, but also on patient preferences and values, and the trade-off between benefits and harms. A series of articles that describe the GRADE methodology can be found on the GRADE working group's website: www.gradeworkinggroup.org.

Analysis and Synthesis

The literature review team will analyze and synthesize data from included studies that address the PICO questions. An evidence profile, including a GRADE Summary of Findings table, will be prepared for each PICO question using Review Manager (RevMan) (2) and GRADEprofiler (GRADEpro) software (5). The Summary of Findings table contains the benefits and harms for each outcome across studies, the assumed and corresponding risk for comparators and interventions (95% CI), the absolute risk and relative effect (95% CI), the number of participants/number of studies, and the certainty in the evidence for each critical and important outcome (i.e., high, moderate, low or very low).

The evidence profile documents the overall certainty in the evidence for each critical and important outcome across studies and summarizes the rationale of the GRADE criteria for rating down (risk of bias, inconsistency, indirectness, imprecision and publication bias), or rating up the certainty in a body of evidence (large magnitude of effect, dose-response gradient, and all plausible confounding that would reduce a demonstrated effect).

Development of Recommendation Statements

PICO questions will be revised into drafted recommendation statements. Using the GRADE Evidence Profiles and Summaries of Findings tables, the voting panel, consisting of 12 rheumatologists, three obstetrician/gynecologists specializing in maternal-fetal medicine, two epidemiologists, and two patient representatives, will consider the drafted recommendation statements in two stages. The first assessment will be done individually, and the results will be anonymous; this vote will only be used to determine where consensus might or might not already exist and develop the voting panel meeting agenda. At the face-to-face voting panel meeting, chaired by the principal investigator, the panelists will discuss the evidence in the context of their clinical experience and expertise to arrive at consensus on the final recommendations. The voting panel meeting discussions will be supported by the literature

review leader, the GRADE expert, and selected members of the literature review team, who will attend the meeting to provide details about the evidence, as requested. Voting panel discussions and decisions will be informed by a separately convened patient panel, which will meet in the days before the voting panel meeting, to provide unique patient perspectives on the drafted recommendations based on their experiences and the available literature.

PLANNED APPENDICES (AT MINIMUM)

A. Final literature search strategies
B. GRADE evidence profiles and summary of findings tables for each PICO question

AUTHORSHIP

Authorship of the guideline will include: principal investigator, Dr. Lisa Sammaritano, as the lead author; Drs. Eliza Chakravarty and Kristen D'Anci, co-literature review leaders; Drs. Bonnie Bermas, Christina Chambers, Megan E. B. Clowse, Michael D. Lockshin and Wendy Marder, content experts; and Dr. Gordon Guyatt, GRADE expert. Members of the literature review team and voting panel will also be authors. The PI will determine final authorship, dependent on the efforts made by individuals throughout the guideline development process, using international authorship standards as guidance.

DISCLOSURES/CONFLICTS OF INTEREST

The ACR's disclosure and COI policies for guideline development will be followed for this project. These can be found in the ACR Guideline Manual on this page of the ACR web site, under Policies & Procedures. *See Appendix B for participant disclosures.*

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APPENDIX A – PICO Questions (PICO questions begin on p. 15)

Outline:

Pre-pregnancy:
1. Contraception
2. Fertility preservation
3. Assisted reproductive technology
4. Counseling in anticipation of pregnancy

Pregnancy:
5. Pregnancy management issues (includes aPL)
6. Management of the anti-Ro/La+ mother
7. Safety of paternal medication exposure
8. Medication safety during pregnancy
9. Corticosteroid safety in pregnancy

Post-pregnancy:
10. Medication safety during lactation
11. Menopause/HRT
12. Long-term issues

Definitions:

Template questions: the base or stem questions for each topic with variables listed that will be expanded into multiple individual questions.

Rheumatic disease (RD): this term includes RA, JIA, psoriatic arthritis, ankylosing spondylitis or other inflammatory arthritis, SLE, Sjogren's, MCTD, UCTD, APS, myositis, systemic vasculitides, or scleroderma and will be used in all questions

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Maternal (or paternal) outcomes:

Quiescent or stable with low activity:
Limited RD activity including those patients on pregnancy-compatible medications and/or <7.5mg/day prednisone

Active disease and/or RD flare:
Active RD that would typically be treated with escalation of immunosuppression or prednisone in the non-pregnant state:

- **Mild-moderate disease activity**: active disease that would be treated with increase in immunosuppression or prednisone in the non-pregnant state
- **Severe disease activity**: active disease with internal organ inflammation (including severe cytopenias, CNS disease, interstitial lung disease, myocarditis, nephritis, noncutaneous vasculitis) and/or prompting hospitalization, treatment with cyclophosphamide (outside of pregnancy) or addition of IV pulse steroids.

RD damage:
Organ damage resulting from RD that may impact maternal / fetal pregnancy outcomes, patient health-related quality of life, or patient lifespan. Including, but not limited, to:

- Severe hypertension, renal insufficiency or ESRD
- Pulmonary disease to include pulmonary hypertension, “shrinking lung,” interstitial fibrosis /restrictive lung disease
- Cardiac disease to include severe cardiac valve disease (Libman-Sacks), cardiomyopathy, CAD
- Diffuse brain disease (psychosis, dementia)
- Osteonecrosis (hip)

- Antiphospholipid syndrome with stroke or MI
- Severe deformities of any joint, including cervical spine (especially C1-C2) and hips
- Advanced skin disease that interferes with labor/delivery, vascular access, or nursing or childcare
- Diffuse muscle weakness including respiratory and swallowing mechanisms
- Vascular damage – including stenosis and aneurysm – from vasculitis (especially Takayasu's)
- Severe neuropathies

Organ failure
Maternal morbidity: infection during pregnancy, adrenal insufficiency, thrombosis
Maternal death

Pregnancy outcomes:
Pregnancy loss
Spontaneous abortion
Stillbirth
Gestational hypertensive disease including preeclampsia
Preterm birth: preterm birth <34 weeks, preterm birth ≥34 and <37 weeks
Induced labor
Premature rupture of membranes
Small for gestational age infants (SGA)
Cesarean section rate

Infant/neonatal outcomes:

Major birth defects (MBD): Structural anomaly with medical or cosmetic significance, present at or before birth
Preterm birth (above)
SGA (above)
Immunosuppression
Organ failure
Adverse vaccine reactions and insufficient vaccine response
Neonatal death

Long-term offspring outcomes:

Neurocognitive effects
Autoimmune disease

Medications:

Pregnancy-compatible DMARD:

Any DMARD/biologic that we conclude is compatible with pregnancy after the medication safety questions are complete.

Immunosuppressive medications:

- Classic, or synthetic, immunosuppressives:
  - Methotrexate
  - Leflunomide

- Azathioprine/6-MP
- Mycophenolate mofetil/mycophenolic acid
- Cyclosporine
- Tacrolimus
- Cyclophosphamide
- Thalidomide/Lenalidomide

- Biologic immunosuppressives – TNF-inhibitors:
  - Infliximab
  - Etanercept
  - Adalimumab
  - Golimumab
  - Certolizumab
- Biologic immunosuppressives – Non-TNF biologics:
  - Anakinra
  - Rituximab
  - Belimumab
  - Abatacept
  - Tocilizumab
  - Secukinumab
  - Ustekinumab
- Novel small molecules:
  - Tofacitinib

- Baracitinib
- Apremilast

Antiphospholipid antibodies (aPL):

Positive aPL: any elevated level of anticardiolipin (aCL), anti-beta2 Glycoprotein I (ab2GPI) or lupus anticoagulant (LAC)

APS laboratory criteria: modified Sapporo criteria

APS: modified Sapporo criteria

Nonstandardized aPL: aPL antibodies other than aCL, ab2GPI or LAC (i.e., anti-phosphatidylserine, anti-prothrombin, etc.)

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PICO QUESTIONS

PRE-PREGNANCY CARE:

1. Contraception:

1A. In women with RD who are of childbearing age [variables listed], what is the impact of hormonal contraception use [variables listed] versus no hormonal contraception use on risk of thrombosis?

Populations: Women with RD at risk for pregnancy

- RD without aPL (aCL, ab2GPI, LAC)
- SLE without aPL
- RD with aPL but no APS
- RD with APS (history of thrombosis or obstetrical complication)
- Primary APS

Intervention: Use of specific forms of effective hormonal birth control, including:

- Estrogen-progestin pill
- Estrogen-progestin patch
- Estrogen-progestin vaginal ring
- IUD with progestin
- Progestin pill
- Progestin implant
- Depot medroxyprogesterone acetate (DMPA)
- Emergency contraception (morning after pill, mifepristone)

Comparator: RD patients at risk for pregnancy not using hormonal birth control, including:

- Male contraception/sterilization
- Copper IUD
- Not sexually active/abstinence
- Barrier contraception
- Tubal ligation/hysterectomy

Outcome:

- Thrombosis

1B. In women of childbearing age with SLE and RA, what is the impact of hormonal contraception use versus no hormonal contraception use on risk of disease flare?

Populations: Women with SLE and RA at risk for pregnancy

- SLE
- RA

Intervention: Use of specific forms of effective hormonal birth control, including:

- Estrogen-progestin pill
- Estrogen-progestin patch
- Estrogen-progestin vaginal ring
- IUD with progestin
- Progestin pill
- Progestin implant
- DMPA
- Emergency contraception (morning after pill, mifepristone)

Comparator: SLE and RA patients at risk for pregnancy not using hormonal birth control, including:

- Male contraception/sterilization
- Copper IUD
- Not sexually active/abstinence
- Barrier contraception
- Tubal ligation/hysterectomy

Outcomes:

- RA flare (for RA)
- SLE flare excluding nephritis (for SLE)
- Lupus nephritis flare (for SLE)

1C. In women with RD of childbearing age [variables listed], what is the impact of IUD use versus no IUD use on risk of pelvic infection?

Populations: Women with RD at risk for pregnancy

- On immunosuppressive medications
- Not on immunosuppressive medications

Intervention: Use of specific forms of effective birth control, including:

- IUD with copper
    - With or without prophylactic antibiotics at insertion
- IUD with progestin
    - With or without prophylactic antibiotics at insertion

Comparator:

- Similar patients not using an IUD

Outcome:

- Infection (pelvic inflammatory disease)

1D. In RD patients of childbearing age [variables listed], what is the impact of having a sterilization procedure, versus non-RD patients, on likelihood of infection and thrombosis?

Populations: Patients with RD at risk for pregnancy

- Women
  - On immunosuppressive medications
  - Not on immunosuppressive medications
- Men
  - On immunosuppressive medications
  - Not on immunosuppressive medications

Intervention: Use of specific forms of permanent birth control including:

- Tubal ligation (women)
- Vasectomy (men)

Comparator:

- General population patients without RD having these procedures

Outcome:

- Infection or complication

1E. In women with RD of childbearing age, what is the impact of using progestin-only contraception [listed] versus not using progestin-only contraception on bone density and fracture rate?

Population:

- Women with RD of childbearing age

Intervention: Using progestin contraception

- IUD with progestin
- Progestin-only pill
- Progestin implant
- DMPA

Comparator:

- Women with RD not using any progestin-only contraception
- Women without RD using any progestin-only contraception

Outcomes:

- Bone density as defined by bone density test (DEXA)
- Fracture rate: vertebral and non-vertebral (including fragility and insufficiency fractures)

1F. In women with RD of childbearing age who are using hormonal contraception [listed], what is the impact of concomitant rheumatology medication use versus no rheumatology medication use on the risk of contraception failure?

Population: Women with RD using hormonal contraception

- Estrogen-progestin pill
- Estrogen-progestin patch
- Estrogen-progestin vaginal ring
- IUD with progestin
- Progestin pill
- Progestin implant
- DMPA
- Emergency contraception (morning after pill, mifepristone)

Intervention: Use of rheumatology medications

- Mycophenolate mofetil or mycophenolic acid
- Methotrexate
- Cyclophosphamide
- Leflunomide
- Tocilizumab
- Thalidomide
- Lenalidomide

Comparator:

- Similar women using the same form of birth control but not taking the above rheum meds

Outcome:

- Unintended pregnancy rate or contraception failure rate

2. Assisted Reproductive Technologies:

2A. In women with SLE who are undergoing assisted reproductive technology, what is the effect of ART/ovarian stimulation versus no ART/ovarian stimulation on maternal and pregnancy outcomes?

Population:

- Women with SLE who are undergoing ART/ovarian stimulation

Interventions:

- Ovulation induction agents (clomiphene, aromatase inhibitors, gonatotropin therapy)
- Assisted reproductive technologies: ovulation induction with in vitro fertilization/embryo transfer
- Multiple vs. single embryo transfer

Comparator:

- Similar patients who are not having ART (flare or damage of RD)

Outcomes:

- Flare of SLE (compare to SLE patients not having the procedure)
- Damage of SLE (including renal failure): compare to SLE patients not having the procedure
- Renal risks (compare multiple vs. single) embryo transfer
- Fetal outcomes, with healthy singleton pregnancy as ideal outcome (i.e., what is the risk to the fetus?)

2B. In women with RD [aPL variable], what is the impact of ART/ovarian stimulation, versus no ART/ovarian stimulation, on risk of maternal thrombosis?

Population: Women with RD who are undergoing assisted reproductive technology (ART)

- With aPL (any)
- With aPL (Sapporo laboratory criteria)
- With aPL (meet criteria for APS)

Interventions: Assisted reproductive technology to include

- Ovulation induction agents (clomiphene, aromatase inhibitors, gonatotropin therapy)
- Preparation for donor egg/embryo transfer (donor egg recipient)
- Assisted reproductive technologies:
    a. In vitro fertilization
    b. Oocyte donation

Comparator:

- Non-RD patients having ART
- Among RD patients undergoing ART (study pop) compare with and without aPL

Outcome:

- Thrombosis

2C. In women with RD who are undergoing assisted reproductive technology, what is the impact of stable/well-controlled disease activity [listed] versus active disease on maternal and pregnancy outcomes?

Population: Women with RD who are considering assisted reproductive technology (ART)

- Stable/well-controlled disease for <1 month on
  - no medication
  - low-dose prednisone
  - background medications c/w pregnancy
- Stable/well controlled disease for one-three months on
  - no medication
  - low-dose prednisone
  - background medications c/w pregnancy
- Stable/well controlled disease for 4-6 months on
  - no medication

- low-dose prednisone
- background medications c/w pregnancy

- Stable/well-controlled disease for at least 6 months on
  - no medication
  - low-dose prednisone
  - background medications c/w pregnancy

Interventions:

- Ovulation induction agents (clomiphene, aromatase inhibitors, gonatotropin therapy)
- Assisted reproductive technologies: ovulation induction with in vitro fertilization/embryo transfer

Comparator (varies with outcome):

- Similar patients with active disease

Outcomes:

- Success of procedure (likelihood of pregnancy)
- Fetal outcomes
- Flare of RD
- Damage of RD

2D. In women with RD who are aPL positive (any) without history of thrombosis who are undergoing assisted reproductive technology, what is the impact of anticoagulation [listed] versus no anticoagulation on maternal and pregnancy outcomes [listed]?

Population:

- Women with RD, aPL positive but no history of thrombosis and not on chronic anticoagulation, who are undergoing ovarian stimulation/assisted reproductive technology (ART)

Interventions**:**

- Low-dose aspirin 81 mg
- Prophylactic LMWH/UF
- Therapeutic LMWH/UF
- LDA +LMWH/UF

Comparator:

- Similar patients undergoing ART and not treated with anticoagulation

Outcomes:

- Thrombosis

2E. In women with RD who are undergoing assisted reproductive technology (ART), what is the impact of discontinuing or changing medications prior to ART if plan is for oocyte or embryo freezing without transfer, versus continuing medications, on maternal and procedure outcomes [listed]?

Population:

- Women with RD on rheumatic disease medications (define)

Intervention:

- Medication adjustment prior to intervention

Comparator:

- No medication adjustment prior to ART

Outcomes:

- Success of procedure (collectively and/or separately: no oocytes recovered, poor fertilization, no embryos)
- Blastocyst or embryo grade/aneuploidy
- Flare of RD
- Damage of RD

2F. In women with SLE who are undergoing assisted reproductive technology (ART), what is the impact of prophylactic prednisone, versus no prophylactic prednisone, on maternal and procedure outcomes?

Population:

- Women with SLE undergoing ART

Intervention:

- Prophylactic prednisone during ovarian stimulation

Comparator:

- No prophylactic prednisone during ovarian stimulation

Outcomes:

- Success of procedure (likelihood of pregnancy)
- Flare of SLE
- Damage of SLE

3. Fertility Preservation:

3A. In premenopausal women receiving CYC [variables listed], what is the impact of administration of a medication intended to preserve fertility [listed] versus no medication to preserve fertility on maternal outcomes?

Population: Any pre-menopausal woman with RD receiving CYC

- Monthly IV
- Euro-lupus
- Oral
- Ages:
  - Teen years
  - Women 20-29
  - Women 30-39
  - Women 40 and older

Intervention:

- GnRH analog (antagonist / agonist) co-therapy during cyclophosphamide
- Oral contraception co-therapy during cyclophosphamide.

Comparator:

- No hormonal co-therapy

Outcomes:

- Return of menstruation following cessation of CYC therapy
- Ability to conceive
- Premature ovarian insufficiency
- RD flare

3B. In a man with RD receiving CYC, what is the impact of administration of testosterone co-therapy versus no testosterone co-therapy on paternal fertility outcomes [listed]?

Population:

- Any man receiving CYC for RD interested in fathering a child in the future
    - Monthly IV
    - Euro-lupus
    - Oral

Intervention:

- Testosterone co-therapy during cyclophosphamide

Comparator:

- Similar patients without testosterone co-therapy

Outcomes:

- Sperm quality:
  - Sperm count following CYC therapy
  - Sperm motility
  - DNA fragmentation of chromatin
- Low testosterone level

3C. In a man with RD, what is the impact of receiving rheumatology medications [listed], versus no rheumatology medications, on paternal fertility outcomes?

Population:

- Any man receiving rheumatology medications for RD interested in fathering a child in the future

Intervention:

- MTX

- Sulfasalazine
- Leflunomide
- CYC
    - IV pulse
    - Eurolupus
    - Oral

Comparator:

- Similar patients not taking that medication

Outcomes:

- Sperm quality:
    - Sperm count
    - Sperm motility
    - DNA fragmentation of chromatin
- Low testosterone level

4. Counseling in Anticipation of Pregnancy:

4A. In women with RD taking mycophenolate mofetil (or mycophenolic acid) for maintenance of quiescent disease who wish to conceive, what is the impact of switching to alternative immunosuppressive agents [listed] prior to attempting conception versus continuing mycophenolate on maternal and pregnancy outcomes [listed]?

Population:

- Women with RD taking mycophenolate for maintenance of quiescent disease who wish to conceive

Intervention:

- Stop mycophenolate prior to pregnancy and start alternative agent including azathioprine, cyclosporin, tacrolimus, prior to pregnancy

Comparator:

- Stop mycophenolate prior to pregnancy without replacing it with alternative agent
- Continue mycophenolate through pregnancy

Outcomes:

- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease including preeclampsia
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Induced labor

- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal/neonatal effects: including immunosuppression, organ failure, adverse vaccine reactions in infant (e.g., BCG)
- Long-term offspring effects
- Flare of RD
- Damage from RD
- Maternal morbidity (including infection and thrombosis)
- Maternal mortality

4B. In women with RD taking a non-TNF-i biologic or new small molecule drug who wish to conceive, what is the impact of switching to a TNF-i or pregnancy compatible drug prior to conception versus not switching on maternal and pregnancy outcomes [listed]?

Population:

- Women with RD taking a non-TNF-i biologic or new small molecule drug who wish to conceive

Intervention:

- Stop the non-TNF-i biologic or small molecule and change to a TNF-i or pregnancy-compatible synthetic DMARD prior to conception

Comparator:

- Stop a non-TNF-I biologic or small molecule for pregnancy and don't replace it with another immunosuppressant
- Continue the initial medication

Outcome:

- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease, including preeclampsia
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal/neonatal effects, including immunosuppression, organ failure, adverse vaccine reactions in infant (e.g., BCG)
- Long-term offspring effects
- Flare of RD
- Damage from RD
- Maternal morbidity (including infection and thrombosis)
- Maternal mortality

4C. In women who have taken leflunomide within 2 years of wanting to conceive, what is the impact of checking drug level or administering washout [listed] versus not checking drug level or administering washout on maternal and pregnancy outcomes [listed]?

Population:

- Women with RD who have taken leflunomide within 2 years of wanting to conceive

Intervention:

- Check leflunomide blood level prior to conception
- Administer cholestyramine prior to conception if leflunomide level is over acceptable range

Comparator:

- Not checking leflunomide blood level prior to conception
- Not administering cholestyramine prior to conception

Outcome:

- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease, including preeclampsia
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal/neonatal effects, including immunosuppression, organ failure, adverse vaccine reactions in infant (e.g., BCG)
- Long-term offspring effects
- Flare of RD
- Damage from RD
- Maternal morbidity (including infection and thrombosis)
- Maternal mortality

4D. In women with RD on NSAIDS who plan to conceive, what is the impact of stopping the NSAID prior to attempting conception versus not stopping the NSAID on maternal and pregnancy outcomes?

Population:

- Women with RD who are trying to conceive and are on NSAIDs

Intervention:

- Stop NSAID prior to attempting pregnancy

Comparator:

- Continue NSAID until after conception has occurred

Outcome:

- Time to conception
- Spontaneous abortion

4E. In patients with RD [listed], what is the impact of having a RD diagnosis compared to not having a RD diagnosis on long-term outcomes in offspring [listed]?

Population:

- Women with RD with
    - SLE
    - RA
    - Other RD
    - APS
    - Anti-Ro/La
- Men with RD with

- SLE
- RA
- Other RD
- APS
- Anti-Ro/La

Intervention:

- Having a RD diagnosis

Comparator:

- Similar patients without these disease states

Outcomes:

- Risk of neurodevelopmental delays in offspring
- Risk of autoimmmune disease in offspring

4F. In women with RD on medication affecting folate metabolism [listed] before pregnancy, what is the impact of taking high-dose folic acid versus not taking high-dose folic acid on pregnancy outcome [listed]?

Population:

- Women with RD on medication [listed] prior to pregnancy

- MTX
- Sulfasalazine

Intervention:

- Addition of high-dose folic acid (pre-pregnancy and pregnancy)

Comparator:

- Women with RD on MTX or sulfasalazine before pregnancy not receiving high dose folic acid

Outcomes:

- MBD
- Spontaneous abortion
- Long term offspring outcomes (neurodevelopmental)

PREGNANCY CARE:

5. Pregnancy Management:

5A. In women with positive aPL [variables listed], does treating with certain medications during pregnancy [listed] versus not treating impact the maternal and pregnancy outcomes [listed]?

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Population:

- Women with positive aPL (aCL, ab2GPI or positive LAC)
  - Not meeting clinical or laboratory criteria for APS (low positive aCL or ab2GPI with negative LAC, or presence of non-standardized aPLs)
  - Not meeting criteria for OB/thrombotic-APS (revised Sapporo criteria)
  - Meeting criteria for OB-APS (revised Sapporo criteria)
  - Meeting criteria for OB-APS (revised Sapporo criteria) and having failed standard heparin + low-dose aspirin (Hep+LDA)
  - Meeting thrombotic APS criteria

Intervention:

- LDA during pregnancy (for women not meeting OB-APS criteria)
- Prophylactic Hep+LDA during pregnancy (for women meeting and not meeting OB-APS criteria)
- Hydroxychloroquine (with or without other treatments) (all groups)
- Prophylactic Hep+LDA with other agent (IVIG, prednisone) during pregnancy (for women meeting OB-APS criteria and failing standard Hep+LDA therapy)
- Full dose Hep+LDA (for thrombotic APS: group 5)

Comparator:

- No treatment during pregnancy (for intervention group A, low-dose aspirin)
- LDA treatment (for intervention group B)
- Prophylactic hep+LDA (for intervention groups D,E)
- No hydroxychloroquine (vs HCQ, Group C)

Outcomes:

- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease, including preeclampsia
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal/neonatal effects, including immunosuppression, organ failure, adverse vaccine reactions in infant (e.g., BCG)
- Long-term offspring effects
- Maternal morbidity (including infection and thrombosis)
- Maternal mortality
- Maternal thrombosis
- Maternal hemorrhage

5B. In women with RD who are considering pregnancy, what is the impact of having quiescent/low activity disease prior to pregnancy [listed] versus having active disease prior to pregnancy on maternal and pregnancy outcomes [listed]?

Population:

- Women with RD who are considering pregnancy

Interventions:

- Quiescent or stable low activity disease for one to three months
- Quiescent or stable low activity disease for six months
- Scleroderma: stable for 2 years

Comparator (varies with outcome):

- Similar patients with active disease

Outcomes:

- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease, including preeclampsia
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal/neonatal effects, including immunosuppression, organ failure, adverse vaccine reactions in infant (e.g., BCG)
- Long-term offspring effects
- Flare of RD
- Damage from RD
- Maternal morbidity (including infection and thrombosis)
- Maternal mortality

5C. In women with RD with currently active disease that would require immunosuppressive therapy in a non-pregnant state, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy [listed] versus no immunosuppressive therapy on maternal and pregnancy outcomes?

Population:

- Women with RD that is currently active and that would require immunosuppressive therapy in a non-pregnant state, including those with:

- Active SLE without nephritis
- SLE nephritis
- Myositis
- Scleroderma
- Inflammatory arthritis (RA, PsA, AS)

Intervention:

- Immunosuppressive therapy (such as sDMARD or bDMARD) compatible with pregnancy (as determined by the analysis in the medication section)

Comparator:

- No treatment for the active RD
- Prednisone in addition to compatible DMARD for the active RD
- Prednisone alone for the active RD

Outcomes:

- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease, including preeclampsia
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)

- Fetal/neonatal effects, including immunosuppression, organ failure, adverse vaccine reactions in infant (e.g., BCG)
- Long-term offspring effects
- Flare of RD
- Damage from RD
- Maternal morbidity (including infection and thrombosis)
- Maternal mortality

5D. In women who are pregnant with scleroderma renal crisis, what is the impact of treatment with ACE-inhibitor or ARB therapy versus similar women not treated with ACE-inhibitor and/or ARB therapy on maternal and pregnancy outcomes [listed]?

Population:
- Women with scleroderma in renal crisis

Intervention:
- Treatment with an ACE-inhibitor or ARB in pregnancy

Comparator:
- No treatment with an ACE-inhibitor or ARB in pregnancy

Outcomes:
- Infant renal function/structure
- Maternal renal function
- Pregnancy loss (spontaneous abortion, stillbirth)
- Maternal death

5E. In women with RD [listed] who are pregnant [variables listed], what is the impact of treatment with low-dose aspirin (LDA) versus no LDA on maternal and pregnancy outcomes?

Population:

- Women with RD who are considering pregnancy
  - Any woman with a RD and
    - Renal disease
    - Hypertension
    - aPL(+) but not meeting modified Sapporo APS criteria
  - SLE
  - Systemic sclerosis
  - RA and other inflammatory arthritis
  - Vasculitis
  - Myositis
  - Sjogren's

Intervention:

- Low-dose aspirin

Comparator:

- Similar patients who are not treated with low-dose aspirin

Outcomes:

- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease, including preeclampsia
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Damage from RD
- Maternal morbidity (including loss of renal function)
- Maternal mortality

5F. In women with SLE who are considering pregnancy or are pregnant [variables listed], what is the impact of treatment with HCQ throughout pregnancy versus no such treatment with HCQ on maternal and pregnancy outcomes [listed]?

Population:

- Women with SLE who are considering pregnancy or are pregnant
  - SLE without renal disease or aPL
  - SLE with renal disease
  - SLE with aPL

Intervention:

- HCQ

Comparator:

- Similar patients who are not treated with HCQ

Outcomes:

- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease, including preeclampsia
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal/neonatal effects, including immunosuppression, organ failure, adverse vaccine reactions in infant (e.g., BCG)
- Long-term offspring effects
- Flare of SLE
- Damage from SLE
- Maternal morbidity (including infection and thrombosis)
- Maternal mortality

5G. In women with SLE, Sjogren's syndrome, systemic sclerosis, or RA, what is the impact of checking autoantibodies [listed] prior to or early in pregnancy versus not checking these antibodies on maternal and pregnancy outcomes?

Population:

- Women with SLE, PSS, SS, or RA who are considering pregnancy or are pregnant

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Interventions:

- Checking autoantibodies
  - aPL (aCL IgG, IgM, antib2GPI IgG, IgM, LAC)
  - Anti-Ro/La

Comparator:

- Similar patients who do not have these autoantibodies checked

Outcomes:

- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease, including preeclampsia
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal/neonatal effects, including immunosuppression, organ failure, adverse vaccine reactions in infant (e.g., BCG)
- Long-term offspring effects
- Maternal thrombotic event (aPL)
- Maternal morbidity
- Maternal mortality
- Neonatal lupus (anti-Ro/La)

5H. In women with SLE, Sjogren's syndrome, systemic sclerosis, or RA, what is the impact of repeated checking of autoantibodies [listed] during pregnancy as compared to not rechecking these antibodies (i.e. checking only once before or early in pregnancy) on maternal and pregnancy outcomes?

Population:

- Women with SLE, Sjogren's syndrome, systemic sclerosis, or RA who are pregnant

Interventions:

- Re-checking autoantibodies (more than the one time preparing for or early in pregnancy)
  - aPL (aCL IgG, IgM; antib2GPI IgG, IgM; LAC)
  - Anti-Ro/La

Comparator:

- Similar patients who do not have these autoantibodies repeated.

Outcomes:

- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease, including preeclampsia
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal/neonatal effects: including immunosuppression, organ failure, adverse vaccine reactions in infant (e.g. BCG)

- Long-term offspring effects
- Maternal thrombotic event (aPL)
- Neonatal lupus (anti-Ro/La)
- Maternal mortality
- Maternal morbidity (including infection and thrombosis)

5I. In women with RD and serious disease-related damage [listed], what is the impact of pregnancy versus not undertaking or continuing pregnancy on maternal and pregnancy outcome?

Population:

- Women with RD and severe disease manifestations/complications including:
  - Severe hypertension, renal insufficiency or ESRD
  - Pulmonary disease to include pulmonary hypertension, "shrinking lung," interstitial fibrosis/restrictive lung disease
  - Cardiac disease to include severe cardiac valve disease (Libman-Sacks), cardiomyopathy, CAD
  - Diffuse brain disease (psychosis, dementia)
  - Osteonecrosis (hip)
  - Antiphospholipid syndrome with stroke or MI
  - Severe deformities of any joint, including cervical spine (especially C1-C2) and hips
  - Advanced skin disease that interferes with labor/delivery, vascular access, or nursing or childcare
  - Diffuse muscle weakness, including respiratory and swallowing
  - Vascular damage – including stenosis and aneurysm – from vasculitis (especially Takayasu's)
  - Severe neuropathies

Intervention:

- Pregnancy

Comparator:

- No pregnancy
- Pregnancy termination

Outcome:

- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease, including preeclampsia
- Preterm birth: preterm birth < 28 weeks, preterm birth ≥ 28 and < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal/neonatal effects, including immunosuppression, organ failure, adverse vaccine reactions in infant (e.g., BCG)
- Long-term offspring effects
- Flare of RD
- Damage from RD
- Maternal morbidity (including infection and thrombosis)
- Maternal death

5J. In women with RD [listed], what is the impact of management by a rheumatologist throughout pregnancy versus no rheumatology management on maternal and pregnancy outcomes [listed]?

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Population:

- Women with RD
  - SLE
  - Inflammatory arthritis
  - Systemic sclerosis
  - Vasculitis
  - UCTD

Intervention:

- Management by a rheumatologist (defined as "regular monitoring for rheumatic disease activity and rheumatic medication management during pregnancy")

Comparator:

- No management by a rheumatologist

Outcome:

- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease, including preeclampsia
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)

- Fetal/neonatal effects, including immunosuppression, organ failure, adverse vaccine reactions in infant (e.g., BCG)
- Long-term offspring effects
- Flare of RD
- Damage from RD
- Maternal morbidity (including infection and thrombosis)
- Maternal mortality

5K. In pregnant women with SLE, what is the impact of monitoring laboratory tests [listed] during pregnancy versus no laboratory test monitoring on maternal and pregnancy outcomes [listed]?

Population:
- Pregnant SLE patients

Intervention:
- Checking laboratory tests, including CBC and urine prot/creat ratio, at least every trimester

Comparator:
- SLE patients who are on any dose of prednisone or IS at the start of pregnancy who do not have these labs checks.

Outcomes:
- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease, including preeclampsia

- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal/neonatal effects, including immunosuppression, organ failure, adverse vaccine reactions in infant (e.g., BCG)
- Long-term offspring effects
- Flare of SLE
- Damage from SLE
- Maternal morbidity (including infection and thrombosis)
- Maternal mortality

5L. In women with SLE who are pregnant and develop laboratory or clinical evidence of SLE flare, what is the impact of new or increased treatment with prednisone or compatible immunosuppressive versus no treatment or no increased treatment on maternal and pregnancy outcomes [listed]?

Population:
- Pregnant SLE patients who have laboratory or clinical evidence of lupus flare

Intervention:
- Increase steroids or allowable immunosuppressive agents

Comparator:
- Pregnant SLE patients who do not receive increased medication

Outcomes:

- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease, including preeclampsia
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal/neonatal effects, including immunosuppression, organ failure, adverse vaccine reactions in infant (e.g., BCG)
- Long-term offspring effects
- Flare of SLE
- Damage from SLE
- Maternal morbidity (including infection and thrombosis)
- Maternal mortality

5M. In a woman with RD who is pregnant [listed], what is the impact of planned preterm delivery (< 37 weeks) due to rheumatic disease, regardless of obstetric parameters (i.e., regardless of NST results, fetal growth, active preeclampsia, etc.) versus no planned preterm delivery for RD reasons on maternal and pregnancy outcomes?

Population:

- Pregnant women with quiescent or stable mild RD activity
- Pregnant women with uncontrolled RD (active RD) and major internal organ inflammation or organ dysfunction (heart, lung, kidney, CNS)
- Women RD and a hip replacement(s)

Intervention:

- Induction of labor prior to term (< 37 weeks gestation)

Comparators:

- Induction of labor after 37 weeks gestation
- Spontaneous delivery after 37 weeks gestation

Outcomes:

- Pregnancy loss: stillbirth
- Gestational hypertensive disease, including preeclampsia
- Preterm birth: preterm birth ≥ 34 and < 37 weeks
- Small for gestational age infants (SGA)
- Fetal/neonatal effects, including immunosuppression, organ failure, adverse vaccine reactions in infant (e.g., BCG)
- Long-term offspring effects
- Flare of RD
- Damage from RD
- Maternal morbidity (including infection and thrombosis)
- Maternal mortality
- Cesarean section

6. Management of the Anti-Ro and/or La Positive Mother:

6A. In a pregnant woman with Ro/La antibodies [history variables listed], does fetal echo screening [intervals listed] versus no fetal echo screening impact offspring outcomes [listed]?

Population:

- Pregnant women with anti-Ro or Ro/La and
  - No history of an infant with CHB or NLE
  - History of an infant with CHB
  - History of an infant with other NLE

Intervention:

- Fetal echo screening at
  - Timing:
    - Weeks 20 and 24
    - 16/18 weeks to 26/28 weeks
  - Frequency
    - Weekly
    - Every 2 weeks

Comparator:

- No screening

Outcome:

- Complete heart block
- Fetal hydrops/other serious complications
- Fetal death or infant death
- Need for a pacemaker in childhood

6B. In a pregnant woman with Ro/La antibodies [history variables listed], what is the impact of taking HCQ throughout pregnancy versus not taking HCQ on offspring outcomes [listed]?

Population:

- Women with anti-Ro or Ro/La and
  - No history of an infant with CHB or NLE
  - History of an infant with CHB
  - History of an infant with other NLE

Intervention:

- Hydroxychloroquine for prevention of CHB

Comparator:

- No treatment with HCQ

Outcomes:

- Complete heart block
- Fetal hydrops/other serious complications
- Fetal death or infant death
- Need for a pacemaker in childhood
- Other neonatal lupus related findings

6C. In a pregnant woman with Ro/La antibodies with abnormal fetal ECHO [listed], what is the impact of taking fluorinated steroid versus no fluorinated steroid treatment on offspring outcomes [listed]?

Population:

- Women with anti-Ro or Ro/La and
  - Fetus with first-degree heart block on echo
  - Fetus with second-degree heart block on echo
  - Fetus with complete heart block on echo
  - Fetus with isolated endocardial fibroelastosis on echo

Intervention:

- Dexamethasone/betamethasone treatment (any dose or duration)

Comparator:

- No treatment with dexamethasone/betamethasone

Outcomes:

- Complete heart block
- Fetal hydrops/other serious complications
- Fetal death or infant death
- Need for a pacemaker in childhood

6D. In a pregnant woman with Ro/La antibodies with abnormal fetal ECHO [listed], what is the impact of IVIG therapy versus no IVIG therapy on offspring outcomes [listed]?

Population:

- Women with anti-Ro or Ro/La and
  - Fetus with first-degree heart block on echo
  - Fetus with second-degree heart block on echo
  - Fetus with CHB on echo
  - Fetus with isolated endocardial fibroelastosis on echo

Intervention:

- IVIG

Comparator:

- No treatment with IVIG

Outcomes:

- Complete heart block
- Fetal hydrops/other serious complications
- Fetal death or infant death
- Need for a pacemaker in childhood

7. Paternal Medication Exposure:

7A. In males with RD on medication who are planning to father a child, what is the impact of stopping medication [listed] prior to conception versus continuing medication on fertility issues and pregnancy outcome?

Population:

- Males with RD who are planning to father a child and who are on medication, including
  - Nonimmunosuppressive:
    - Classic NSAIDs
    - Cox2 inhibitors
    - Antimalarials
    - Sulfasalazine
    - Colchicine
    - Classic, or synthetic, immunosupressives:
      - Methotrexate
      - Leflunomide
      - Azathioprine/6-MP
      - Mycophenolate mofetil/mycophenolic acid
      - Cyclosporine
      - Tacrolimus
      - Cyclophosphamide

- Thalidomide/Lenalidomide
- Biologic immunosuppressives (TNF-inhibitors):
  - Infliximab
  - Etanercept
  - Adalimumab
  - Golimumab
  - Certolizumab
- Biologic immunosuppressives (Non-TNF biologics):
  - Anakinra
  - Rituximab
  - Belimumab
  - Abatacept
  - Tocilizumab
  - Secukinumab
  - Ustekinumab
- Novel small molecules:
  - Tofacitinib
  - Baracitinib
  - Apremilast
- Other:
  - IVIG
  - Anticoagulants:

- Warfarin
- DOACs (rivaroxaban, dabigatran, apixaban, edoxaban)
- Heparin/LMWH
- Other antiplatelet agents

Intervention:

- Stop medication prior to conception

Comparator:

- Continue chronic medication

Outcomes:

- MBD
- Spontaneous abortion
- Sperm quality (sperm count, morphology, motility)
- Time to conception
- Need for assisted reproductive technology (ART)
- Pregnancy
- RD flare
- RD damage

8. Medication Safety During Pregnancy:

8A. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing medications [listed] versus stopping medications before or during pregnancy on maternal and pregnancy outcomes [listed]?

Population:

- Women with RDs who are pregnant or planning pregnancy and on medication, including
    - Nonimmunosuppressive:
        - Classic NSAIDs
        - Cox2 inhibitors
        - Antimalarials
        - Sulfasalazine
        - Colchicine
    - Classic, or synthetic, immunosupressives:
        - Methotrexate
        - Leflunomide
        - Azathioprine/6-MP
        - Mycophenolate mofetil/mycophenolic acid
        - Cyclosporine
        - Tacrolimus
        - Cyclophosphamide
        - Thalidomide/Lenalidomide
    - Biologic immunosuppressives (TNF-inhibitors):
        - Infliximab
        - Etanercept

- Adalimumab
- Golimumab
- Certolizumab

- Biologic immunosuppressives (Non-TNF biologics):
  - Anakinra
  - Rituximab
  - Belimumab
  - Abatacept
  - Tocilizumab
  - Secukinumab
  - Ustekinumab
- Novel small molecules:
  - Tofacitinib
  - Baracitinib
  - Apremilast
- Other:
  - IVIG
  - Anticoagulants:
    - Warfarin
    - DOACs (rivaroxaban, dabigatran, apixaban, edoxaban)
    - Heparin/LMWH
    - Other antiplatelet agents

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Interventions (vary with drug):

- Stop in pre-conception planning phase
- Stop when pregnancy suspected/confirmed
- Continue medication throughout pregnancy (T1, T2, T3)
- Continue medication throughout first trimester only (for TNF-i and NSAIDs only)
- Continue medication through to end of second trimester (for TNF-i and NSAIDs only)

Comparator:

- Not using the medication before pregnancy
- Not using the drug during pregnancy (stopping drug prior to pregnancy)
- Not using drug during the relevant trimesters

Outcomes:

- Pregnancy loss, including spontaneous abortion and stillbirth
- MBD
- Gestational hypertensive disease, including preeclampsia
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal/neonatal effects, including immunosuppression, organ failure, adverse vaccine reactions in infant (e.g., BCG), and efficacy of vaccines in neonates
- Long-term offspring effects, including neurodevelopmental and autoimmune disease)
- Flare of RD
- Damage from RD

- Maternal morbidity (including infection and thrombosis)

9. Corticosteroids in Pregnancy:

9A. In women with RD and variable disease activity [listed], what is the impact of taking prednisone or other non-fluorinated steroid [listed] versus not taking any corticosteroid on maternal and fetal outcomes [listed]?

Population:

- Pregnant women with RD and
  - No current RD activity but on steroid (unable to taper off steroids)
  - Mild to moderate RD activity on steroid
  - Severe RD activity, including internal-organ inflammation from a systemic rheumatic disease (i.e., SLE, vasculitis, etc.)

Intervention:

- Prednisone or equivalent non-fluorinated steroid at dose of:
  - < 7.5mg a day (low dose)
  - 7.5mg to 20mg a day (moderate dose)
  - > 20mg a day (high dose)
  - IV pulse steroids (methylprednisolone) or IM steroid

Comparator:

- No prednisone treatment
- On other DMARDs/biologics compatible with pregnancy

Outcomes:

- Pregnancy loss, including spontaneous abortion and stillbirth
- MBD
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Premature rupture of membranes
- Small for gestational age infants
- Gestational hypertensive disease, including preeclampsia
- Gestational diabetes
- Fetal/neonatal effects, including immunosuppression, organ failure, adverse vaccine reactions in infant (e.g., BCG)
- Long-term offspring effects, including neurodevelopmental and autoimmune disease)
- Maternal morbidity, including infection during pregnancy and adrenal insufficiency
- Maternal mortality
- RD flare

9B. In women with RD on chronic prednisone (or non-fluorinated steroid equivalent) greater than 7.5 mg daily for greater than 6 months before pregnancy, what is the impact of tapering off steroid when pregnancy is diagnosed versus continuing on the same dose on maternal and fetal outcomes [listed]?

Population:

- Women with RD on chronic prednisone or non-fluorinated steroid equivalent greater than 7.5 mg daily for greater than one year

Intervention:

- Tapering down to average daily dose of ≤ 7.5mg steroid when pregnancy diagnosed
- Tapering off steroid

Comparator:

- Continue stable steroid dose (> 7.5mg)

Outcome:

- Pregnancy loss, including spontaneous abortion and stillbirth
- MBD
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Premature rupture of membranes
- Small for gestational age infants
- Gestational hypertensive disease, including preeclampsia
- Gestational diabetes
- Long-term outcomes, including growth and development
- Maternal morbidity, including infection during pregnancy and adrenal insufficiency
- Maternal mortality
- RD flare
- RD damage

9C. In women with RD on chronic steroid (or non-fluorinated steroid equivalent) greater than 7.5 mg daily for greater than 6 months prior to delivery, what is the impact of administration of stress-dose steroid at the time of delivery [listed] versus no stress-dose steroid on maternal and fetal outcomes [listed]?

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Population:

- Women with RD on chronic steroid (or non-fluorinated steroid equivalent) greater than 7.5 mg daily for greater than 6 months and delivering by any mode of delivery

Intervention:

- Stress-dose steroid at the time of delivery

Comparator:

- No stress-dose steroid

Outcome:

- Pregnancy loss, including stillbirth
- MBD
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Premature rupture of membranes
- Small for gestational age infants
- Gestational hypertensive disease, including preeclampsia
- Gestational diabetes
- Long-term outcomes, including growth and development
- Maternal morbidity, including infection and adrenal insufficiency
- Maternal mortality
- RD flare
- RD damage

POST-PREGNANCY CARE

10. Lactation and Medications:

10A. In women with RD who are considering breastfeeding, what is the impact of taking medication [listed] during breastfeeding versus not taking medication on drug levels and neonatal outcomes [listed]?

Population:

- Women with RD who are lactating and considering breastfeeding

Intervention:

- Continuing/starting medication while breastfeeding, including
    - Nonimmunosuppressive:
        - Classic NSAIDs
        - Cox2 inhibitors
        - Antimalarials
        - Sulfasalazine
        - Colchicine
    - Classic, or synthetic, immunosupressives:
        - Methotrexate
        - Leflunomide
        - Azathioprine/6-MP

- Mycophenolate mofetil/mycophenolic acid
- Cyclosporine
- Tacrolimus
- Cyclophosphamide
- Thalidomide/Lenalidomide

- Biologic immunosuppressives (TNF-inhibitors):
  - Infliximab
  - Etanercept
  - Adalimumab
  - Golimumab
  - Certolizumab
- Biologic immunosuppressives (Non-TNF biologics):
  - Anakinra
  - Rituximab
  - Belimumab
  - Abatacept
  - Tocilizumab
  - Secukinumab
  - Ustekinumab
- Novel small molecules:
  - Tofacitinib
  - Baracitinib

- Apremilast
- Other:
  - IVIG
  - Anticoagulants:
    - Warfarin
    - DOACs (rivaroxaban, dabigatran, apixaban, edoxaban)
    - Heparin/LMWH
    - Other antiplatelet agents

Comparator:

- Not taking medication while breastfeeding
- Not breastfeeding

Outcomes:

- Transmission to breast milk
- Transmission to infant (serum levels)
- Clinical side effects in offspring:
  - Neonatal/infancy, including hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
  - Long-term effects, including growth and development

11. Menopause:

11A. In postmenopausal women with SLE, what is the impact of HRT versus no HRT on risk of SLE flare?

Population:

- Post-menopausal women with SLE

Intervention:

- Use of oral postmenopausal hormone therapy, including estrogen or estrogen/progestin
- Use of estrogen/progestin patch

Comparison:

- Similar patients not using postmenopausal hormone therapy

Outcome:

- SLE flare

11B. In postmenopausal women with RD and aPL [variables listed] who experience menopausal symptoms, what is the impact of HRT versus no HRT on thrombosis risk?

Population:

- Postmenopausal women with RD and positive aPL
  - With positive aPL and no history of thrombosis
  - With thrombotic APS on long-term anticoagulation

Intervention:

- Oral postmenopausal hormone therapy, including estrogen or estrogen/progestin
- Estrogen/progestin patch

Comparison:

- Similar patients not using postmenopausal hormone therapy

Outcome:

- Thrombosis

12. Long-Term Issues:

12A. In women with OB APS (revised Sapporo criteria), what is the impact of long-term, low-dose aspirin after pregnancy versus no long-term, low-dose aspirin on the risk of thrombosis?

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Population:

- Women with positive aPL who meet criteria of OB-APS but do not have a history of thrombosis

Intervention:

- Low-dose aspirin long-term

Comparator:

- No treatment with long-term, low-dose aspirin

Outcome:

- Risk of thrombosis

APPENDIX B – Participant Disclosures

In order for the College to most effectively further its mission and to otherwise maintain its excellent reputation in the medical community and with the public, it is important that confidence in the College's integrity be maintained. The cornerstone of the ACR's Disclosure Policy is disclosure of actual and potential conflicts so that they can be evaluated by the College in order to avoid undue influence of potential conflicts. The purpose of the ACR's Disclosure Policy is identification of relationships which may pose actual or potential conflicts. These actual or potential conflicts can then be evaluated by the College so that adjustments can be made that will avoid any undue influence. This policy is based on the principle that, in many cases, full disclosure of the actual or potentially conflicting relationship will of itself suffice to protect the integrity of the College and its interests.

Participants	Role	Primary employer	Sources of personal income	Research grants/contracts	Investments to include medical industry and nonmedical industry	Organizational benefit	Activities with other organizations	Family or other relations
Lisa Sammaritano	Core Team/PI	Hospital for Special Surgery	N/A	Robin Sillau; Memorial Research Fund for Connective Tissue Disease	N/A	N/A	Uptodate	N/A
Michael Lockshin	Core Team	Hospital for Special Surgery	Raynes-Mcarty; O'Brien & Ryan	N/A	N/A	Barbara Volken Center	N/A	N/A
Wendy Marder	Core Team	University of Michigan	N/A	NIH/NIAMS; Center for Disease Control	N/A	N/A	N/A	N/A
Gordon Guyatt	Core Team/GRADE Expert	McMaster University	N/A	N/A	N/A	N/A	N/A	N/A
Kristen D'Anci, PhD	Core Team/methodologic lit review lead	ECRI	N/A	N/A	N/A	N/A	N/A	N/A
Eliza Chakravarty	Core Team/rheumatology clinical lit review lead	Oklahoma Medical Research Foundation	American Board of Internal Medicine; NIH	UCB	N/A	N/A	American Board of Internal Medicine	N/A
Bonnie Bermas	CoreTeam/content expert	University of Texas Southwestern	UptoDate; UCB	N/A	N/A	N/A	N/A	N/A
Christina Chambers	CoreTeam/content expert	University of California, San Diego	Birth Defects Research Part A	NIH/NIAAA; NIH/HIGM/IHC; NIH/NIMH; NIH/NIEHS; Hoffman La Roche; NIH/NCATS; Genzyme(Sanofi-Aventis); UCB Pharma, Inc.; Janssen Biotech Inc.; CA Department of Health; Pfizer; AAAAI; Celgene; Takeda; GlaxoSmithKline LLC..; Sanofi; Amgen; Gerber Foundation	N/A	N/A	N/A	N/A
Megan E. B. Clowse	CoreTeam/content expert	Duke University	UCB; BMS	AHRQ; Janssen; Pfizer; PCORI; UCB	N/A	UCB; Pfizer; BMS; Abbvie; NIAMS	N/A	N/A
Elizabeth Perkins	ACR Board of Directors Liaison	Rheumatology Care Center, LLC	Lilly USA; Amgen; MEDAC	N/A	N/A	N/A	N/A	N/A
Adegbenga Bankole	Expert Panel	Carilion Clinic	N/A	Amgen; Human Genome Sciences	N/A	N/A	N/A	N/A
Karen Costenbader	Expert Panel	Brigham and Women's Hospital	GSK; Merck; ACR; Astra Zeneca; UptoDate; J. Clinical Practice	NIH; Merck	Alkermes; Cel-sci corp.; Generex	N/A	N/A	N/A
Lisa Christopher-Stine MD, MPH	Expert Panel	Johns Hopkins University	Mallinchrodt; Optioncare; Octoapharma; MedImmune; Genesis Health; Inova Diagnostics	NIH/NHLBI	N/A	N/A	N/A	N/A
Michael Weisman	Expert Panel	Cedar-Sinai Medical Center	Thorpe & Howell; UCB; Iduis Pharm; Ampel Biosolutions, LLC; Paul Hastings; GSK; Novartis; Snow, Christensen; Martineau	Human Gemome Sciences; UCB Biosciences, Inc.; Eli Lilly; Genentech; DOD/Immunomedics	N/A	N/A	N/A	N/A
Teresa Aberle	Expert Panel	Oklahoma Medical Research Foundation	N/A	Pfizer; GSK; BMS; Merck; Roche; Novartis; Neovac; Eli Lily; Nichi-Iko	N/A	N/A	N/A	N/A
Amanda Eudy	Lit Review Team	Duke University Medical Center	GlaxoSmithKline	N/A	N/A	N/A	N/A	N/A
Amit Aakash Shah	Lit Review Team	ACR	N/A	N/A	N/A	N/A	N/A	N/A
Arundathi Jayatilleke	Lit Review Team	Drexel University	ACR CARE Writer	Quintiles-GSK	N/A	N/A	N/A	N/A
Marat Turgunbaev	Lit Review Team	ACR	N/A	N/A	N/A	N/A	N/A	N/A
Nancy Sullivan	Lit Review Team	ECRI	N/A	N/A	N/A	N/A	N/A	N/A
Laura Tarter	Lit Review Team	Brigham and Women	N/A	N/A	N/A	N/A	N/A	N/A
Arthur Kavanaugh	Voting Panel	UCSD Medical; VA San Diego	AbbVie; Celegene; Pfizer; UCB; Janssen; Novartis; Gilead; BMS	NIH	N/A	N/A	N/A	N/A
Carl Laskin	Voting Panel	Self-employed	AbbVie; GSK; UCB	NIH	N/A	N/A	N/A	N/A
D. Ware Branch	Voting Panel	University of Utah; Intermountain Health	UCB Pharm.	UCB; NIAMS	N/A	N/A	N/A	N/A
Emily Somers	Voting Panel	University of Michigan	N/A	CDC; NIH	N/A	N/A	N/A	N/A
Evelyne Vinet	Voting Panel	McGill University Healthcare; Research Institute of the McGill University Healthcare Centre	N/A	CIHR; CIORA	N/A	McGill Univ. Dept of Medicine; FROS grant	Pregnancy working group for the Canadian recommendations for SLE monitoring	N/A
Jane Salmon	Voting Panel	Hospital for Special Surgery	Medical malpractice; Exagen; Academic institutions and societies; BMS; UCB	NIH, Bayer Healthcare; UCB	BMS; Biogen Idec, Johnson and Johnson/same for Express Scripts; Regeneron; Merck	N/A	Alliance for Lupus Research; Kunkel Society; Lupus Science and Medicine; Annals of Rheumatic Disease	N/A
Jill Buyon	Voting Panel	NYU School of Medicine	Lupus Science and Medicine; BMS; Gerson Lehrman Group; Eisai Inc.	NIH/NIAMS; Donor Funds; Colton Foundation; NIH/Office of the Director; eXagen Diagnostics; NIH/NICHD	N/A	N/A	N/A	N/A
Jinoos Yazdany	Voting Panel	UCSF	N/A	AHRQ; CDC; NIAMS; Pfizer	N/A	N/A	N/A	N/A
John Cush	Voting Panel	Baylor Research Institute	Pfizer; Janssen; Abbvie; Novartis; Celgene; Astra-Zeneca; Genentech; UCB; BMS; Lilly; Horizon; Amgen; Roche	N/A	N/A	N/A	N/A	N/A

Julia Simard	Voting Panel	Stanford University	Brown School of Public Health	NIH/NIAMS;Karolinska SFO subcontract; NIH/NIA	N/A	N/A	Arthritis Care & Research	N/A
Lauren A. Plante	Voting Panel	Drexel University College of Medicine	Cambridge University Press; Texas Tech University El Paso	NICHD	N/A	N/A	American College of Obstetricians & Gynecologists; Society of Maternal-Fetal Medicine	N/A
Maurice Druzin	Voting Panel	Stanford Medicine	N/A	Emory	N/A	N/A	N/A	N/A
Medha Barbhaiya	Voting Panel	Brigham and Women's Hospital	N/A	Rheumatology Research Foundation; Brighman & Women's Hospital	N/A	N/A	N/A	N/A
Sara Tedeschi	Voting Panel	Brigham and Women's Hospital	N/A	Lupus Foundation of America	N/A	N/A	Arthritis Care & Research	N/A
Virginia Steen	Voting Panel	Georgetown University Medical Center	Gilead; Bayer; Reata; Universities Groundround lectures	N/A	N/A	N/A	N/A	N/A
C. Whitney White **Patient rep**	Voting Panel/Patient Rep	Sanford University	Abbvie; Pfizer	N/A	N/A	N/A	AL Society of Health System Pharmacists	N/A
Rachelle Crow-Hercher **Patient rep**	Voting Panel/Patient Rep	Umemployed	N/A	PCORI	N/A	N/A	N/A	N/A