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

Project Plan – November 2017

PARTICIPANTS

Core Oversight Team

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1 **ORGANIZATIONAL LEADERSHIP AND SUPPORT**

2

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

6

7 **BACKGROUND**

8

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

14

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

24

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



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

42
43 Pregnancy, while perhaps the best-studied reproductive issue, remains an area of uncertainty for many
44 rheumatologists and patients. Adverse pregnancy outcomes, including pregnancy loss, preterm delivery,
45 and small-for-gestational-age infants, are more common in patients with certain rheumatic disorders.
46 Hypertensive disorders of pregnancy, including preeclampsia, are also more common. A balance
47 between maintaining adequate disease control and ensuring safety for the fetus can be difficult to
48 achieve. Factors that may limit the rheumatologist’s ability to counsel and manage patients include lack
49 of clinical trial data in pregnancy, limited understanding of drug metabolism, transfer, and risks of
50 teratogenicity of medications during pregnancy, and difficulty assessing the impact of poorly controlled
51 disease on pregnancy outcome.

52
53 Although benefits of breastfeeding are well established, those benefits must be balanced against the
54 potential impact of rheumatic disease medications in women who are lactating. Breastfeeding while
55 receiving therapy ultimately is determined by individual choice, but patients require up-to-date
56 information in order to weigh the potential risk of a medication used to control disease during lactation
57 versus the benefits of breastfeeding. Data in this area, although limited, are evolving, especially in the
58 case of certain commonly used medications such as TNF-inhibitors.

59
60 In recent years, short- and long-term issues for offspring of rheumatic disease patients, including
61 concerns of neonatal infection risk related to immunosuppressive exposure and longer-term issues
62 related to developmental delays (whether related to maternal disease, presence of maternal
63 autoantibody, or antepartum medication use) has become of greater concern.

64
65 Safety of hormone replacement therapy for severe vasomotor symptoms and prevention of bone loss in
66 menopausal rheumatic disease patients is a final and important reproductive health question.

67
68 **OBJECTIVES**

69
70 The objective of this project is to develop recommendations related to the management of reproductive
71 health issues for rheumatic disease patients. Specifically, we aim to focus on the following areas:

72
73
74



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- 75 **1. Pre-pregnancy:**
76 a. Contraception safety and efficacy
77 b. Fertility preservation in the setting of cyclophosphamide therapy
78 c. Assisted reproductive technology safety and management
79 d. Counseling in anticipation of pregnancy
80 **2. Pregnancy:**
81 a. Pregnancy management including management of antiphospholipid antibody-positive
82 patients
83 b. Management and monitoring of the anti-Ro/La+ mother
84 c. Safety of paternal medication exposure
85 d. Medication safety during pregnancy
86 e. Corticosteroid safety in pregnancy
87 **3. Post-pregnancy:**
88 a. Medication safety during lactation
89 b. Long-term issues in the offspring
90 c. Menopause and use of hormone replacement therapy

91

92 **METHODS**

93

94 *Identification of Studies*

95

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

102

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

107

108 *Search Limits*

109

110 Only English language articles will be retrieved.

111



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112 *Grey Literature*

113

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

116

117 *Literature Search Update*

118

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

120

121 *Inclusion/Exclusion Criteria*

122

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

125

126 *Management of Studies and Data*

127

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

135

136 *Phases*

137

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

147

148 |



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149 *GRADE Methodology*

150

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

158

159 *Analysis and Synthesis*

160

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

168

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

174

175 *Development of Recommendation Statements*

176

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



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

191

192 **PLANNED APPENDICES (AT MINIMUM)**

193

194 A. Final literature search strategies

195 B. GRADE evidence profiles and summary of findings tables for each PICO question

196

197 **AUTHORSHIP**

198

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

205

206 **DISCLOSURES/CONFLICTS OF INTEREST**

207

208 The ACR’s disclosure and COI policies for guideline development will be followed for this project. These
209 can be found in the ACR Guideline Manual on [this page of the ACR web site](#), under Policies &
210 Procedures. *See Appendix B for participant disclosures.*

211

212 **REFERENCES**

213

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

231

232 **Outline:**

233

234 **Pre-pregnancy:**

235 1. Contraception

236 2. Fertility preservation

237 3. Assisted reproductive technology

238 4. Counseling in anticipation of pregnancy

239

240 **Pregnancy:**

241 5. Pregnancy management issues (includes aPL)

242 6. Management of the anti-Ro/La+ mother

251

252 **Definitions:**

253

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

256

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

259

243 7. Safety of paternal medication exposure

244 8. Medication safety during pregnancy

245 9. Corticosteroid safety in pregnancy

246

247 **Post-pregnancy:**

248 10. Medication safety during lactation

249 11. Menopause/HRT

250 12. Long-term issues



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260 **Maternal (or paternal) outcomes:**

261

262 **Quiescent or stable with low activity:**

263 Limited RD activity including those patients on pregnancy-compatible medications and/or <7.5mg/day prednisone

264

265 **Active disease and/or RD flare:**

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

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

272

273 **RD damage:**

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

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



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

287

288 **Organ failure**

289 **Maternal morbidity:** infection during pregnancy, adrenal insufficiency, thrombosis

290 **Maternal death**

291

292 **Pregnancy outcomes:**

293 Pregnancy loss

294 Spontaneous abortion

295 Stillbirth

296 Gestational hypertensive disease including preeclampsia

297 Preterm birth: preterm birth <34 weeks, preterm birth ≥34 and <37 weeks

298 Induced labor

299 Premature rupture of membranes

300 Small for gestational age infants (SGA)

301 Cesarean section rate



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302

303 **Infant/neonatal outcomes:**

304 Major birth defects (MBD): Structural anomaly with medical or cosmetic significance, present at or before birth

305 Preterm birth (above)

306 SGA (above)

307 Immunosuppression

308 Organ failure

309 Adverse vaccine reactions and insufficient vaccine response

310 Neonatal death

311

312 **Long-term offspring outcomes:**

313 Neurocognitive effects

314 Autoimmune disease

315

316 **Medications:**

317 **Pregnancy-compatible DMARD:**

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

319

320 **Immunosuppressive medications:**

321 ○ Classic, or synthetic, immunosuppressives:

322 ○ Methotrexate

323 ○ Leflunomide



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- 324 ○ Azathioprine/6-MP
- 325 ○ Mycophenolate mofetil/mycophenolic acid
- 326 ○ Cyclosporine
- 327 ○ Tacrolimus
- 328 ○ Cyclophosphamide
- 329 ○ Thalidomide/Lenalidomide
- 330 ○ Biologic immunosuppressives – TNF-inhibitors:
 - 331 ○ Infliximab
 - 332 ○ Etanercept
 - 333 ○ Adalimumab
 - 334 ○ Golimumab
 - 335 ○ Certolizumab
- 336 ○ Biologic immunosuppressives – Non-TNF biologics:
 - 337 ○ Anakinra
 - 338 ○ Rituximab
 - 339 ○ Belimumab
 - 340 ○ Abatacept
 - 341 ○ Tocilizumab
 - 342 ○ Secukinumab
 - 343 ○ Ustekinumab
- 344 ○ Novel small molecules:
 - 345 ○ Tofacitinib



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- 346 ○ Baracitinib
347 ○ Apremilast

348

349 **Antiphospholipid antibodies (aPL):**

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

351 **APS laboratory criteria:** modified Sapporo criteria

352 **APS:** modified Sapporo criteria

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

354

355



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356 **PICO QUESTIONS**

357

358 **PRE-PREGNANCY CARE:**

359

360 **1. Contraception:**

361 ***1A. In women with RD who are of childbearing age [variables listed], what is the impact of hormonal contraception use [variables***
362 ***listed] versus no hormonal contraception use on risk of thrombosis?***

363

364 **Populations:** Women with RD at risk for pregnancy

365 • RD without aPL (aCL, ab2GPI, LAC)

366 • SLE without aPL

367 • RD with aPL but no APS

368 • RD with APS (history of thrombosis or obstetrical
369 complication)

370 • Primary APS

371

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

373 • Estrogen-progestin pill

374 • Estrogen-progestin patch

375 • Estrogen-progestin vaginal ring

376 • IUD with progestin

377 • Progestin pill

378 • Progestin implant

379 • Depot medroxyprogesterone acetate (DMPA)

380 • Emergency contraception (morning after pill,

381 mifepristone)

382

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



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- 384 • Male contraception/sterilization
385 • Copper IUD
386 • Not sexually active/abstinence

- 387 • Barrier contraception
388 • Tubal ligation/hysterectomy

389

390 Outcome:

- 391 • Thrombosis

392

393 ***1B. In women of childbearing age with SLE and RA, what is the impact of hormonal contraception use versus no hormonal***
394 ***contraception use on risk of disease flare?***

395

396 Populations: Women with SLE and RA at risk for pregnancy

- 397 • SLE
398 • RA

399

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

- | | |
|---------------------------------------|--|
| 401 • Estrogen-progestin pill | 406 • Progestin implant |
| 402 • Estrogen-progestin patch | 407 • DMPA |
| 403 • Estrogen-progestin vaginal ring | 408 • Emergency contraception (morning after pill, |
| 404 • IUD with progestin | 409 mifepristone) |
| 405 • Progestin pill | |

410



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

- 412 • Male contraception/sterilization
- 413 • Copper IUD
- 414 • Not sexually active/abstinence
- 415 • Barrier contraception
- 416 • Tubal ligation/hysterectomy

417

418 Outcomes:

- 419 • RA flare (for RA)
- 420 • SLE flare excluding nephritis (for SLE)
- 421 • Lupus nephritis flare (for SLE)

422

423 ***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***
424 ***infection?***

425

426 Populations: Women with RD at risk for pregnancy

- 427 • On immunosuppressive medications
- 428 • Not on immunosuppressive medications

429

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

- 431 • IUD with copper
 - 432 ○ With or without prophylactic antibiotics at insertion
- 433 • IUD with progestin
 - 434 ○ With or without prophylactic antibiotics at insertion



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435

436 Comparator:

- 437 • Similar patients not using an IUD

438

439 Outcome:

- 440 • Infection (pelvic inflammatory disease)

441

442 ***1D. In RD patients of childbearing age [variables listed], what is the impact of having a sterilization procedure, versus non-RD***
443 ***patients, on likelihood of infection and thrombosis?***

444

445 Populations: Patients with RD at risk for pregnancy

- 446 • Women

447 ○ On immunosuppressive medications

448 ○ Not on immunosuppressive medications

- 449 • Men

450 ○ On immunosuppressive medications

451 ○ Not on immunosuppressive medications

452

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

- 454 • Tubal ligation (women)

- 455 • Vasectomy (men)



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479 Outcomes:

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

482

483 ***1F. In women with RD of childbearing age who are using hormonal contraception [listed], what is the impact of concomitant***
484 ***rheumatology medication use versus no rheumatology medication use on the risk of contraception failure?***

485

486 Population: Women with RD using hormonal contraception

- | | |
|---------------------------------------|--|
| 487 • Estrogen-progestin pill | 492 • Progestin implant |
| 488 • Estrogen-progestin patch | 493 • DMPA |
| 489 • Estrogen-progestin vaginal ring | 494 • Emergency contraception (morning after pill, |
| 490 • IUD with progestin | 495 mifepristone) |
| 491 • Progestin pill | |

496

497 Intervention: Use of rheumatology medications

- | | |
|--|--------------------|
| 498 • Mycophenolate mofetil or mycophenolic acid | 502 • Tocilizumab |
| 499 • Methotrexate | 503 • Thalidomide |
| 500 • Cyclophosphamide | 504 • Lenalidomide |
| 501 • Leflunomide | |

505

506



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507 Comparator:

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

509

510 Outcome:

- 511 • Unintended pregnancy rate or contraception failure rate

512

513 **2. Assisted Reproductive Technologies:**

514

515 ***2A. In women with SLE who are undergoing assisted reproductive technology, what is the effect of ART/ovarian stimulation versus***
516 ***no ART/ovarian stimulation on maternal and pregnancy outcomes?***

517

518 Population:

- 519 • Women with SLE who are undergoing ART/ovarian stimulation

520

521 Interventions:

- 522 • Ovulation induction agents (clomiphene, aromatase
523 inhibitors, gonatotropin therapy)

- 524 • Assisted reproductive technologies: ovulation induction
525 with in vitro fertilization/embryo transfer

- 526 • Multiple vs. single embryo transfer

527

528 Comparator:

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



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555 Comparator:

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

558

559 Outcome:

- 560 • Thrombosis

561

562 ***2C. In women with RD who are undergoing assisted reproductive technology, what is the impact of stable/well-controlled disease***
563 ***activity [listed] versus active disease on maternal and pregnancy outcomes?***

564

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

- 566 • Stable/well-controlled disease for <1 month on
567 ○ no medication
568 ○ low-dose prednisone
569 ○ background medications c/w pregnancy
570 • Stable/well controlled disease for one-three months on
571 ○ no medication
572 ○ low-dose prednisone
573 ○ background medications c/w pregnancy
574 • Stable/well controlled disease for 4-6 months on
575 ○ no medication



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- 576 ○ low-dose prednisone
- 577 ○ background medications c/w pregnancy
- 578 ● Stable/well-controlled disease for at least 6 months on
- 579 ○ no medication
- 580 ○ low-dose prednisone
- 581 ○ background medications c/w pregnancy

- 582
- 583 Interventions:
- 584 ● Ovulation induction agents (clomiphene, aromatase inhibitors, gonatotropin therapy)
 - 585 ● Assisted reproductive technologies: ovulation induction with in vitro fertilization/embryo transfer

- 586
- 587 Comparator (varies with outcome):
- 588 ● Similar patients with active disease

- 589
- 590 Outcomes:
- | | |
|--|--------------------|
| 591 ● Success of procedure (likelihood of pregnancy) | 593 ● Flare of RD |
| 592 ● Fetal outcomes | 594 ● Damage of RD |

595

596 ***2D. In women with RD who are aPL positive (any) without history of thrombosis who are undergoing assisted reproductive***

597 ***technology, what is the impact of anticoagulation [listed] versus no anticoagulation on maternal and pregnancy outcomes***

598 ***[listed]?***



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599

600 Population:

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

603

604 Interventions:

- 605 • Low-dose aspirin 81 mg
606 • Prophylactic LMWH/UF
607 • Therapeutic LMWH/UF
608 • LDA +LMWH/UF

609

610 Comparator:

- 611 • Similar patients undergoing ART and not treated with anticoagulation

612

613 Outcomes:

- 614 • Thrombosis

615

616 ***2E. In women with RD who are undergoing assisted reproductive technology (ART), what is the impact of discontinuing or***
617 ***changing medications prior to ART if plan is for oocyte or embryo freezing without transfer, versus continuing medications, on***
618 ***maternal and procedure outcomes [listed]?***

619

620 Population:

- 621 • Women with RD on rheumatic disease medications (define)



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622

623 Intervention:

- 624 • Medication adjustment prior to intervention

625

626 Comparator:

- 627 • No medication adjustment prior to ART

628

629 Outcomes:

- 630 • Success of procedure (collectively and/or separately: no

631 oocytes recovered, poor fertilization, no embryos)

- 632 • Blastocyst or embryo grade/aneuploidy

- 633 • Flare of RD

634 • Damage of RD

635

636 ***2F. In women with SLE who are undergoing assisted reproductive technology (ART), what is the impact of prophylactic prednisone,***
637 ***versus no prophylactic prednisone, on maternal and procedure outcomes?***

638

639 Population:

- 640 • Women with SLE undergoing ART

641

642 Intervention:

- 643 • Prophylactic prednisone during ovarian stimulation

644



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645 Comparator:

- 646 • No prophylactic prednisone during ovarian stimulation

647

648 Outcomes:

- 649 • Success of procedure (likelihood of pregnancy)

- 651 • Damage of SLE

- 650 • Flare of SLE

652

653 **3. Fertility Preservation:**

654

655 ***3A. In premenopausal women receiving CYC [variables listed], what is the impact of administration of a medication intended to***
656 ***preserve fertility [listed] versus no medication to preserve fertility on maternal outcomes?***

657

658 Population: Any pre-menopausal woman with RD receiving CYC

- 659 • Monthly IV

- 660 • Euro-lupus

- 661 • Oral

- 662 • Ages:

- 663 ○ Teen years

- 664 ○ Women 20-29

- 665 ○ Women 30-39

- 666 ○ Women 40 and older



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667

668 Intervention:

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

671

672 Comparator:

- 673 • No hormonal co-therapy

674

675 Outcomes:

- 676 • Return of menstruation following cessation of CYC therapy 678 • Premature ovarian insufficiency
677 • Ability to conceive 679 • RD flare

680

681 ***3B. In a man with RD receiving CYC, what is the impact of administration of testosterone co-therapy versus no testosterone co-***
682 ***therapy on paternal fertility outcomes [listed]?***

683

684 Population:

- 685 • Any man receiving CYC for RD interested in fathering a child in the future
686 ○ Monthly IV
687 ○ Euro-lupus
688 ○ Oral

689



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690 Intervention:

- 691 • Testosterone co-therapy during cyclophosphamide

692

693 Comparator:

- 694 • Similar patients without testosterone co-therapy

695

696 Outcomes:

- 697 • Sperm quality:
- 698 ○ Sperm count following CYC therapy
 - 699 ○ Sperm motility
 - 700 ○ DNA fragmentation of chromatin
- 701 • Low testosterone level

702

703 ***3C. In a man with RD, what is the impact of receiving rheumatology medications [listed], versus no rheumatology medications, on***
704 ***paternal fertility outcomes?***

705

706 Population:

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

708

709 Intervention:

- 710 • MTX



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- 711 • Sulfasalazine
712 • Leflunomide
713 • CYC
714 ○ IV pulse
715 ○ Euro lupus
716 ○ Oral
717
718 Comparator:
719 • Similar patients not taking that medication
720
721 Outcomes:
722 • Sperm quality:
723 ○ Sperm count
724 ○ Sperm motility
725 ○ DNA fragmentation of chromatin
726 • Low testosterone level
727
728
729
730
731



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732 **4. Counseling in Anticipation of Pregnancy:**

733

734 ***4A. In women with RD taking mycophenolate mofetil (or mycophenolic acid) for maintenance of quiescent disease who wish to***
735 ***conceive, what is the impact of switching to alternative immunosuppressive agents [listed] prior to attempting conception versus***
736 ***continuing mycophenolate on maternal and pregnancy outcomes [listed]?***

737

738 Population:

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

740

741 Intervention:

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

744

745 Comparator:

- 746 • Stop mycophenolate prior to pregnancy without replacing it with alternative agent

- 747 • Continue mycophenolate through pregnancy

748

749 Outcomes:

- 750 • Pregnancy loss: spontaneous abortion, stillbirth

- 751 • MBD

- 752 • Gestational hypertensive disease including preeclampsia

- 753 • Preterm birth: preterm birth < 34 weeks, preterm birth \geq

- 754 34 and < 37 weeks

- 755 • Induced labor



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

766

767 ***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***
768 ***switching to a TNF-i or pregnancy compatible drug prior to conception versus not switching on maternal and pregnancy outcomes***
769 ***[listed]?***

770

771 Population:

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

773

774 Intervention:

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

777

778 Comparator:

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



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781

782 Outcome:

- 783 • Pregnancy loss: spontaneous abortion, stillbirth
- 784 • MBD
- 785 • Gestational hypertensive disease, including preeclampsia
- 786 • Preterm birth: preterm birth < 34 weeks, preterm birth ≥
- 787 34 and < 37 weeks
- 788 • Induced labor
- 789 • Premature rupture of membranes
- 790 • Small for gestational age infants (SGA)

- 791 • Fetal/neonatal effects, including immunosuppression,
- 792 organ failure, adverse vaccine reactions in infant (e.g.,
- 793 BCG)
- 794 • Long-term offspring effects
- 795 • Flare of RD
- 796 • Damage from RD
- 797 • Maternal morbidity (including infection and thrombosis)
- 798 • Maternal mortality

799

800 ***4C. In women who have taken leflunomide within 2 years of wanting to conceive, what is the impact of checking drug level or***
801 ***administering washout [listed] versus not checking drug level or administering washout on maternal and pregnancy outcomes***
802 ***[listed]?***

803

804 Population:

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

806

807 Intervention:

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



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810

811 Comparator:

- 812 • Not checking leflunomide blood level prior to conception
813 • Not administering cholestyramine prior to conception

814

815 Outcome:

- 816 • Pregnancy loss: spontaneous abortion, stillbirth
817 • MBD
818 • Gestational hypertensive disease, including preeclampsia
819 • Preterm birth: preterm birth < 34 weeks, preterm birth ≥
820 34 and < 37 weeks
821 • Induced labor
822 • Premature rupture of membranes
823 • Small for gestational age infants (SGA)

- 824 • Fetal/neonatal effects, including immunosuppression,
825 organ failure, adverse vaccine reactions in infant (e.g.,
826 BCG)
827 • Long-term offspring effects
828 • Flare of RD
829 • Damage from RD
830 • Maternal morbidity (including infection and thrombosis)
831 • Maternal mortality

832

833 ***4D. In women with RD on NSAIDs who plan to conceive, what is the impact of stopping the NSAID prior to attempting conception***
834 ***versus not stopping the NSAID on maternal and pregnancy outcomes?***

835

836 Population:

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

838



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839 Intervention:

- 840 • Stop NSAID prior to attempting pregnancy

841

842 Comparator:

- 843 • Continue NSAID until after conception has occurred

844

845 Outcome:

- 846 • Time to conception
847 • Spontaneous abortion

848

849 ***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
850 outcomes in offspring [listed]?***

851

852 Population:

- 853 • Women with RD with
854 ○ SLE
855 ○ RA
856 ○ Other RD
857 ○ APS
858 ○ Anti-Ro/La
859 • Men with RD with



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- 860 ○ SLE
- 861 ○ RA
- 862 ○ Other RD
- 863 ○ APS
- 864 ○ Anti-Ro/La

865

866 Intervention:

- 867 • Having a RD diagnosis

868

869 Comparator:

- 870 • Similar patients without these disease states

871

872 Outcomes:

- 873 • Risk of neurodevelopmental delays in offspring
- 874 • Risk of autoimmune disease in offspring

875

876 ***4F. In women with RD on medication affecting folate metabolism [listed] before pregnancy, what is the impact of taking high-***
877 ***dose folic acid versus not taking high-dose folic acid on pregnancy outcome [listed]?***

878

879 Population:

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



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- 881 ○ MTX
- 882 ○ Sulfasalazine

883

884 Intervention:

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

886

887 Comparator:

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

889

890 Outcomes:

- 891 • MBD
- 892 • Spontaneous abortion
- 893 • Long term offspring outcomes (neurodevelopmental)

894

895 **PREGNANCY CARE:**

896

897 **5. Pregnancy Management:**

898

899 ***5A. In women with positive aPL [variables listed], does treating with certain medications during pregnancy [listed] versus not***
900 ***treating impact the maternal and pregnancy outcomes [listed]?***

901

902



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903 Population:

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

911

912 Intervention:

- 913 • LDA during pregnancy (for women not meeting OB-APS
- 914 criteria)
- 915 • Prophylactic Hep+LDA during pregnancy (for women
- 916 meeting and not meeting OB-APS criteria)
- 917 • Hydroxychloroquine (with or without other treatments)
- 918 (all groups)
- 919 • Prophylactic Hep+LDA with other agent (IVIg, prednisone)
- 920 during pregnancy (for women meeting OB-APS criteria and
- 921 failing standard Hep+LDA therapy)
- 922 • Full dose Hep+LDA (for thrombotic APS: group 5)

923

924 Comparator:

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



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930

931 Outcomes:

- | | | | |
|-----|--|-----|---|
| 932 | • Pregnancy loss: spontaneous abortion, stillbirth | 940 | • Fetal/neonatal effects, including immunosuppression, |
| 933 | • MBD | 941 | organ failure, adverse vaccine reactions in infant (e.g., |
| 934 | • Gestational hypertensive disease, including preeclampsia | 942 | BCG) |
| 935 | • Preterm birth: preterm birth < 34 weeks, preterm birth ≥ | 943 | • Long-term offspring effects |
| 936 | 34 and < 37 weeks | 944 | • Maternal morbidity (including infection and thrombosis) |
| 937 | • Induced labor | 945 | • Maternal mortality |
| 938 | • Premature rupture of membranes | 946 | • Maternal thrombosis |
| 939 | • Small for gestational age infants (SGA) | 947 | • Maternal hemorrhage |

948

949 ***5B. In women with RD who are considering pregnancy, what is the impact of having quiescent/low activity disease prior to***
950 ***pregnancy [listed] versus having active disease prior to pregnancy on maternal and pregnancy outcomes [listed]?***

951

952 Population:

- 953 • Women with RD who are considering pregnancy

954

955 Interventions:

- | | | | |
|-----|---|-----|-----------------------------------|
| 956 | • Quiescent or stable low activity disease for one to three | 959 | • Scleroderma: stable for 2 years |
| 957 | months | | |
| 958 | • Quiescent or stable low activity disease for six months | | |



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960

961 Comparator (varies with outcome):

- 962 • Similar patients with active disease

963

964 Outcomes:

- 965 • Pregnancy loss: spontaneous abortion, stillbirth
966 • MBD
967 • Gestational hypertensive disease, including preeclampsia
968 • Preterm birth: preterm birth < 34 weeks, preterm birth ≥
969 34 and < 37 weeks
970 • Induced labor
971 • Premature rupture of membranes
972 • Small for gestational age infants (SGA)

- 973 • Fetal/neonatal effects, including immunosuppression,
974 organ failure, adverse vaccine reactions in infant (e.g.,
975 BCG)
976 • Long-term offspring effects
977 • Flare of RD
978 • Damage from RD
979 • Maternal morbidity (including infection and thrombosis)
980 • Maternal mortality

981

982 ***5C. In women with RD with currently active disease that would require immunosuppressive therapy in a non-pregnant state, what***
983 ***is the impact of treatment with immunosuppressive therapy compatible with pregnancy [listed] versus no immunosuppressive***
984 ***therapy on maternal and pregnancy outcomes?***

985

986 Population:

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



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- 989 ○ Active SLE without nephritis
- 990 ○ SLE nephritis
- 991 ○ Myositis
- 992 ○ Scleroderma
- 993 ○ Inflammatory arthritis (RA, PsA, AS)

994

995 Intervention:

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

998

999 Comparator:

- 1000 ● No treatment for the active RD
- 1001 ● Prednisone in addition to compatible DMARD for the active RD
- 1002 ● Prednisone alone for the active RD

1004

1005 Outcomes:

- 1006 ● Pregnancy loss: spontaneous abortion, stillbirth
- 1007 ● MBD
- 1008 ● Gestational hypertensive disease, including preeclampsia
- 1009 ● Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- 1010 ● Induced labor
- 1011 ● Premature rupture of membranes
- 1012 ● Small for gestational age infants (SGA)



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- 1014 • Fetal/neonatal effects, including immunosuppression,
- 1015 organ failure, adverse vaccine reactions in infant (e.g.,
- 1016 BCG)
- 1017 • Long-term offspring effects
- 1018 • Flare of RD

- 1019 • Damage from RD
- 1020 • Maternal morbidity (including infection and thrombosis)
- 1021 • Maternal mortality

1022

1023 ***5D. In women who are pregnant with scleroderma renal crisis, what is the impact of treatment with ACE-inhibitor or ARB therapy***
1024 ***versus similar women not treated with ACE-inhibitor and/or ARB therapy on maternal and pregnancy outcomes [listed]?***

1025

1026 Population:

- 1027 • Women with scleroderma in renal crisis

1028

1029 Intervention:

- 1030 • Treatment with an ACE-inhibitor or ARB in pregnancy

1031

1032 Comparator:

- 1033 • No treatment with an ACE-inhibitor or ARB in pregnancy

1034

1035 Outcomes:

- 1036 • Infant renal function/structure
- 1037 • Maternal renal function

- 1038 • Pregnancy loss (spontaneous abortion, stillbirth)
- 1039 • Maternal death



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1040

1041 ***5E. In women with RD [listed] who are pregnant [variables listed], what is the impact of treatment with low-dose aspirin (LDA)***
1042 ***versus no LDA on maternal and pregnancy outcomes?***

1043

1044 Population:

- 1045 • Women with RD who are considering pregnancy
- 1046 ○ Any woman with a RD and
- 1047 ○ Renal disease
- 1048 ○ Hypertension
- 1049 ○ aPL(+) but not meeting modified Sapporo APS criteria
- 1050 ○ SLE
- 1051 ○ Systemic sclerosis
- 1052 ○ RA and other inflammatory arthritis
- 1053 ○ Vasculitis
- 1054 ○ Myositis
- 1055 ○ Sjogren's

1056

1057 Intervention:

- 1058 • Low-dose aspirin

1059

1060



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1061 Comparator:

- 1062 • Similar patients who are not treated with low-dose aspirin

1063

1064 Outcomes:

- 1065 • Pregnancy loss: spontaneous abortion, stillbirth

- 1066 • MBD

- 1067 • Gestational hypertensive disease, including preeclampsia

- 1068 • Preterm birth: preterm birth < 34 weeks, preterm birth \geq
1069 34 and < 37 weeks

- 1070 • Induced labor

- 1071 • Premature rupture of membranes

- 1072 • Small for gestational age infants (SGA)

- 1073 • Damage from RD

- 1074 • Maternal morbidity (including loss of renal function)

- 1075 • Maternal mortality

1076

1077 ***5F. In women with SLE who are considering pregnancy or are pregnant [variables listed], what is the impact of treatment with***
1078 ***HCQ throughout pregnancy versus no such treatment with HCQ on maternal and pregnancy outcomes [listed]?***

1079

1080 Population:

- 1081 • Women with SLE who are considering pregnancy or are pregnant

- 1082 ○ SLE without renal disease or aPL

- 1083 ○ SLE with renal disease

- 1084 ○ SLE with aPL

1085

1086



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1087 Intervention:

- 1088 • HCQ
- 1089

1090 Comparator:

- 1091 • Similar patients who are not treated with HCQ
- 1092

1093 Outcomes:

- 1094 • Pregnancy loss: spontaneous abortion, stillbirth
- 1095 • MBD
- 1096 • Gestational hypertensive disease, including preeclampsia
- 1097 • Preterm birth: preterm birth < 34 weeks, preterm birth ≥
- 1098 34 and < 37 weeks
- 1099 • Induced labor
- 1100 • Premature rupture of membranes
- 1101 • Small for gestational age infants (SGA)

- 1102 • Fetal/neonatal effects, including immunosuppression,
- 1103 organ failure, adverse vaccine reactions in infant (e.g.,
- 1104 BCG)
- 1105 • Long-term offspring effects
- 1106 • Flare of SLE
- 1107 • Damage from SLE
- 1108 • Maternal morbidity (including infection and thrombosis)
- 1109 • Maternal mortality

1110

1111 ***5G. In women with SLE, Sjogren's syndrome, systemic sclerosis, or RA, what is the impact of checking autoantibodies [listed] prior***

1112 ***to or early in pregnancy versus not checking these antibodies on maternal and pregnancy outcomes?***

1113

1114 Population:

- 1115 • Women with SLE, PSS, SS, or RA who are considering pregnancy or are pregnant



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1116

1117 Interventions:

- 1118 • Checking autoantibodies
- 1119 ○ aPL (aCL IgG, IgM, antiβ2GPI IgG, IgM, LAC)
- 1120 ○ Anti-Ro/La

1121

1122 Comparator:

- 1123 • Similar patients who do not have these autoantibodies checked

1124

1125 Outcomes:

- 1126 • Pregnancy loss: spontaneous abortion, stillbirth
- 1127 • MBD
- 1128 • Gestational hypertensive disease, including preeclampsia
- 1129 • Preterm birth: preterm birth < 34 weeks, preterm birth ≥
- 1130 34 and < 37 weeks
- 1131 • Induced labor
- 1132 • Premature rupture of membranes
- 1133 • Small for gestational age infants (SGA)

1142

- 1134 • Fetal/neonatal effects, including immunosuppression,
- 1135 organ failure, adverse vaccine reactions in infant (e.g.,
- 1136 BCG)
- 1137 • Long-term offspring effects
- 1138 • Maternal thrombotic event (aPL)
- 1139 • Maternal morbidity
- 1140 • Maternal mortality
- 1141 • Neonatal lupus (anti-Ro/La)



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1143 ***5H. In women with SLE, Sjogren’s syndrome, systemic sclerosis, or RA, what is the impact of repeated checking of autoantibodies***
1144 ***[listed] during pregnancy as compared to not rechecking these antibodies (i.e. checking only once before or early in pregnancy)***
1145 ***on maternal and pregnancy outcomes?***

1146

1147 **Population:**

- 1148 • Women with SLE, Sjogren’s syndrome, systemic sclerosis, or RA who are pregnant

1149

1150 **Interventions:**

- 1151 • Re-checking autoantibodies (more than the one time preparing for or early in pregnancy)
- 1152 ○ aPL (aCL IgG, IgM; antiβ2GPI IgG, IgM; LAC)
- 1153 ○ Anti-Ro/La

1154

1155 **Comparator:**

- 1156 • Similar patients who do not have these autoantibodies repeated.

1157

1158 **Outcomes:**

- 1159 • Pregnancy loss: spontaneous abortion, stillbirth
- 1160 • MBD
- 1161 • Gestational hypertensive disease, including preeclampsia
- 1162 • Preterm birth: preterm birth < 34 weeks, preterm birth ≥
- 1163 34 and < 37 weeks

- 1164 • Induced labor
- 1165 • Premature rupture of membranes
- 1166 • Small for gestational age infants (SGA)
- 1167 • Fetal/neonatal effects: including immunosuppression,
- 1168 organ failure, adverse vaccine reactions in infant (e.g. BCG)



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- 1169 • Long-term offspring effects
- 1170 • Maternal thrombotic event (aPL)
- 1171 • Neonatal lupus (anti-Ro/La)
- 1172 • Maternal mortality
- 1173 • Maternal morbidity (including infection and thrombosis)

1174

1175 ***5I. In women with RD and serious disease-related damage [listed], what is the impact of pregnancy versus not undertaking or***
1176 ***continuing pregnancy on maternal and pregnancy outcome?***

1177

1178 Population:

- 1179 • Women with RD and severe disease manifestations/complications including:
 - 1180 ○ Severe hypertension, renal insufficiency or ESRD
 - 1181 ○ Pulmonary disease to include pulmonary hypertension, “shrinking lung,” interstitial fibrosis/restrictive lung disease
 - 1182 ○ Cardiac disease to include severe cardiac valve disease (Libman-Sacks), cardiomyopathy, CAD
 - 1183 ○ Diffuse brain disease (psychosis, dementia)
 - 1184 ○ Osteonecrosis (hip)
 - 1185 ○ Antiphospholipid syndrome with stroke or MI
 - 1186 ○ Severe deformities of any joint, including cervical spine (especially C1-C2) and hips
 - 1187 ○ Advanced skin disease that interferes with labor/delivery, vascular access, or nursing or childcare
 - 1188 ○ Diffuse muscle weakness, including respiratory and swallowing
 - 1189 ○ Vascular damage – including stenosis and aneurysm – from vasculitis (especially Takayasu’s)
 - 1190 ○ Severe neuropathies

1191



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1192 Intervention:

- 1193 • Pregnancy

1194

1195 Comparator:

- 1196 • No pregnancy
1197 • Pregnancy termination

1198

1199 Outcome:

- 1200 • Pregnancy loss: spontaneous abortion, stillbirth
1201 • MBD
1202 • Gestational hypertensive disease, including preeclampsia
1203 • Preterm birth: preterm birth < 28 weeks, preterm birth ≥
1204 28 and < 34 weeks, preterm birth ≥ 34 and < 37 weeks
1205 • Induced labor
1206 • Premature rupture of membranes
1207 • Small for gestational age infants (SGA)

- 1208 • Fetal/neonatal effects, including immunosuppression,
1209 organ failure, adverse vaccine reactions in infant (e.g.,
1210 BCG)
1211 • Long-term offspring effects
1212 • Flare of RD
1213 • Damage from RD
1214 • Maternal morbidity (including infection and thrombosis)
1215 • Maternal death

1216

1217 ***5J. In women with RD [listed], what is the impact of management by a rheumatologist throughout pregnancy versus no***
1218 ***rheumatology management on maternal and pregnancy outcomes [listed]?***

1219

1220



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1221 Population:

- 1222 • Women with RD
- 1223 ○ SLE
- 1224 ○ Inflammatory arthritis
- 1225 ○ Systemic sclerosis
- 1226 ○ Vasculitis
- 1227 ○ UCTD

1228

1229 Intervention:

- 1230 • Management by a rheumatologist (defined as “regular monitoring for rheumatic disease activity and rheumatic medication management during pregnancy”)

1232

1233 Comparator:

- 1234 • No management by a rheumatologist

1235

1236 Outcome:

- | | |
|---|--|
| 1237 • Pregnancy loss: spontaneous abortion, stillbirth | 1242 • Induced labor |
| 1238 • MBD | 1243 • Premature rupture of membranes |
| 1239 • Gestational hypertensive disease, including preeclampsia | 1244 • Small for gestational age infants (SGA) |
| 1240 • Preterm birth: preterm birth < 34 weeks, preterm birth ≥ | |
| 1241 34 and < 37 weeks | |



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- 1245 • Fetal/neonatal effects, including immunosuppression,
- 1246 organ failure, adverse vaccine reactions in infant (e.g.,
- 1247 BCG)
- 1248 • Long-term offspring effects
- 1249 • Flare of RD
- 1250 • Damage from RD
- 1251 • Maternal morbidity (including infection and thrombosis)
- 1252 • Maternal mortality

1253

1254 ***5K. In pregnant women with SLE, what is the impact of monitoring laboratory tests [listed] during pregnancy versus no laboratory***
1255 ***test monitoring on maternal and pregnancy outcomes [listed]?***

1256

1257 Population:

- 1258 • Pregnant SLE patients

1259

1260 Intervention:

- 1261 • Checking laboratory tests, including CBC and urine prot/creat ratio, at least every trimester

1262

1263 Comparator:

- 1264 • SLE patients who are on any dose of prednisone or IS at the start of pregnancy who do not have these labs checks.

1265

1266 Outcomes:

- 1267 • Pregnancy loss: spontaneous abortion, stillbirth
- 1268 • MBD
- 1269 • Gestational hypertensive disease, including preeclampsia



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- | | | | |
|------|--|------|---|
| 1270 | • Preterm birth: preterm birth < 34 weeks, preterm birth ≥ | 1278 | • Long-term offspring effects |
| 1271 | 34 and < 37 weeks | 1279 | • Flare of SLE |
| 1272 | • Induced labor | 1280 | • Damage from SLE |
| 1273 | • Premature rupture of membranes | 1281 | • Maternal morbidity (including infection and thrombosis) |
| 1274 | • Small for gestational age infants (SGA) | 1282 | • Maternal mortality |
| 1275 | • Fetal/neonatal effects, including immunosuppression, | | |
| 1276 | organ failure, adverse vaccine reactions in infant (e.g., | | |
| 1277 | BCG) | | |

1283

1284 ***5L. In women with SLE who are pregnant and develop laboratory or clinical evidence of SLE flare, what is the impact of new or***
1285 ***increased treatment with prednisone or compatible immunosuppressive versus no treatment or no increased treatment on***
1286 ***maternal and pregnancy outcomes [listed]?***

1287

1288 Population:

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

1290

1291 Intervention:

- Increase steroids or allowable immunosuppressive agents

1293

1294 Comparator:

- Pregnant SLE patients who do not receive increased medication



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1296

1297 Outcomes:

- | | | | |
|------|--|------|---|
| 1298 | • Pregnancy loss: spontaneous abortion, stillbirth | 1306 | • Fetal/neonatal effects, including immunosuppression, |
| 1299 | • MBD | 1307 | organ failure, adverse vaccine reactions in infant (e.g., |
| 1300 | • Gestational hypertensive disease, including preeclampsia | 1308 | BCG) |
| 1301 | • Preterm birth: preterm birth < 34 weeks, preterm birth ≥ | 1309 | • Long-term offspring effects |
| 1302 | 34 and < 37 weeks | 1310 | • Flare of SLE |
| 1303 | • Induced labor | 1311 | • Damage from SLE |
| 1304 | • Premature rupture of membranes | 1312 | • Maternal morbidity (including infection and thrombosis) |
| 1305 | • Small for gestational age infants (SGA) | 1313 | • Maternal mortality |

1314

1315 ***5M. In a woman with RD who is pregnant [listed], what is the impact of planned preterm delivery (< 37 weeks) due to rheumatic***
1316 ***disease, regardless of obstetric parameters (i.e., regardless of NST results, fetal growth, active preeclampsia, etc.) versus no***
1317 ***planned preterm delivery for RD reasons on maternal and pregnancy outcomes?***

1318

1319 Population:

- | | | | |
|------|--|------|-------------------------------------|
| 1320 | • Pregnant women with quiescent or stable mild RD activity | 1324 | • Women RD and a hip replacement(s) |
| 1321 | • Pregnant women with uncontrolled RD (active RD) and | | |
| 1322 | major internal organ inflammation or organ dysfunction | | |
| 1323 | (heart, lung, kidney, CNS) | | |

1325



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1326 **Intervention:**

- 1327 • Induction of labor prior to term (< 37 weeks gestation)

1328

1329 **Comparators:**

- 1330 • Induction of labor after 37 weeks gestation

- 1331 • Spontaneous delivery after 37 weeks gestation

1332

1333 **Outcomes:**

- 1334 • Pregnancy loss: stillbirth

- 1335 • Gestational hypertensive disease, including preeclampsia

- 1336 • Preterm birth: preterm birth ≥ 34 and < 37 weeks

- 1337 • Small for gestational age infants (SGA)

- 1338 • Fetal/neonatal effects, including immunosuppression,

- 1339 organ failure, adverse vaccine reactions in infant (e.g.,

- 1340 BCG)

- 1341 • Long-term offspring effects

- 1342 • Flare of RD

- 1343 • Damage from RD

- 1344 • Maternal morbidity (including infection and thrombosis)

- 1345 • Maternal mortality

- 1346 • Cesarean section

1347

1348 **6. Management of the Anti-Ro and/or La Positive Mother:**

1349

1350 ***6A. In a pregnant woman with Ro/La antibodies [history variables listed], does fetal echo screening [intervals listed] versus no***

1351 ***fetal echo screening impact offspring outcomes [listed]?***

1352



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1353 Population:

- 1354 • Pregnant women with anti-Ro or Ro/La and
- 1355 ○ No history of an infant with CHB or NLE
- 1356 ○ History of an infant with CHB
- 1357 ○ History of an infant with other NLE

1358

1359 Intervention:

- 1360 • Fetal echo screening at
- 1361 ○ Timing:
- 1362 ○ Weeks 20 and 24
- 1363 ○ 16/18 weeks to 26/28 weeks
- 1364 ○ Frequency
- 1365 ○ Weekly
- 1366 ○ Every 2 weeks

1367

1368 Comparator:

- 1369 • No screening

1370

1371 Outcome:

- 1372 • Complete heart block
- 1373 • Fetal hydrops/other serious complications
- 1374 • Fetal death or infant death
- 1375 • Need for a pacemaker in childhood



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1376

1377 ***6B. In a pregnant woman with Ro/La antibodies [history variables listed], what is the impact of taking HCQ throughout pregnancy***
1378 ***versus not taking HCQ on offspring outcomes [listed]?***

1379

1380 Population:

- 1381 • Women with anti-Ro or Ro/La and
1382 ○ No history of an infant with CHB or NLE
1383 ○ History of an infant with CHB
1384 ○ History of an infant with other NLE

1385

1386 Intervention:

- 1387 • Hydroxychloroquine for prevention of CHB

1388

1389 Comparator:

- 1390 • No treatment with HCQ

1391

1392 Outcomes:

- 1393 • Complete heart block

- 1394 • Fetal hydrops/other serious complications

- 1395 • Fetal death or infant death

1398

- 1396 • Need for a pacemaker in childhood

- 1397 • Other neonatal lupus related findings



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1399

1400 ***6C. In a pregnant woman with Ro/La antibodies with abnormal fetal ECHO [listed], what is the impact of taking fluorinated***
1401 ***steroid versus no fluorinated steroid treatment on offspring outcomes [listed]?***

1402

1403 Population:

- 1404 • Women with anti-Ro or Ro/La and
- 1405 ○ Fetus with first-degree heart block on echo
- 1406 ○ Fetus with second-degree heart block on echo
- 1407 ○ Fetus with complete heart block on echo
- 1408 ○ Fetus with isolated endocardial fibroelastosis on echo

1409

1410 Intervention:

- 1411 • Dexamethasone/betamethasone treatment (any dose or duration)

1412

1413 Comparator:

- 1414 • No treatment with dexamethasone/betamethasone

1415

1416 Outcomes:

- 1417 • Complete heart block
- 1418 • Fetal hydrops/other serious complications
- 1419 • Fetal death or infant death
- 1420 • Need for a pacemaker in childhood

1421



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1422 **6D. In a pregnant woman with Ro/La antibodies with abnormal fetal ECHO [listed], what is the impact of IVIG therapy versus no**
1423 **IVIG therapy on offspring outcomes [listed]?**

1424

1425 Population:

- 1426 • Women with anti-Ro or Ro/La and
 - 1427 ○ Fetus with first-degree heart block on echo
 - 1428 ○ Fetus with second-degree heart block on echo
 - 1429 ○ Fetus with CHB on echo
 - 1430 ○ Fetus with isolated endocardial fibroelastosis on echo

1431

1432 Intervention:

- 1433 • IVIG

1434

1435 Comparator:

- 1436 • No treatment with IVIG

1437

1438 Outcomes:

- 1439 • Complete heart block
- 1440 • Fetal hydrops/other serious complications
- 1441 • Fetal death or infant death
- 1442 • Need for a pacemaker in childhood

1443

1444



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1445 **7. Paternal Medication Exposure:**

1446

1447 ***7A. In males with RD on medication who are planning to father a child, what is the impact of stopping medication [listed] prior to***
1448 ***conception versus continuing medication on fertility issues and pregnancy outcome?***

1449

1450 Population:

1451 • Males with RD who are planning to father a child and who are on medication, including

1452 ○ Nonimmunosuppressive:

1453 ○ Classic NSAIDs

1454 ○ Cox2 inhibitors

1455 ○ Antimalarials

1456 ○ Sulfasalazine

1457 ○ Colchicine

1458 ○ Classic, or synthetic, immunosuppressives:

1459 ○ Methotrexate

1460 ○ Leflunomide

1461 ○ Azathioprine/6-MP

1462 ○ Mycophenolate mofetil/mycophenolic acid

1463 ○ Cyclosporine

1464 ○ Tacrolimus

1465 ○ Cyclophosphamide



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- 1466 ○ Thalidomide/Lenalidomide
- 1467 ○ Biologic immunosuppressives (TNF-inhibitors):
- 1468 ○ Infliximab
- 1469 ○ Etanercept
- 1470 ○ Adalimumab
- 1471 ○ Golimumab
- 1472 ○ Certolizumab
- 1473 ○ Biologic immunosuppressives (Non-TNF biologics):
- 1474 ○ Anakinra
- 1475 ○ Rituximab
- 1476 ○ Belimumab
- 1477 ○ Abatacept
- 1478 ○ Tocilizumab
- 1479 ○ Secukinumab
- 1480 ○ Ustekinumab
- 1481 ○ Novel small molecules:
- 1482 ○ Tofacitinib
- 1483 ○ Baracitinib
- 1484 ○ Apremilast
- 1485 ○ Other:
- 1486 ○ IVIG
- 1487 ○ Anticoagulants:



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- 1488 ▪ Warfarin
1489 ▪ DOACs (rivaroxaban, dabigatran, apixaban, edoxaban)
1490 ▪ Heparin/LMWH
1491 ▪ Other antiplatelet agents

1492

1493 **Intervention:**

- 1494 • Stop medication prior to conception

1495

1496 **Comparator:**

- 1497 • Continue chronic medication

1498

1499 **Outcomes:**

- | | | | |
|------|---|------|---|
| 1500 | • MBD | 1504 | • Need for assisted reproductive technology (ART) |
| 1501 | • Spontaneous abortion | 1505 | • Pregnancy |
| 1502 | • Sperm quality (sperm count, morphology, motility) | 1506 | • RD flare |
| 1503 | • Time to conception | 1507 | • RD damage |

1508

1509 **8. Medication Safety During Pregnancy:**

1510

1511 ***8A. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing medications [listed] versus***
1512 ***stopping medications before or during pregnancy on maternal and pregnancy outcomes [listed]?***



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1513

1514 Population:

1515 • Women with RDs who are pregnant or planning pregnancy and on medication, including

1516 ○ Nonimmunosuppressive:

1517 ○ Classic NSAIDs

1518 ○ Cox2 inhibitors

1519 ○ Antimalarials

1520 ○ Sulfasalazine

1521 ○ Colchicine

1522 ○ Classic, or synthetic, immunosuppressives:

1523 ○ Methotrexate

1524 ○ Leflunomide

1525 ○ Azathioprine/6-MP

1526 ○ Mycophenolate mofetil/mycophenolic acid

1527 ○ Cyclosporine

1528 ○ Tacrolimus

1529 ○ Cyclophosphamide

1530 ○ Thalidomide/Lenalidomide

1531 ○ Biologic immunosuppressives (TNF-inhibitors):

1532 ○ Infliximab

1533 ○ Etanercept



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- 1534 ○ Adalimumab
- 1535 ○ Golimumab
- 1536 ○ Certolizumab
- 1537 ○ Biologic immunosuppressives (Non-TNF biologics):
- 1538 ○ Anakinra
- 1539 ○ Rituximab
- 1540 ○ Belimumab
- 1541 ○ Abatacept
- 1542 ○ Tocilizumab
- 1543 ○ Secukinumab
- 1544 ○ Ustekinumab
- 1545 ○ Novel small molecules:
- 1546 ○ Tofacitinib
- 1547 ○ Baracitinib
- 1548 ○ Apremilast
- 1549 ○ Other:
- 1550 ○ IVIG
- 1551 ○ Anticoagulants:
- 1552 ▪ Warfarin
- 1553 ▪ DOACs (rivaroxaban, dabigatran, apixaban, edoxaban)
- 1554 ▪ Heparin/LMWH
- 1555 ▪ Other antiplatelet agents



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1556

1557 Interventions (vary with drug):

- 1558 • Stop in pre-conception planning phase
- 1559 • Stop when pregnancy suspected/confirmed
- 1560 • Continue medication throughout pregnancy (T1, T2, T3)

- 1561 • Continue medication throughout first trimester only (for TNF-i and NSAIDs only)
- 1562
- 1563 • Continue medication through to end of second trimester (for TNF-i and NSAIDs only)
- 1564

1565

1566 Comparator:

- 1567 • Not using the medication before pregnancy
- 1568 • Not using the drug during pregnancy (stopping drug prior to pregnancy)
- 1569

- 1570 • Not using drug during the relevant trimesters

1571

1572 Outcomes:

- 1573 • Pregnancy loss, including spontaneous abortion and stillbirth
- 1574
- 1575 • MBD
- 1576 • Gestational hypertensive disease, including preeclampsia
- 1577 • Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- 1578
- 1579 • Induced labor
- 1580 • Premature rupture of membranes

- 1581 • Small for gestational age infants (SGA)
- 1582 • Fetal/neonatal effects, including immunosuppression, organ failure, adverse vaccine reactions in infant (e.g., BCG), and efficacy of vaccines in neonates
- 1583
- 1584
- 1585 • Long-term offspring effects, including neurodevelopmental and autoimmune disease)
- 1586
- 1587 • Flare of RD
- 1588 • Damage from RD



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- 1589 • Maternal morbidity (including infection and thrombosis)

1590

1591 **9. Corticosteroids in Pregnancy:**

1592

1593 ***9A. In women with RD and variable disease activity [listed], what is the impact of taking prednisone or other non-fluorinated***
1594 ***steroid [listed] versus not taking any corticosteroid on maternal and fetal outcomes [listed]?***

1595

1596 Population:

- 1597 • Pregnant women with RD and
1598 ○ No current RD activity but on steroid (unable to taper off steroids)
1599 ○ Mild to moderate RD activity on steroid
1600 ○ Severe RD activity, including internal-organ inflammation from a systemic rheumatic disease (i.e., SLE, vasculitis, etc.)

1601

1602 Intervention:

- 1603 • Prednisone or equivalent non-fluorinated steroid at dose of:
1604 ○ < 7.5mg a day (low dose)
1605 ○ 7.5mg to 20mg a day (moderate dose)
1606 ○ > 20mg a day (high dose)
1607 ○ IV pulse steroids (methylprednisolone) or IM steroid

1608

1609



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1610 Comparator:

- 1611 • No prednisone treatment
- 1612 • On other DMARDs/biologics compatible with pregnancy

1613

1614 Outcomes:

- | | |
|---|--|
| 1615 • Pregnancy loss, including spontaneous abortion and | 1624 • Fetal/neonatal effects, including immunosuppression, |
| 1616 stillbirth | 1625 organ failure, adverse vaccine reactions in infant (e.g., |
| 1617 • MBD | 1626 BCG) |
| 1618 • Preterm birth: preterm birth < 34 weeks, preterm birth ≥ | 1627 • Long-term offspring effects, including neurodevelopmental |
| 1619 34 and < 37 weeks | 1628 and autoimmune disease) |
| 1620 • Premature rupture of membranes | 1629 • Maternal morbidity, including infection during pregnancy |
| 1621 • Small for gestational age infants | 1630 and adrenal insufficiency |
| 1622 • Gestational hypertensive disease, including preeclampsia | 1631 • Maternal mortality |
| 1623 • Gestational diabetes | 1632 • RD flare |

1633

1634 ***9B. In women with RD on chronic prednisone (or non-fluorinated steroid equivalent) greater than 7.5 mg daily for greater than 6***
1635 ***months before pregnancy, what is the impact of tapering off steroid when pregnancy is diagnosed versus continuing on the same***
1636 ***dose on maternal and fetal outcomes [listed]?***

1637

1638 Population:

- 1639 • Women with RD on chronic prednisone or non-fluorinated steroid equivalent greater than 7.5 mg daily for greater than one year



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1640

1641 Intervention:

1642 • Tapering down to average daily dose of ≤ 7.5 mg steroid when pregnancy diagnosed

1643 • Tapering off steroid

1644

1645 Comparator:

1646 • Continue stable steroid dose (> 7.5 mg)

1647

1648 Outcome:

1649 • Pregnancy loss, including spontaneous abortion and
1650 stillbirth

1651 • MBD

1652 • Preterm birth: preterm birth < 34 weeks, preterm birth \geq
1653 34 and < 37 weeks

1654 • Premature rupture of membranes

1655 • Small for gestational age infants

1656 • Gestational hypertensive disease, including preeclampsia

1664

1665 ***9C. In women with RD on chronic steroid (or non-fluorinated steroid equivalent) greater than 7.5 mg daily for greater than 6***
1666 ***months prior to delivery, what is the impact of administration of stress-dose steroid at the time of delivery [listed] versus no***
1667 ***stress-dose steroid on maternal and fetal outcomes [listed]?***

1657 • Gestational diabetes

1658 • Long-term outcomes, including growth and development

1659 • Maternal morbidity, including infection during pregnancy
1660 and adrenal insufficiency

1661 • Maternal mortality

1662 • RD flare

1663 • RD damage



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1668

1669 Population:

- 1670 • Women with RD on chronic steroid (or non-fluorinated steroid equivalent) greater than 7.5 mg daily for greater than 6 months
1671 and delivering by any mode of delivery

1672

1673 Intervention:

- 1674 • Stress-dose steroid at the time of delivery

1675

1676 Comparator:

- 1677 • No stress-dose steroid

1678

1679 Outcome:

- 1680 • Pregnancy loss, including stillbirth

- 1681 • MBD

- 1682 • Preterm birth: preterm birth < 34 weeks, preterm birth ≥
1683 34 and < 37 weeks

- 1684 • Premature rupture of membranes

- 1685 • Small for gestational age infants

- 1686 • Gestational hypertensive disease, including preeclampsia

- 1687 • Gestational diabetes

- 1688 • Long-term outcomes, including growth and development

- 1689 • Maternal morbidity, including infection and adrenal
1690 insufficiency

- 1691 • Maternal mortality

- 1692 • RD flare

- 1693 • RD damage

1694

1695



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1696 **POST-PREGNANCY CARE**

1697 **10. Lactation and Medications:**

1698

1699 ***10A. In women with RD who are considering breastfeeding, what is the impact of taking medication [listed] during breastfeeding***
1700 ***versus not taking medication on drug levels and neonatal outcomes [listed]?***

1701

1702 **Population:**

- 1703 • Women with RD who are lactating and considering breastfeeding

1704

1705 **Intervention:**

- 1706 • Continuing/starting medication while breastfeeding, including

1707

- Nonimmunosuppressive:

1708

- Classic NSAIDs

1709

- Cox2 inhibitors

1710

- Antimalarials

1711

- Sulfasalazine

1712

- Colchicine

1713

- Classic, or synthetic, immunosuppressives:

1714

- Methotrexate

1715

- Leflunomide

1716

- Azathioprine/6-MP



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- 1717 ○ Mycophenolate mofetil/mycophenolic acid
- 1718 ○ Cyclosporine
- 1719 ○ Tacrolimus
- 1720 ○ Cyclophosphamide
- 1721 ○ Thalidomide/Lenalidomide
- 1722 ○ Biologic immunosuppressives (TNF-inhibitors):
- 1723 ○ Infliximab
- 1724 ○ Etanercept
- 1725 ○ Adalimumab
- 1726 ○ Golimumab
- 1727 ○ Certolizumab
- 1728 ○ Biologic immunosuppressives (Non-TNF biologics):
- 1729 ○ Anakinra
- 1730 ○ Rituximab
- 1731 ○ Belimumab
- 1732 ○ Abatacept
- 1733 ○ Tocilizumab
- 1734 ○ Secukinumab
- 1735 ○ Ustekinumab
- 1736 ○ Novel small molecules:
- 1737 ○ Tofacitinib
- 1738 ○ Baracitinib



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- 1739 ○ Apremilast
- 1740 ○ Other:
- 1741 ○ IVIG
- 1742 ○ Anticoagulants:
- 1743 ▪ Warfarin
- 1744 ▪ DOACs (rivaroxaban, dabigatran, apixaban, edoxaban)
- 1745 ▪ Heparin/LMWH
- 1746 ▪ Other antiplatelet agents
- 1747
- 1748 Comparator:
- 1749 • Not taking medication while breastfeeding
- 1750 • Not breastfeeding
- 1751
- 1752 Outcomes:
- 1753 • Transmission to breast milk
- 1754 • Transmission to infant (serum levels)
- 1755 • Clinical side effects in offspring:
- 1756 ○ Neonatal/infancy, including hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS,
1757 adverse vaccine reaction, other
- 1758 ○ Long-term effects, including growth and development
- 1759



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Project Plan – November 2017

1760 **11. Menopause:**

1761

1762 **11A. In postmenopausal women with SLE, what is the impact of HRT versus no HRT on risk of SLE flare?**

1763

1764 Population:

- Post-menopausal women with SLE

1766

1767 Intervention:

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

1770

1771 Comparison:

- Similar patients not using postmenopausal hormone therapy

1773

1774 Outcome:

- SLE flare

1776

1777 **11B. In postmenopausal women with RD and aPL [variables listed] who experience menopausal symptoms, what is the impact of**
1778 **HRT versus no HRT on thrombosis risk?**

1779

1780



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1781 Population:

- 1782 • Postmenopausal women with RD and positive aPL
1783 ○ With positive aPL and no history of thrombosis
1784 ○ With thrombotic APS on long-term anticoagulation

1785

1786 Intervention:

- 1787 • Oral postmenopausal hormone therapy, including estrogen or estrogen/progestin
1788 • Estrogen/progestin patch

1789

1790 Comparison:

- 1791 • Similar patients not using postmenopausal hormone therapy

1792

1793 Outcome:

- 1794 • Thrombosis

1795

1796 **12. Long-Term Issues:**

1797

1798 ***12A. In women with OB APS (revised Sapporo criteria), what is the impact of long-term, low-dose aspirin after pregnancy versus***
1799 ***no long-term, low-dose aspirin on the risk of thrombosis?***

1800

1801



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1802 Population:

- 1803 • Women with positive aPL who meet criteria of OB-APS but do not have a history of thrombosis
- 1804

1805 Intervention:

- 1806 • Low-dose aspirin long-term
- 1807

1808 Comparator:

- 1809 • No treatment with long-term, low-dose aspirin
- 1810

1811 Outcome:

- 1812 • Risk of thrombosis
- 1813
- 1814
- 1815
- 1816
- 1817

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
Adebenga Bankole	Expert Panel	Carlilon 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	Mallinchrordt; 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 Genome 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 Lilly; 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 Jayatileke	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; Celgene; 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 grant; FROS	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
			Cambridge University Press; Texas Tech University El Paso				American College of Obstetricians & Gynecologists; Society of Maternal-Fetal Medicine	
Lauren A. Plante	Voting Panel	Drexel University College of Medicine	University El Paso	NICHD	N/A	N/A		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; Brigham & 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	Unemployed	N/A	PCORI	N/A	N/A	N/A	N/A