

# Reproductive Health in Women with Systemic Autoimmune Disease



**Mehret Birru Talabi, MD PhD**

Assistant Professor of Medicine

Division of Rheumatology and Clinical Immunology

---

Director, Women's and Reproductive Health Rheumatology Clinic, UPMC

Assistant Dean and Co-Director, Medical Scientist Training Program

University of Pittsburgh School of Medicine

**CONVERGE** @Pitt  
The Center for Innovative Research  
on Gender Health Equity

The logo for CONVERGE @Pitt features the text 'CONVERGE @Pitt' in a bold, sans-serif font. Below it, the full name 'The Center for Innovative Research on Gender Health Equity' is written in a smaller font. To the right of the text is a blue arrow pointing to the right. The background of the logo is white with several thin, colorful lines (green, blue, purple) that appear to be part of a larger graphic or network.

# Disclosures: None

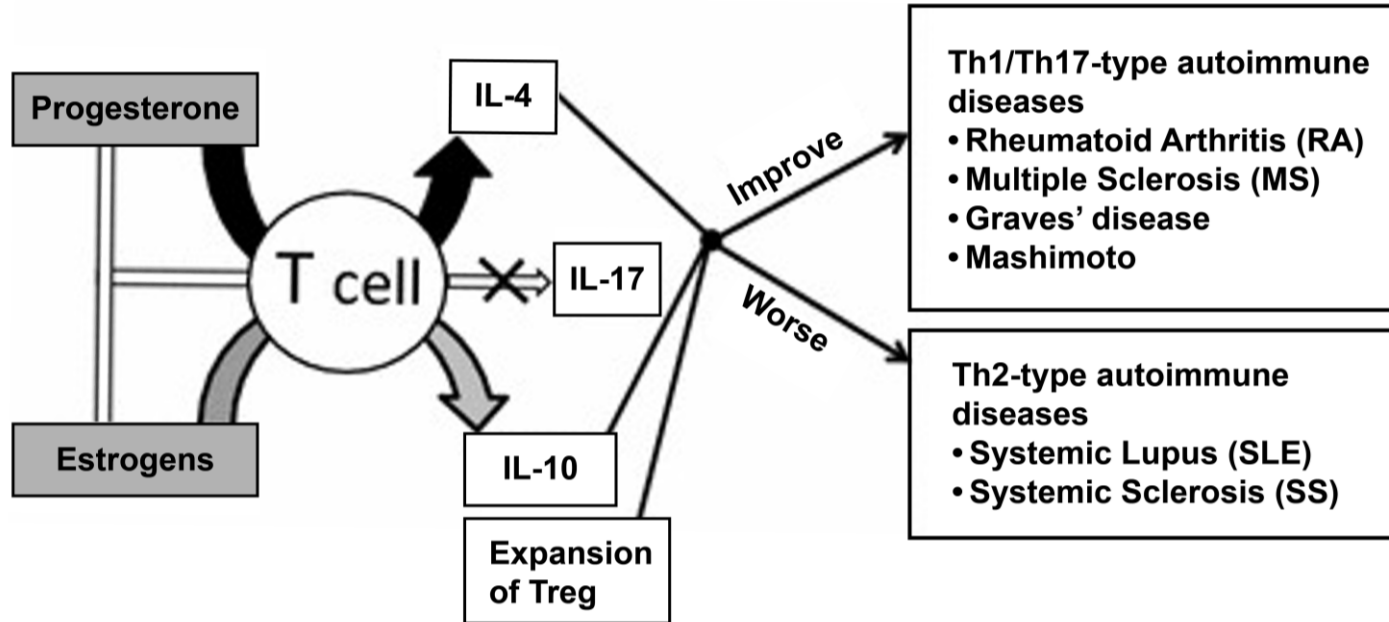


# Overview

---

- **Basic principles**
- **Case 1: Pregnancy**
- **Case 2: Contraception**
- **Case 3: Fertility**

# High Estrogen States Affect Immunologic Milieu



Piccinni *et al.*, Clin Mol Allergy. 2016; Moulton, Frontiers Immunol 2018; Sohn Nature 2021

# Reference

## Arthritis Care & Research











Vol. 72, No. 4, April 2020, pp 461–488

DOI 10.1002/acr.24130

© 2020, American College of Rheumatology

AMERICAN COLLEGE  
of RHEUMATOLOGY  
*Empowering Rheumatology Professionals*

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

Lisa R. Sammaritano,<sup>1</sup> Bonnie L. Bermas,<sup>2</sup> Eliza E. Chakravarty,<sup>3</sup> Christina Chambers,<sup>4</sup> Megan E. B. Clowse,<sup>5</sup>  Michael D. Lockshin,<sup>1</sup> Wendy Marder,<sup>6</sup> Gordon Guyatt,<sup>7</sup> D. Ware Branch,<sup>8</sup> Jill Buyon,<sup>9</sup> Lisa Christopher-Stine,<sup>10</sup>  Rachelle Crow-Hercher,<sup>11</sup> John Cush,<sup>12</sup> Maurice Druzin,<sup>13</sup> Arthur Kavanaugh,<sup>4</sup> Carl A. Laskin,<sup>14</sup> Lauren Plante,<sup>15</sup> Jane Salmon,<sup>1</sup>  Julia Simard,<sup>13</sup>  Emily C. Somers,<sup>6</sup>  Virginia Steen,<sup>16</sup> Sara K. Tedeschi,<sup>17</sup>  Evelyne Vinet,<sup>18</sup>  C. Whitney White,<sup>19</sup> Jinoos Yazdany,<sup>20</sup>  Medha Barbhuiya,<sup>1</sup>  Brittany Bettendorf,<sup>21</sup> Amanda Eudy,<sup>5</sup> Arundathi Jayatilleke,<sup>15</sup> Amit Aakash Shah,<sup>22</sup> Nancy Sullivan,<sup>23</sup> Laura L. Tarter,<sup>17</sup> Mehret Birru Talabi,<sup>24</sup>  Marat Turgunbaev,<sup>22</sup> Amy Turner,<sup>22</sup> and Kristen E. D'Anci<sup>23</sup>

Co-published in Arthritis & Rheumatology:



# Case 1:

**Pregnancy**



# Case: Michelle



- **25 YO, hx of SLE diagnosed at age 21**
  - Photosensitive rash, oral ulcers, recurrent pericarditis, inflammatory arthritis
  - ANA 1:1280 speckled, low C3 and C4, dsDNA++
- **Prescribed:**
  - **Hydroxychloroquine**
  - **Methotrexate**
- **Referred to UPMC Lupus Center of Excellence**
- **Obstetric History:**
  - **G0**
  - Wants to conceive a pregnancy in the next few months

# People with Rheumatic Diseases (RMDs) can die from pregnancy



- **Systemic Lupus Erythematosus (SLE)**
- **Antiphospholipid antibody syndrome (APS)**
- Sjogren's Syndrome
- Vasculitis
- Scleroderma
- Myositis
- Spondyloarthritis
- Rheumatoid arthritis (RA)



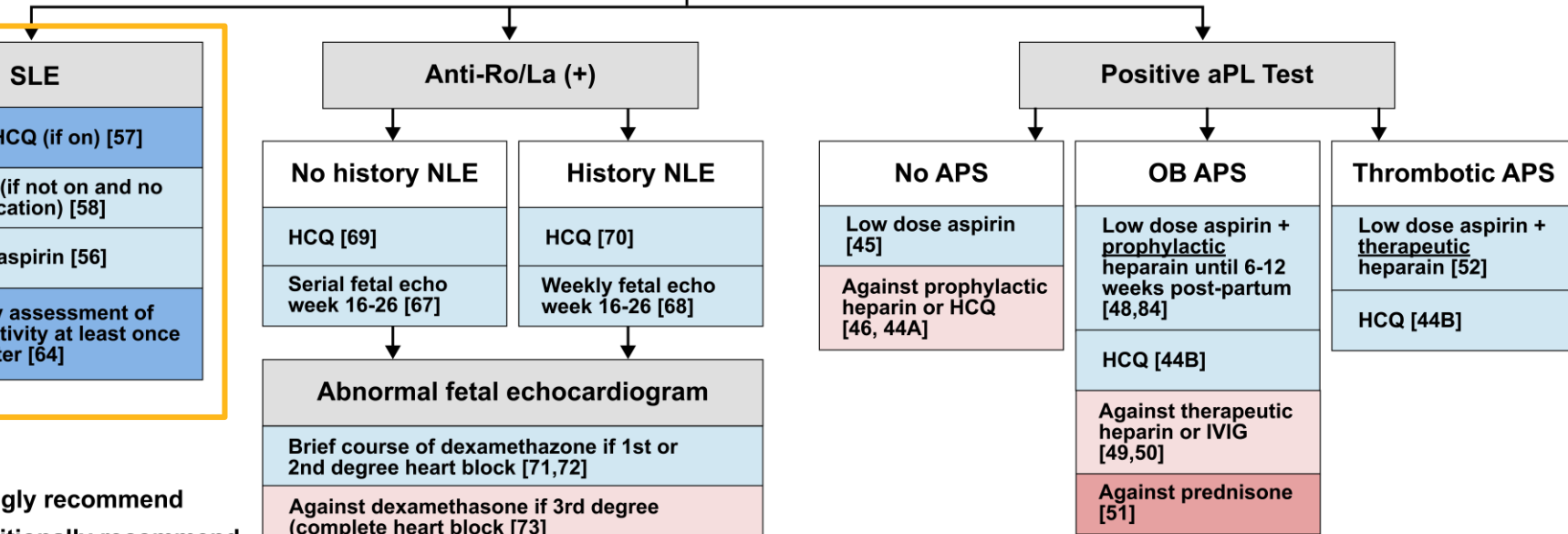
Complications	Disease	Healthy
Miscarriage	40%	15%
Stillbirth	16%	1%
Preterm birth	39%	9%
Growth restriction	30%	5%
Preeclampsia	2-4x risk	-

Clowse *et al.*, 2013; Mehta *et al.*, 2019; Clowse *et al.*, 2018; Clowse *et al.*, 2016; CDC Facts Stillbirth 2017; Ho *et al.*, 2011; Kwok *et al.*, 2011; Ostensen *et al.*, 2015; Weber-Schoendorfer *et al.*, 2014; Wallenius *et al.* 2015; Barrett *et al.*, 1999



# Pre-Pregnancy and Pregnancy Counseling

Assess patients beginning early pregnancy\*



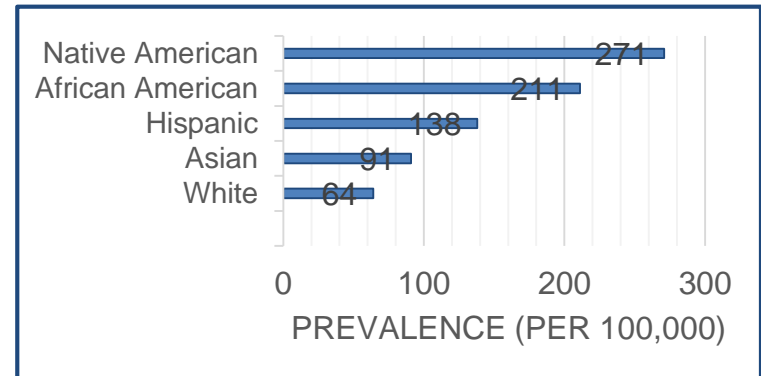
- Strongly recommend
- Conditionally recommend
- Strongly recommend against
- Conditionally recommend against

Bracket [#] refer to recommendation # (See appendix 7)

Legend: HCQ= hydroxychloroquine; NLE = neonatal lupus; APS = antiphospholipid antibody syndrome; OB APS = obstetric APS

# Systemic Lupus Erythematosus (SLE)

- Autoimmune disease that results in inflammation and tissue damage
- 85% of patients are female
  - Prevalence peaks in reproductive years
- Characterized by flares, spontaneous remission
- Can affect any organ
  - Skin, joints, heart, kidneys, lungs, nervous system



# SLE and pregnancy



## Complications

- Maternal flares are common (25-60%)
- Preeclampsia risk 2-fold higher than healthy people
  - Risk is higher with presence of antiphospholipid antibodies (40% of SLE patients have +aPLs)
- Fetal complications related to placental dysfunction: growth restriction, preterm delivery, fetal loss
- **Hydroxychloroquine (HCQ):**
  - Reduces SLE disease activity
  - Reduces risk of preeclampsia and preterm birth

# Trend labs, as changes of normal pregnancy can be hard to differentiate from SLE flares.....

---

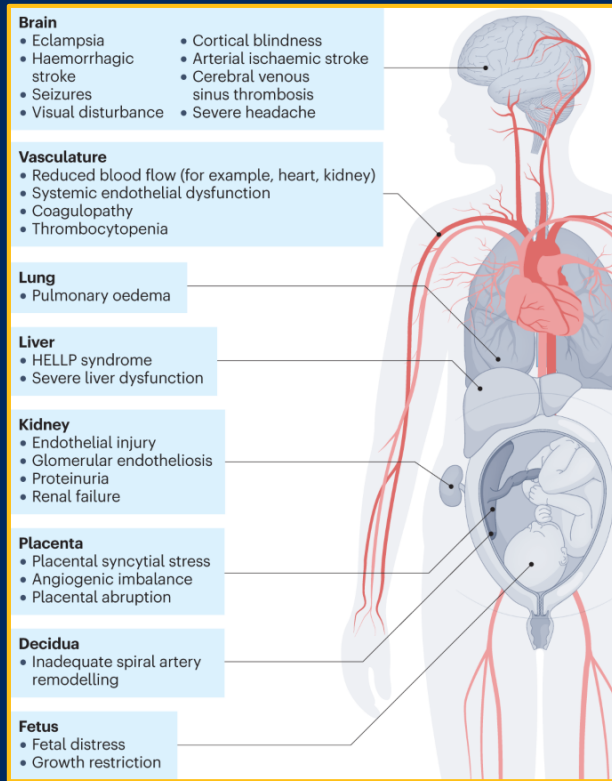
**C3 and C4 rise by  
10-50%**

**Physiologic proteinuria  
< 300 mg/d**

**ESR can increase by 30-70%  
(CRP a little more useful for  
RMD patients)**

**Mild anemia and  
thrombocytopenia (100-150K)  
are common**

# Preeclampsia causes maternal and fetal death



- Among the 4 top causes of U.S. maternal death
  - Occurs > 20 weeks of gestation
  - SBP  $\geq 140$  or DBP  $\geq 90$  mm Hg
  - Platelets  $\downarrow$
  - Creatinine  $\uparrow$
  - Proteinuria  $\uparrow$
  - Edema  $\uparrow$
- Mimics lupus nephritis

Nature Reviews Disease Primers: Preeclampsia

# Preeclampsia prevention for pregnant RMD patients

## American College of Obstetricians and Gynecologists Opinion

**Table 1.** Clinical Risk Assessment for Preeclampsia\*

<b>Risk Level</b>	<b>Risk Factors</b>	<b>Recommendation</b>
High	<ul style="list-style-type: none"><li>• History of preeclampsia, especially when accompanied by an adverse outcome</li><li>• Multifetal gestation</li><li>• Chronic hypertension</li><li>• Type 1 or 2 diabetes</li><li>• Renal disease</li><li>• Autoimmune disease (systemic lupus erythematosus, antiphospholipid syndrome)</li></ul>	<ul style="list-style-type: none"><li>• “Low-dose aspirin (LDASA) 81 mg/day prophylaxis is recommended in women at high risk of preeclampsia”</li><li>• “LDASA should be initiated between 12 weeks and 28 weeks of gestation (optimally before 16 weeks) and continued daily until delivery”</li></ul>

RA, PsA, vasculitis also associated with 2-fold or higher risk of preeclampsia

Low-dose aspirin use during pregnancy. ACOG Committee Opinion No. 743. Obstet Gynecol 2018; Secher et al., RMD Open 2022; Machen et al., Rheum Dis Clin North America 2017

# Disease-modifying anti-rheumatic drugs (DMARDs) may confer fetal risk

	<b>Pregnancy Loss (1st trimester)</b>	<b>Congenital Anomalies</b>
<b>Normal pregnancy</b>	15%	3%
<b>Hydroxychloroquine</b>	No increased risk	No increased risk
<b>Azathioprine</b>	No increased risk	No increased risk
<b>TNF-alpha inhibitors</b>	No increased risk	No increased risk
<b>FETOTOXIC DMARDs (exposure in 1st trimester):</b>		
<b>Methotrexate</b>	~40%	~7%
<b>Mycophenolate mofetil &amp; Mycophenolic Acid</b>	~40%	~25%

# Meds During Pregnancy and Lactation



**FDA**  
**recommends**  
**avoiding use of**  
**NSAIDs in**  
**pregnancy at 20**  
**weeks or later**  
**because they**  
**can result in low**  
**amniotic fluid.**

10-15-2020 FDA  
 Drug Safety  
 Communication.

Medication	Pre-conception	During pregnancy	Breastfeeding
<b>Conventional medications</b>			
Hydroxychloroquine	++	++	++
Sulfasalazine	++	++	++
Colchicine	++	++	++
Azathioprine, 6-mercaptopurine	++	++	+ Low transfer
Prednisone	+ Taper to <20mg/day by adding pregnancy- compatible immunospressants	+ Taper to <20mg/day by adding pregnancy- compatible immunospressants	+ After a does of <20mg, delay breastfeeding for 4 hours
Cycloporine, tacrolimus	+ Monitor blood pressure	+ Monitor blood pressure	+ Monitor blood pressure
Nonsteroidal antiinflammatory drugs (cyclooxygenase 2 inhibitors not preferred)	+ Discontinue if the woman is having difficulty conceiving	+ Continue in the first and second trimesters; discontinue in the third trimester	+ Ibuprofen preferred

++ Strongly recommend     
 xx Strongly recommend against  
+ Conditionally recommend     
 x Conditionally recommend against



# Biologic Medication Safety

Medication	Pre-conception	During pregnancy	Breastfeeding
<b>Tumor necrosis factor inhibitors</b> (tumor necrosis factor inhibitors are considered compatible with pregnancy)			
Certolizumab	++	++	++
Infliximab, etanercept, adalimumab, golimumab	+ Continue through conception	+ Continue in 1st and 2nd trimesters; discontinue in 3rd trimester several half-lives prior to delivery	++
Rituximab	+ Discontinue at contraception	+ Life-/organ-threatening disease	++
<b>Other biologics</b> (limited safety data; limited transfer in early pregnancy but high transfer in second half of pregnancy)			
Anakinra, belimumab, abatacept, tocilizumab, secukinumab, ustekinumab	+ Discontinue at conception	X Discontinue during pregnancy	+ Expect minimal transfer due to large molecular size, but no available data

++

Strongly recommend

xx

Strongly recommend against

+

Conditionally recommend

x

Conditionally recommend against

Gorodensky JH, Bernatsky S, Afif W, Filion KB, Vinet É. Ustekinumab safety in pregnancy: a comprehensive review. Arthritis Care Res (Hoboken). 2021 Nov 8 in press.

# Medications to Avoid

Medication	Pre-conception	During pregnancy	Breastfeeding
<b>Not compatible with pregnancy</b>			
<b>Methotrexate</b>	<b>XX</b> Stop 1-3 months prior to conception	<b>XX</b> Stop and give folic acid 5mg/day	<b>X</b> Limited data suggest low transfer
<b>Lefunomide</b>	<b>XX</b> Cholestyramine wash-out if detectable levels	<b>XX</b> Stop and give cholestyramine wash-out	<b>XX</b>
<b>Mycophenolate mofetil and mycophenolic acid</b>	<b>XX</b> Stop >6 weeks prior to conception to assess disease stability	<b>XX</b>	<b>XX</b>
<b>Cyclophosphamide</b>	<b>XX</b> Stop 1-3 months prior to conception	<b>+</b> Life-/organ-threatening disease in 2nd and 3rd trimesters	<b>XX</b>
<b>Thalidomide</b>	<b>XX</b> Stop 1-3 months prior to conception	<b>XX</b>	<b>XX</b>
<b>Tofacitinib, apremilast, baricitinib</b>	Unable to determine due to the lack of data; small molecular size suggests transfer across the placenta and into breast milk.		

**++** Strongly recommend

**XX** Strongly recommend against

**+** Conditionally recommend

**X** Conditionally recommend against

# Case 2: Contraception



# Case: Maya



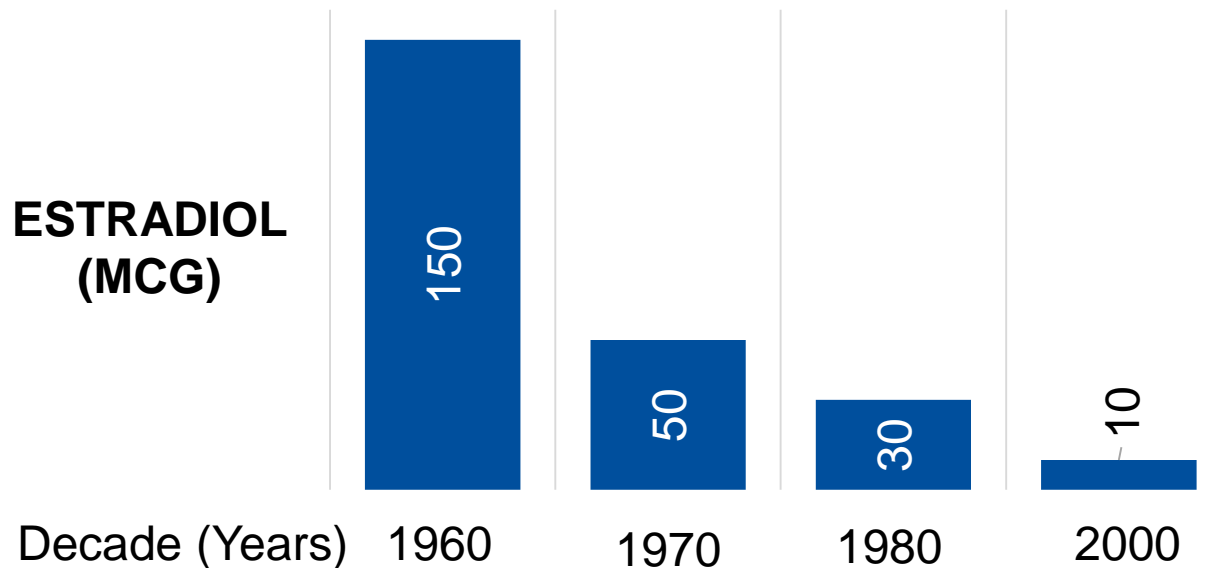
- **29 YO, hx of SLE diagnosed at age 16**
  - Fatigue, rashes, serositis, Raynaud's, livedo reticularis
  - ANA 1:640 speckled, low C3 and C4, **+Lupus anticoagulant**
- **Prescribed:**
  - Hydroxychloroquine
  - Low dose aspirin (LDASA)
- **Obstetric History:**
  - **G1P1**
    - Pregnancy complicated by preeclampsia, delivery at 34 weeks
  - **Wants to avoid pregnancy**
  - **Using condoms**

# Older contraceptives may have augmented SLE disease activity

---

- **Combined oral contraceptives (COC) were found to induce development of anti-nuclear antibodies among young females followed prospectively (1970s)**
- **Among females with SLE who used COCs (N=21), 43% developed a flare within 3 months of starting contraception (1980s)**
  - 19% of flares included lupus nephritis
    - Females using higher doses of estradiol (50 v 30 mcg) trended towards greater likelihood of developing renal disease

# Estradiol levels in combined oral contraceptives (COCs) over time



# Estrogen-containing contraception appears to be safe in stable SLE

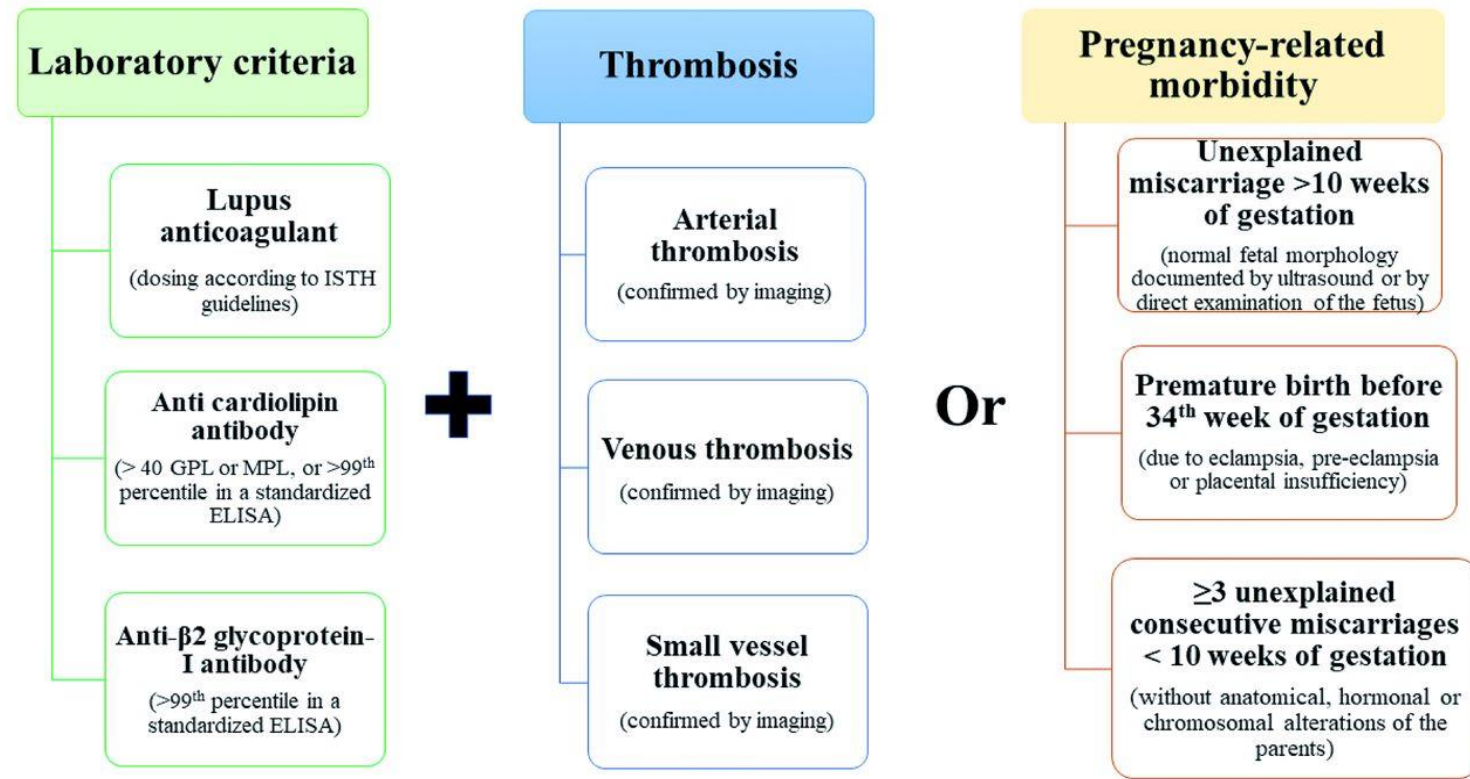
## SELENA trial

- **183 females with inactive or stable active SLE**
  - Exclusions: aPL (lupus anticoagulant, anticardiolipin or beta 2 glycoprotein antibodies, or prior thrombosis)
- Patients were randomized to receive combined estrogen-progestin (35 mcg estradiol) COC vs placebo
- One year follow-up
- Rates of SLE flares did not differ between groups

## Sanchez-Guerrero *et al.*

- **162 females with stable SLE**
  - Exclusions: prior thrombosis, severely active SLE (SLEDAI>30), smoking >15 cigarettes/d, cancer, platelets<50K, liver/CV disease
- Randomized to COC (30 mcg estradiol) vs oral progestin-only pill vs copper IUD
- Followed over 1 year
- No difference in disease activity across groups; trended downwards across groups
- Thromboses seen in hormone groups (COC [n=2], progestin [n=2]); none in IUD group
  - All patients with thrombosis had antiphospholipid antibodies

# Antiphospholipid antibodies and APS



ISTH: International Society on Thrombosis and Haemostasis



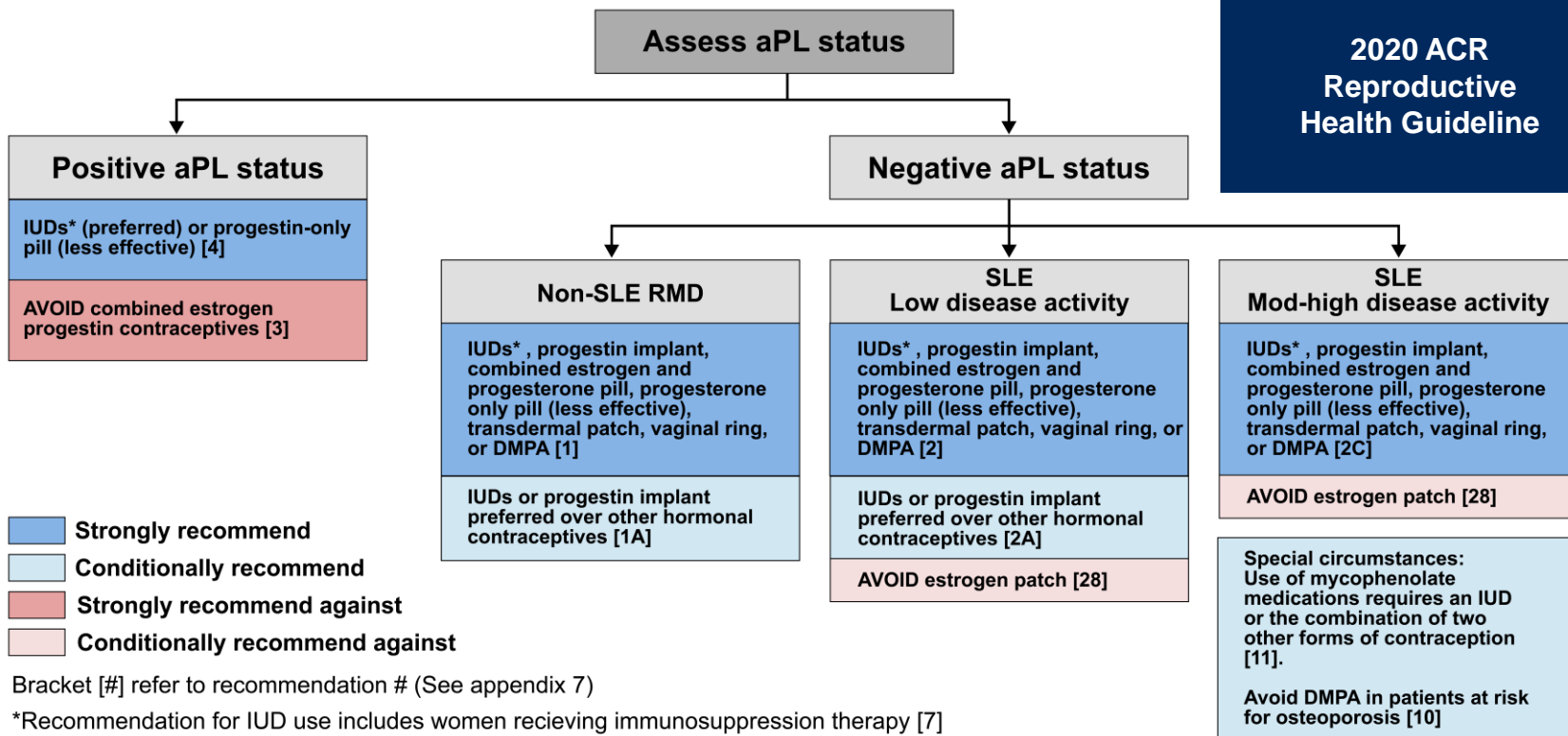
# Thrombotic Risks & Contraception – aPL+ antibodies

---

- Lupus anticoagulant (LAC) conveys greatest risk
  - 4 to 16-fold increased risk for future thromboembolism if LAC positive vs negative
  - Varying association between thrombosis and B2GP and ACL antibodies
    - Higher the titer, higher the risk
  - Elevated risk in **triple positivity** = LAC + B2GP + ACL
- No RCTs assess contraception safety among APS patients
  - Estrogen-containing contraception associated with 2-5x higher risk of venous thromboembolism, stroke, or myocardial infarction
    - 1-5/10,000 young females have a VTE
    - 2-10/10,000 if using estrogen-containing contraception
    - **Risk of thrombosis with estrogen-containing contraception is felt to be unacceptably high for people with aPL+**

# American College of Rheumatology Reproductive Health Guideline: Contraception

2020 ACR  
Reproductive  
Health Guideline



**Legend: aPL = antiphospholipid antibody(-ies); DMPA = depot medroxyprogesterone acetate shot**

# I. Progestin-Only: Lower thromboembolism risk than estrogen, safe for most

## IMPLANT



Safe for SLE,  
aPL+

## IUD



Safe for SLE,  
aPL+

## “MINI PILL”



Safe for SLE,  
aPL+

## DEPO SHOT



Safe for SLE,  
**Avoid if aPL+**

# Safe for all patients, including SLE and aPL+

**IMPLANT**



**INTRAUTERINE  
DEVICE**

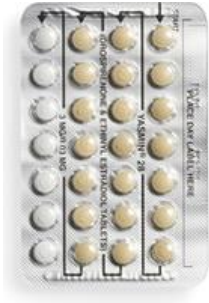


**“MINI PILL”**



## II. Estrogen-Containing Methods: Safe for some

### PILL



**NOT Safe for  
aPL+**

### RING



**NOT Safe for  
aPL+**

### PATCH



**Avoid in SLE  
NOT Safe for aPL+**

*Relative* contraindications: hypertension, CVD, migraine with aura, smoking if  $\geq 35$  YO, and history of thromboembolism, stroke or breast cancer

# PROGESTIN-ONLY PILL: OVER THE COUNTER (early 2024)

Safe for all patients, including SLE and aPL+



- Opill was FDA approved on 7/13/23
- U.S. joins 100 other countries in which OCPs are over the counter
- Cost TBD

# EMERGENCY CONTRACEPTION:

## Safe for all patients, including SLE and aPL+



- Progestin-only
- Not abortifacients
- EC pills are effective for up to 5 days after unprotected sex, but effectiveness wanes with each day
- Some EC pills are available over the counter

# Contraception Method Effectiveness

**Highly Effective  
(<1% Failure)**



- **Implant**
- **IUD**
- **Sterilization**

**Moderately effective  
(6-9% failure)**



- **Patch**
- **Depo**
- **Mini Pill**
- **Vaginal Ring**
- **Combination Pill**

**Least effective  
(18-25% failure)**



- **Condom**
- **Spermicide**
- **Diaphragm**
- **Fertility awareness**



# Patient Resources: ACR-Bedsider Collaboration

## WHAT BIRTH CONTROL IS SAFE WITH RHEUMATIC DISEASE?\*

**Safe for all**

Most effective at preventing pregnancy.

Can be used alone or with any another method for STIs protection.

IUDs    Implant    Mini-Pill    Condom    EXIT

These methods as well as fertility awareness, diaphragms, and sterilization are safe for everyone with rheumatic disease—including lupus!

**Safe for most**

Steroid medications and the shot can affect bone health.

Think about another method if you have very active lupus.

Shot    Ring    Pill

The benefits of these methods generally outweigh the potential risks.

Consider other methods if you have positive antiphosphotpid antibodies.

**It depends**

Patch

Most birth control methods are safe for people with rheumatic disease—including lupus.

For more information about your birth control options, go to [Bedsider.org/rheum](http://Bedsider.org/rheum)

Consider other methods if you have lupus or positive antiphosphotpid antibodies.

\*There are many rheumatic and musculoskeletal diseases and conditions including fibromyalgia, lupus, psoriatic arthritis, rheumatoid arthritis, and scleroderma. For a complete list go to [www.bedsider.org/health/conditions/conditions/conditions](http://www.bedsider.org/health/conditions/conditions/conditions)

Products displayed are for informational purposes only. ACD does not support any brand or manufacturer.



# Case 3: Fertility



# Case: Monica



- **34 YO, hx of Rheumatoid Arthritis diagnosed at age 27**
  - CCP>250, RF+, three radiographic erosions at R MCP 3-5
- **Trying to conceive a pregnancy**
  - **G0**
- **Prescribed:**
  - **Adalimumab (TNF-alpha inhibitor)**
  - She **self-discontinued adalimumab six months ago** due to concerns that it might be unsafe for a fetus
- **Physical exam:**
  - Tearful, tired-appearing
  - Synovitis in all MCPs and 3/5 PIPs bilaterally

# Rheumatoid Arthritis (RA)

## Disease

- Symmetric, polyarticular, chronic inflammatory arthritis

## Sex

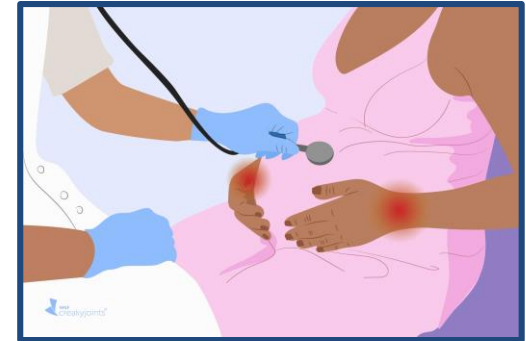
- Female to male ratio: 3:1

## Age

- Common onset: 30s-50s

## Pregnancy

- Pregnant people may experience remission (~16%)

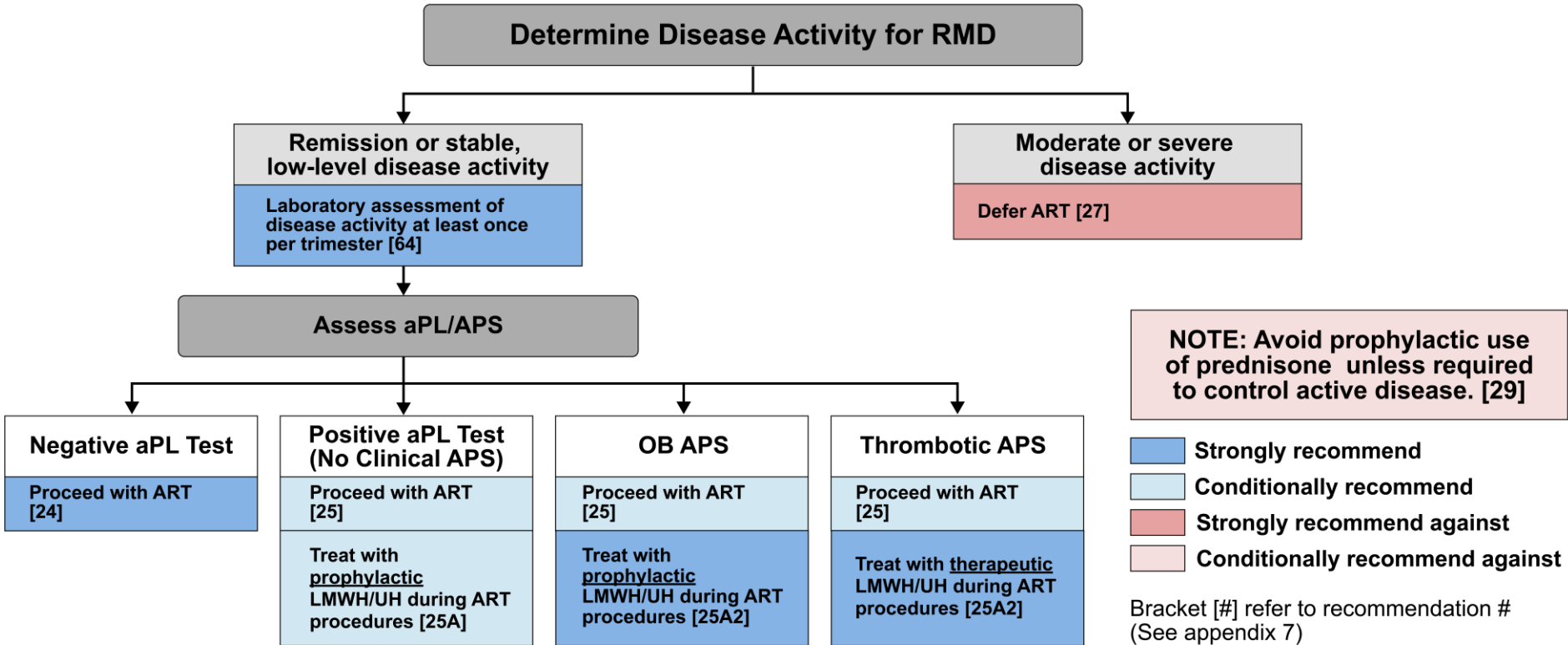


# Disease activity impacts fertility in RA



- Slight reduction in fertility
- Longer time to pregnancy with:
  - Increased age
  - Nulliparity
  - Preconception use of NSAIDs or prednisone (esp if  $>7.5$  mg/day)
  - Uncontrolled disease activity is a risk factor for infertility
    - Treatment may be necessary

# ACR RHG Fertility and Assisted Reproductive Technologies



Legend: CYC = cyclophosphamide; UH = unfractionated heparin

# Assisted Reproductive Technologies



**Efficacy is around 30% for patients with RMDs, similar to general population**

<b>Common methods</b>	
<b>Ovarian stimulation</b>	Luteinizing hormone (LH), Follicle-stimulating hormone (FSH), and HCG are used to stimulate oocytes
<b>In vitro fertilization</b>	Ovaries are stimulated, then oocytes are surgically extracted, fertilized, and implanted into female
<b>Cryo-preservation</b>	Ovaries are stimulated and then cryopreserved. Can also be fertilized, in which case the embryos are cryopreserved

# ART and disease activity

---

- **ART may increase estrogen levels by 10-fold**
  - Lupus flares among 10-43% of women with SLE who undergo ART
    - Flares include rash, alopecia, arthritis; no new renal disease
- **Defer ART while RMD is moderately or severely active**
  - Continue pregnancy-compatible meds or biologics for patients with stable disease who are planning for pregnancy
  - Any med is OK except cyclophosphamide (CYC) for patients who do plan for immediate pregnancy
    - CYC can induce infertility



# Thank You!

Sonya Borrero, MD MS  
Megan Clowse, MD MPH  
Olivia Stransky, MPH  
Leslie Pierce, MS

All of the patients and clinicians who have contributed to this work

---

**Mehret Birru Talabi, MD PhD | [birrums@upmc.edu](mailto:birrums@upmc.edu)**

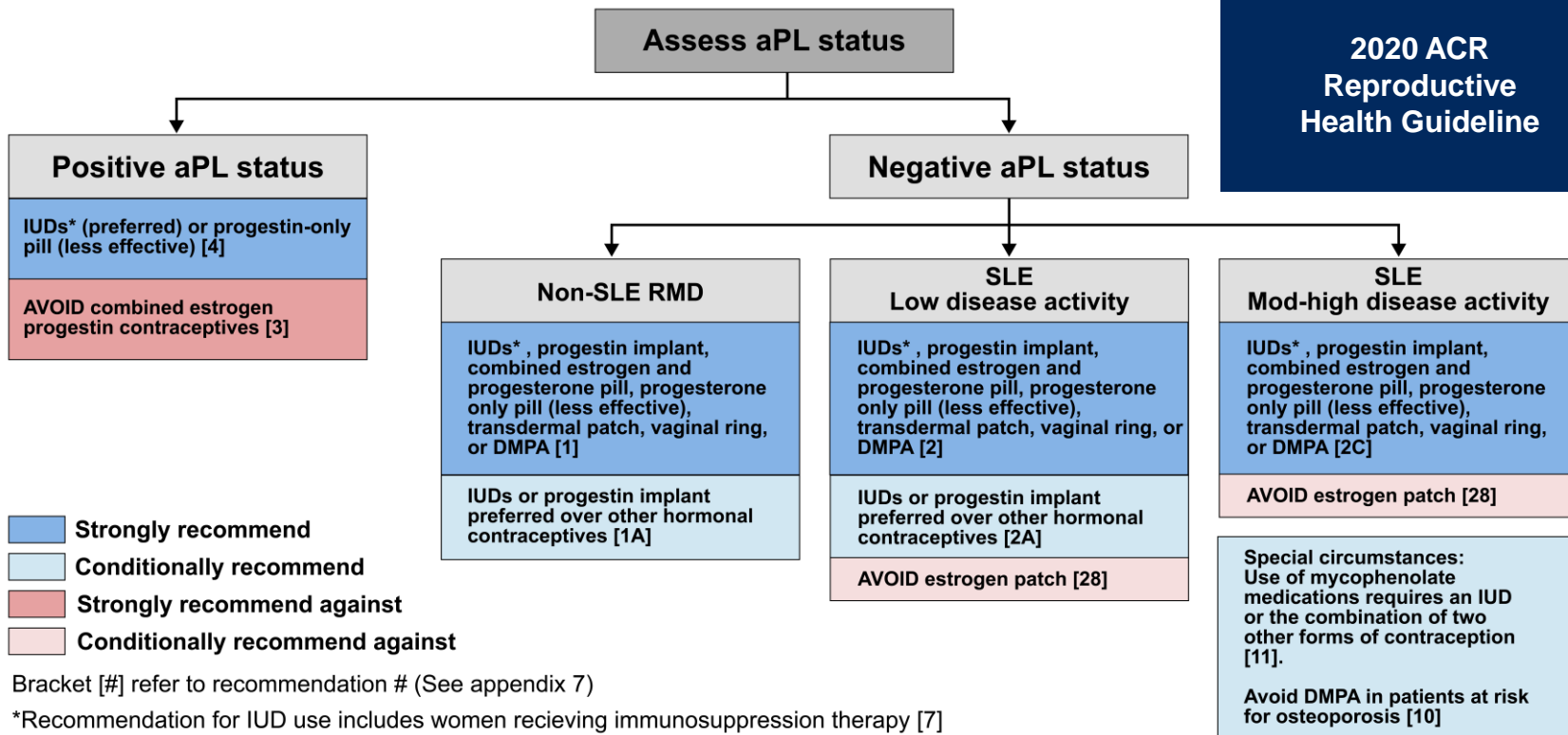
## **Work supported by:**

NIAMS K23 Career Development Award  
RWJ Harold Amos Medical Faculty Development Award  
NICHD R21 (PI: Talabi)    NIAMS R01 (PI: Clowse)



# American College of Rheumatology Reproductive Health Guideline

2020 ACR  
Reproductive  
Health Guideline



Bracket [#] refer to recommendation # (See appendix 7)

\*Recommendation for IUD use includes women receiving immunosuppression therapy [7]

**Legend: aPL = antiphospholipid antibody(-ies); DMPA = depot medroxyprogesterone acetate shot**