Pregnancy and Rheumatic Diseases: A Primer for the Internist

Chelsey J. F. Smith, MD


Can I ask if she's pregnant NOW?!
Not unless you you can see the head actually CROWNING.
I love messing with these guys.
PREGNANCY Humor.com

Who cares?

- Autoimmune diseases and pregnancies are among us
- Women > men affected, often of child-bearing age
- Teratogenic medications often used
- Educating our patients effectively is essential

Outline

- Normal pregnancy state
- Management and pregnancy outcomes in:
  - Systemic lupus erythematosus (SLE)
  - Inflammatory arthritides
    - Rheumatoid arthritis (RA)
    - Psoriatic arthritis (PsA) and ankylosing spondylitis (AS)
- Contraception

Physiologic changes in pregnancy

- Hemodynamic changes: CO and HR ↑, SVR and BP ↓
- Heme: Anemia, WBCs ↑, platelets ↓, hypercoagulable state
- Respiratory: Dyspnea (FRC ↓), minute ventilation ↑
- CV: Arrhythmias and palpitations
- Renal: GFR ↑, urine protein excretion ~200 mg/24 hr in 2/3 trimesters
- GI: N/V, bloating, constipation, GERD, hemorrhoids
- MSK: SI joint loosening, widening pubic symphysis, lumbar lordosis
- Endocrine: mild peripheral insulin resistance, ↑estrogen/progesterone

Immunology of pregnancy

- Shift from Th1 to Th2 Cytokines
  - cellular immunosuppression: ↓IL-2, TNF-a, IFN-γ
  - humoral immunostimulation: ↑IL-4, IL-6, IL-10
- Three phases
  - 1st trimester: Pro-inflammatory
    - Allows for successful implantation, cellular "invasion," repair of uterine epithelium, removal of cellular debris
  - 2nd-mid 3rd trimester: Anti-inflammatory
    - Fetal growth and development
  - Late 3rd trimester: Pro-inflammatory
    - Preparation for childbirth, promotes uterine contraction, rejection of placenta

Mor G, Cardenas I. Am J Reprod Immunol 2010
Chatterjee P, et al. Front Immunol 2014

Immunology of pregnancy

- Regulatory T cells
  - Numbers increase during pregnancy
  - Protect fetus from alloreactive immune responses at maternal–fetal interface
  - Increased numbers in third trimester have correlated with improved disease activity in RA

- Changes in protein production and acute phase reactants
  - ↑complement (esp C3)
  - ↑ESR and CRP (esp ESR)
  - ↑AlkP (secreted by placenta)

de Man YA, et al. Arthritis Rheum 2007
Heikkinen J, et al. Clin Exp Immunol 2004
Forger F, et al. Ann Rheum Dis 2008

AIDs you may see pregnant

- Rheumatoid arthritis
- Seronegative SpA
- JIA
- SLE
- Antiphospholipid syndrome
- Scleroderma
- Dermatomyositis
- Sjogrens
- Vasculitis (Takayasu's, Behcets, GPA)
- Auto-inflammatory disease
- AOSD
- Other specialties:
  - GI (IBD)
  - Neuro (MS)
  - Endocrine (Addison's, Hashimoto's)
  - Dermatology (psoriasis, cutaneous LE, bullous diseases, etc)

Review Question

- A 34-year old lupus patient with past history including lupus nephritis and +SSA positivity currently has well-controlled disease on mycophenolate mofetil and hydroxychloroquine, and is off prednisone at this time. She wants to get pregnant.
- How would you manage her medications?

Pre-pregnancy counseling: Rules of thumb

- Planned pregnancies are the best pregnancies
- Uncontrolled disease activity portends worse outcomes
  - Advise remission for 6-12 months prior to conception
  - Address medication safety
- When should you consider **discouraging** pregnancy?
  - Creatinine >2 mg/dL
  - Prior arterial thrombosis
  - Pulmonary hypertension
  - Severe organ damage

SLE: Questions

- Can women with SLE get pregnant? Should they?
- Are lupus pregnancies normal pregnancies?
- What happens to the children of SLE mothers?

SLE: Risk stratification

- SLE pregnancies are high risk
  - ↑ Preeclampsia (~10-15%), eclampsia/HELLP (~1-1.5%)
  - ↑ Preterm birth (~25-35%), IUGR, SGA, PROM
  - Pregnancy loss in active SLE and APL antibodies
  - Flaring disease activity may occur in any trimester
- Outcomes generally favorable for patients without risk factors, with stable mild/moderate disease
- Risk stratification by:
  - Disease activity
  - Autoantibody profile
  - Previous vascular and pregnancy morbidity
  - Hypertension
  - Medication use

Andreoli L, et al. Ann Rheum Dis 2017
Bermas BL and Sammaritano LR. Fertil Res Pract 2015

SLE: Predictors of adverse outcomes

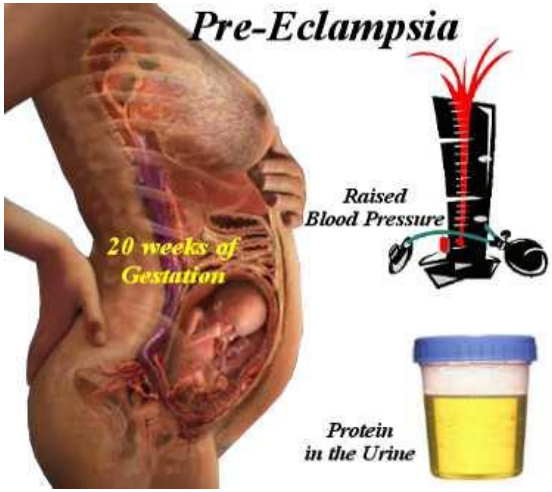
Risk Factor	Adverse outcome
Active/flaring SLE	preeclampsia/eclampsia, C section, fetal loss, preterm
Renal disease	any*
HTN	preeclampsia, preterm
Glucocorticoid use (esp ≥10-20 mg/day prednisone)	preterm
Discontinuation of HCQ	SLE exacerbation/flare
Lupus anticoagulant positivity	any*
Non-White ethnicity	any*

Buyon JP, et al. Ann Intern Med 2015
Andreoli L, et al. Ann Rheum Dis 2017

*any defined as fetal or neonatal death, preterm, HTN or preeclampsia, SGA

SLE and Preeclampsia

- Up to 30% of SLE patients
  - esp in active disease or hx renal disease
- ↑ blood pressure, edema, and proteinuria
- > 20 weeks' gestation
- Variants:
  - Eclampsia (seizures, coma)
  - HELLP syndrome: Hemolysis, Elevated Liver enzymes, and Low Platelets
- Treatment
  - Bedrest, close monitoring, Mg sulfate, delivery



Schramm AM and Clowse ME. Autoimmune Dis 2014
Buyon JP, et al. Ann Intern Med 2015

Lupus nephritis vs Preeclampsia?

- Diagnosis not always clear
  - Non-specific symptoms
    - Proteinuria, HTN, thrombocytopenia, elevated liver enzymes, deterioration in renal function
  - Symptoms of preeclampsia may persist for weeks post-partum
  - Both may occur simultaneously
- Helpful distinguishing factors:
  - Preeclampsia usually > 20 weeks
  - Urinary sediment
  - Complement levels, other signs of lupus activity
  - Uric acid
    - Levels correlate with severity of preeclampsia
  - Kidney biopsy

Lam C, et al. Semin Nephrol 2005

Neonatal lupus

- Anti-SSA/Ro or anti-SSB/La ab
  - Cutaneous lupus (birth-6 weeks) (7-16%)
    - Transient, resembles SCLE in adults
  - Congenital heart block/cardiomyopathy (in utero, 18-24 wks) (2%)
    - Management: fetal echoes starting ~16-18 weeks +/- dexamethasone
    - Having one child affected greatly increases risk of recurrence
      - Hydroxychloroquine reduces subsequent risk by **20%**

Izmirly PM, et al. Circulation 2012
Friedman D, et al. Images Paediatr Cardiol 2003

Medication Safety update

- FDA proposed new Pregnancy and Lactation Labeling Rule (PLLR)
- ABCDX categories → Narrative descriptions
  - summary statement up front
  - clinical considerations section
  - supporting data

Kavanaugh A, et al. Arthritis Care Res 2015

SLE: Medical management

- Control disease and prevent adverse outcomes
- Hydroxychloroquine (HCQ)
  - Safe and associated with better pregnancy outcomes
  - Reduces risk of SLE flare during pregnancy
  - Associated with less prednisone use in pregnancy
  - Lowers risk of neonatal lupus and congenital heart block in infants of patients at risk (+anti-SSA/Ro or +anti-SSB/La)
  - No reported risk of congenital or ophthalmologic abnormalities
  - Safe in breastfeeding

Henderson JT, et al. Ann Intern Med 2014
Izmirly PM, et al. Circulation 2012
Cortés-Hernández J et al. Rheumatology 2002
Levy RA, et al. Lupus 2001
Clowse ME, et al. Arthritis Rheum 2006

SLE: Medical management

- Low dose ASA for preeclampsia prevention
  - Initiated prior to 16 weeks' gestation and through 3rd trimester
  - May decrease risk for preterm preeclampsia in those at risk
  - Add to LMWH in those with APLS

- Corticosteroids
  - Often necessary to control disease
  - <20 mg/day ideal dosing during pregnancy
  - Risk of gestational diabetes, preterm birth, ?cleft lip/palate

Henderson JT, et al. Ann Intern Med 2014
Bandoli G, et al. Rheum Dis Clin North Am 2017
Rolnik DL, et al. NEJM 2017

SLE: Medical management

- Low risk considerations
  - HCQ
  - azathioprine (AZA)
  - calcineurin inhibitors (tacrolimus, cyclosporine)
- Moderate risk considerations
  - IVIG (low/moderate)
    - Limited data, often used in combination with high risk drugs
  - rituximab
    - Risk of B cell depletion and cytopenias with late-term use
- High risk
  - MMF and cyclophosphamide contraindicated
- belimumab: limited data

Gotestam Skorpen C, et al. Ann Rheum Dis 2016

SLE in pregnancy: What you can do

- Refer to rheumatology and high risk OB early
- Control disease
  - HCQ
  - Consider: AZA, calcineurin inhibitors, IVIG
  - Labs: CBC, C3/C4, dsDNA, UA at beginning of pregnancy to follow
- Prevent adverse outcomes
  - HCQ
  - Low dose ASA
    - Maintain high suspicion for preeclampsia after 20 weeks
  - Control HTN
    - Methyldopa, labetolol, hydralazine, nifedipine
  - Labs: LAC and SSA/B to risk stratify
    - Fetal echoes in SSA/B positive women

Podymow T and August P. Hypertension 2008

Review Question

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Review Question

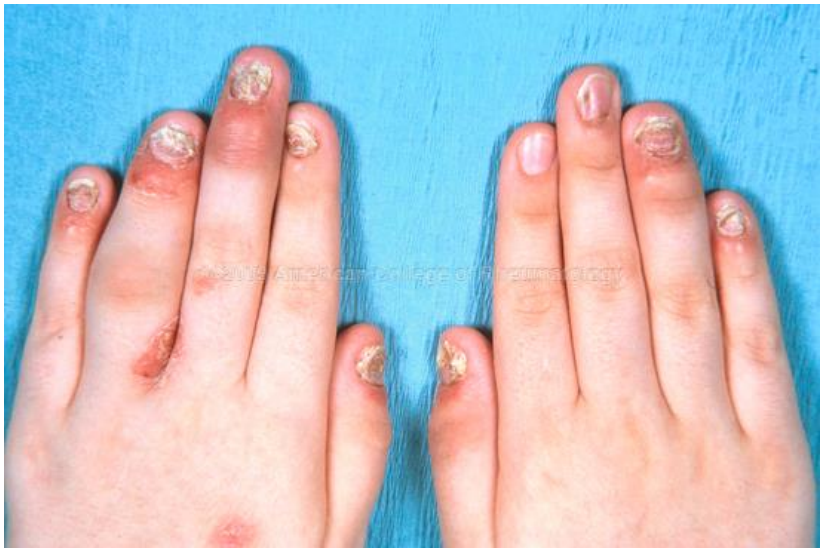
- A 34-year old lupus patient with past history including lupus nephritis and +SSA positivity currently has well-controlled disease on mycophenolate mofetil and hydroxychloroquine, and is off prednisone at this time. She wants to get pregnant.
- How would you manage her medications?
- Her provider switches her from MMF to azathioprine and continues hydroxychloroquine. The patient is concerned, however, about the medications because they are listed as Category D and C, respectively.
- How should this patient be advised?

Review Question

- A 25-year old woman presents to your clinic with new-onset active arthritis and morning stiffness. You suspect she may have rheumatoid arthritis. She is tearful, stating she doesn't want to have a chronic disease and is worried she won't be able to have a family. She was hoping to get pregnant in the next 2 years.
- How should the patient be counseled?
- What medications might be appropriate to use, and what should be avoided?

Inflammatory arthritis: Questions

- Do women with RA have difficulty getting pregnant?
- Does disease activity improve during pregnancy?
- Are RA pregnancies normal pregnancies?
- What happens post-partum?



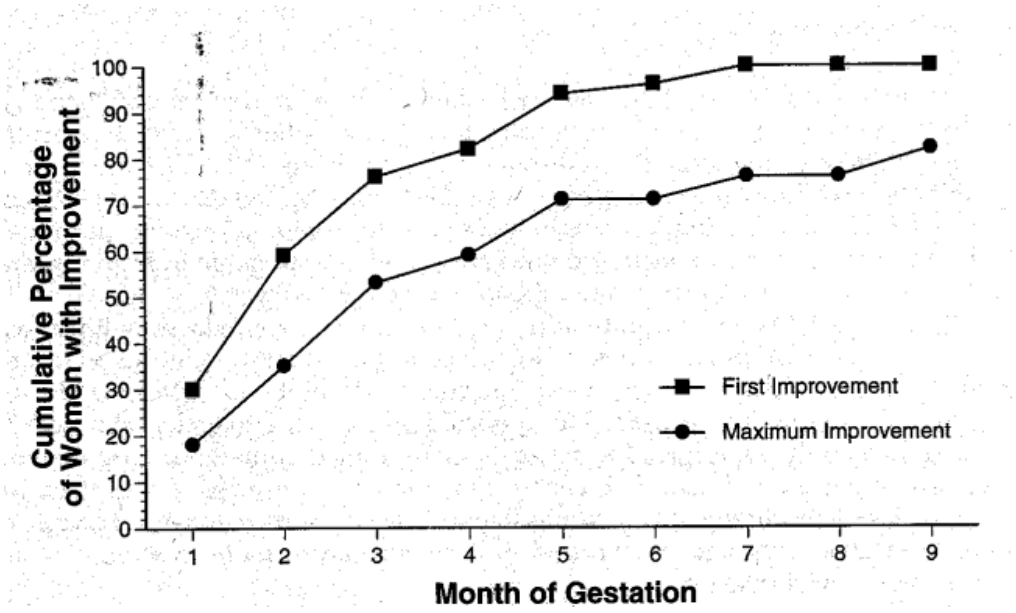
RA: Subfertility

- Women with RA have fewer children than desired (≥50%)
  - Personal choice
    - Concern for disability and effect on child care
    - Concern that disease or medications will harm a baby
    - Concern that baby will develop RA
  - Infertility
    - "Unexplained subfertility" or anovulation
    - Associated with NSAID use
    - Fertility treatments favorable
- Prolonged time to conceive >12 mos (42%)
  - Risk factors:
    - Older age, nulliparity, higher disease activity, NSAID use, prednisone >7.5 mg daily

Brouwer J, et al. Arthritis Care Res 2017
Clowse ME, et al. Arthritis Care Res 2012
Brouwer J. Ann Rheum Dis. 2014

RA: Disease activity

- Hench 1938: Relief of RA symptoms in 90% of women in 34 patient cohort

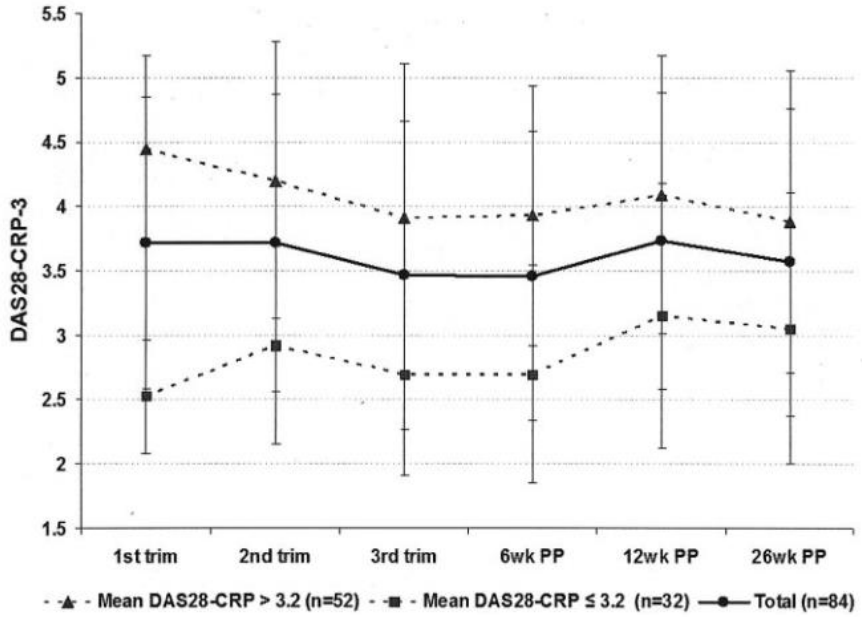


- Older studies suggest up to 75% women experience improvement in their disease during pregnancy

Hench P. Mayo Clin Proc 1938
Nelson JL and Ostensen M. Rheum Dis Clin North Am 1997

RA: Disease activity

- Dutch Pregnancy-induced Amelioration of Rheumatoid Arthritis (PARA) prospective study of 84 RA patients:



- Low disease activity PC stayed low during pregnancy
- Moderate-severe disease activity PC, ~half had moderate response during pregnancy
- Less medication used during pregnancy than PC or postpartum

de Man YA, et al. Arthritis Rheum 2008

RA: Pregnancy outcomes

- Adverse pregnancy outcomes
  - Preterm birth
  - Lower birth weight and SGA
  - Higher rate Caesarean section
  - Preeclampsia

- Increased risk for complications with:
  - Increased RA activity
  - Discontinuing medication
  - Corticosteroid use

de Man YA, et al. Arthritis Rheum 2009
Langen ES. Am J Perinatol 2014
Bermas BL and Sammaritano LR. Fertil Res Pract 2015

RA: Medical management

- Low risk medications
  - HCQ
  - sulfasalazine
  - TNF-a inhibitors
- Low/medium risk:
  - NSAIDs
  - corticosteroids
- High risk medications (contraindicated)
  - methotrexate
  - leflunomide – washout with cholestyramine
- Insufficient data
  - anakinra, rituximab, abatacept, tocilizumab, tofacitinib

Gotestam Skorpen C, et al. Ann Rheum Dis 2016

RA: Medical management

- TNF-a inhibitors
  - adalimumab, golimumab, infliximab, etanercept – may discontinue prior to 3rd trimester if disease controlled
  - certolizumab pegol
- Consider continuing through pregnancy if disease activity high
  - No evidence for birth defects or other long-term sequelae
- No live vaccinations in infant's first 6 months (rotavirus)

Gotestam Skorpen C, et al. Ann Rheum Dis 2016

RA: Medical management

- NSAIDs
  - Pre-conception: infertility risk
  - Early pregnancy: possible risk of SAB
  - 3rd trimester: oligohydramnios, fetal periventricular hemorrhage, premature closure of ductus arteriosus > 30 weeks
  - COX-2 inhibitors should be avoided

Gotestam Skorpen C, et al. Ann Rheum Dis 2016
Bermas BL. Curr Opin Rheumatol 2014

RA: Disease flares postpartum

- Pro-inflammatory immune profile in labor/delivery → may affect disease activity postpartum
- Postpartum period challenging
  - Flares make caring for newborn difficult
  - Breastfeeding may induce postpartum flares
- Prospective study of 140 women in UK
  - 66% reported worsening symptoms in the first 6 months after delivery
- PARA study
  - 50% with increased disease activity after delivery
  - 39% with at least moderate flare postpartum

Bermas B. Rheum Dis Clin North Am 2017
de Man YA, et al. Arthritis Rheum 2008
Barrett JH, et al. Arthritis Rheum 1999
Barrett JH, et al. Arthritis Rheum 2000

Psoriatic Arthritis

- Very little data, unclear if disease improves in pregnancy
- Association with metabolic syndrome
  - Excessive weight gain associated with gestational diabetes, preterm birth, preeclampsia
- Medical Management:
  - NSAIDs
  - corticosteroids
  - TNF-a inhibitors: low risk
  - Newer biologics/synthetic DMARDs with not enough data in pregnancy
    - secukinumab, ixekizumab, ustekinumab, apremilast

Polachek A, et al. Semin Arthritis Rheum 2017
Gotestam Skorpen C, et al. Ann Rheum Dis 2016

Ankylosing Spondylitis

- Disease either is stable or flares during pregnancy (2nd trimester), postpartum flares common
  - Role of Tregs
- High risk: Higher rates of c section, preterm, SGA
  - Both elective and emergent c sections
  - Influenced by disease severity and comorbidities
- TNF inhibitors can help stabilize disease activity and prevent flares during pregnancy

Jakobsson GL, et al. Ann Rheum Dis 2016
Forger F, et al. Arthritis Rheum 2007
Ursin K, et al. Rheumatology (Oxford) 2018
van den Brandt S, et al. Arthritis Res Ther 2017

Inflammatory Arthritis: What you can do

- Encourage your patients to plan ahead
- Consider d/c NSAIDs if patients having difficulty getting pregnant
- Discontinue all teratogenic medications
  - methotrexate
  - leflunomide (cholestyramine)
- Prednisone tapered to lowest effective dose
- Control disease activity and watch patients postpartum
- Be positive!

Review Question

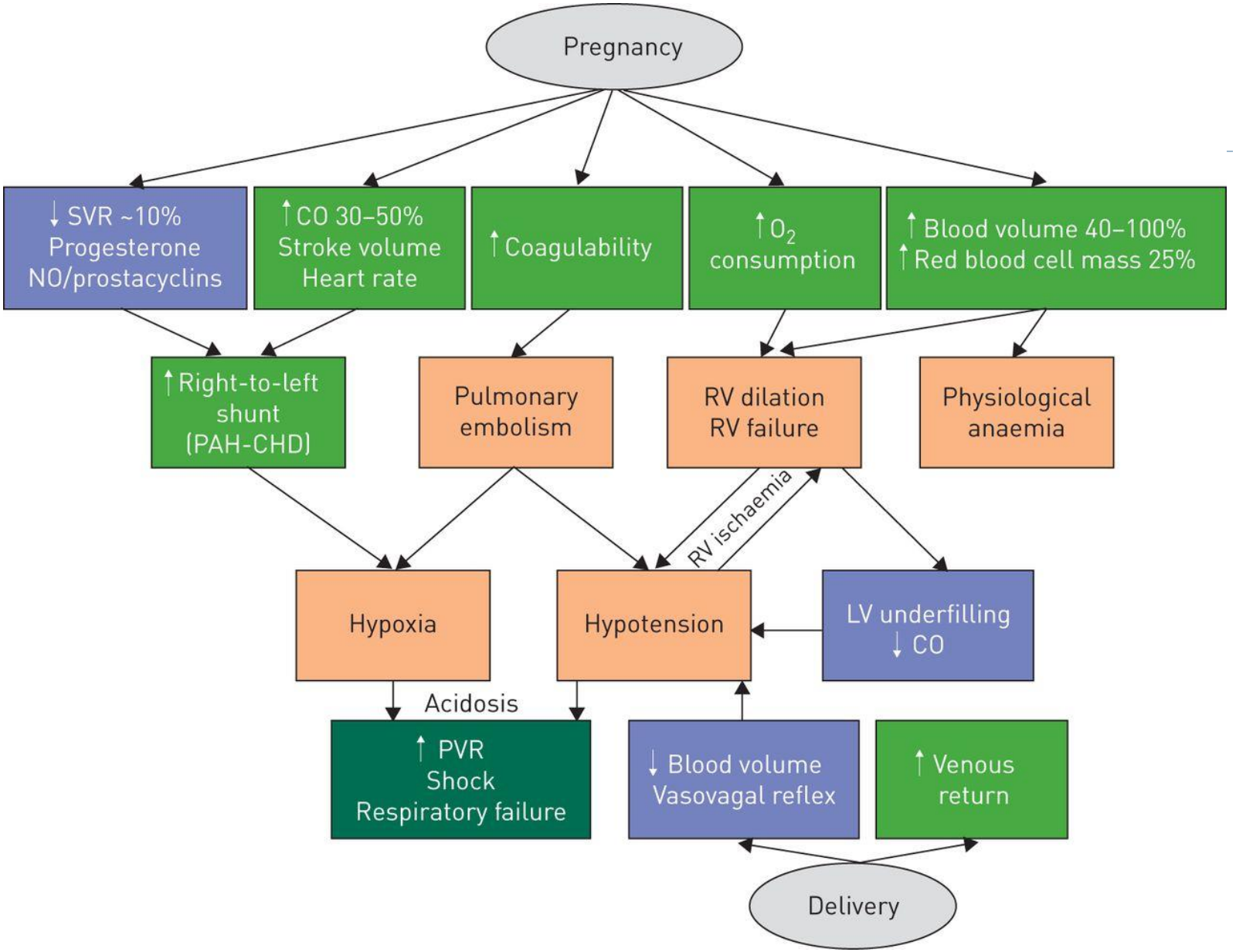
- A 25-year old woman presents to your clinic with new-onset active arthritis and morning stiffness. You suspect she may have rheumatoid arthritis. She is tearful, stating she doesn't want to have a chronic disease and is worried she won't be able to have a family. She was hoping to get pregnant in the next 2 years.
- How should the patient be counseled?
- What medications might be appropriate to use, and what should be avoided?

Scleroderma and pregnancy

- PAH = highest risk
  - Hemodynamically and PAH medications teratogenic
    - ERAs (bosentan, ambrisentan), warfarin
  - Multidisciplinary team needed
- Higher risk of renal crisis
- Diffuse disease, early disease (<4 years), certain antibody profile predict more aggressive disease
- Higher risk preterm delivery, IUGR, VLBW

- Avoid pregnancy in women with severe organ damage

Gei A and Montúfar-Rueda C. Clin Obstet Gynecol. 2014
Østensen M et al. Autoimmunity Reviews 2015
Taraborelli M, et al. Arthritis Rheum 2012



Hsu CH, et al. Int J Clin Pract Suppl 2011

Review Question

- Your 35 year old male patient is on methotrexate and sulfasalazine for RA. He and his wife would like to try for a second child. Should he be concerned about possible infertility?

What about Dad?

- **Cyclophosphamide** – oligospermia/azoospermia, low levels of testosterone and inhibin β; elevated levels of FSH
  - May improve after discontinuing medication
  - May be irreversible at higher doses
- **Sulfasalazine** – oligospermia, abnormal morphology of sperm cells and reduced sperm motility
  - Normal hormonal levels
  - Effect transient
- **Methotrexate**
  - No evidence for infertility or birth defects

Østensen M. Nat Rev Rheumatol 2017

Review Question

- A 21 year old female on hydroxychloroquine is hospitalized for flare of her lupus which now is involving her kidneys. She is placed on mycophenolate mofetil, given IV methylprednisolone, and sent home on prednisone 60 mg. She comes to see you after discharge from the hospital.
- What should you focus on at your appointment?

Contraception and counseling

- We need to do better
  - <50% of rheumatologists/gastroenterologists discuss family planning with patient's OBGYN or PCP
  - Patients feel family planning and pregnancy-related concerns not adequately addressed during medical appointments
  - Only 30-40% consider advice consistent across specialties

Chakravarty E, et al. BMJ Open 2014

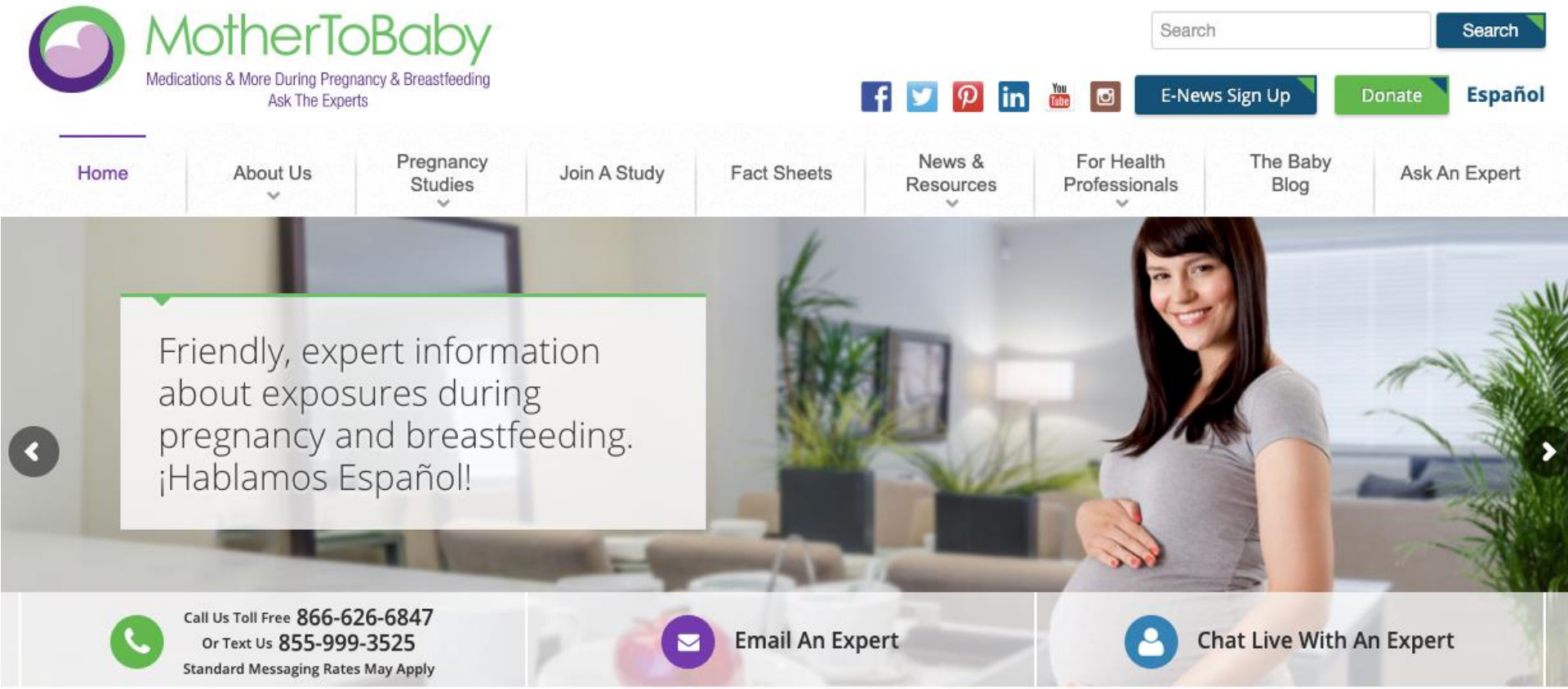
Contraception and counseling

- SLE and APLS patients are high risk for VTE
  - Avoid estrogen compounds
  - IUD (Skyla or Mirena)
  - Progestin-only pill (micronor or Mini pill)
  - Implant etonogestrel (Implanon, Nexplanon)
  - Medroxyprogesterone shot (Depo-provera)
- Most effective contraception is IUD
- Plan B progesterone-only emergency contraception

- Side note: Higher risk of HPV/cervical CA

Pre-pregnancy counseling: Considerations

- Maternal age
- Disease activity and recent flares
  - Advise remission ≥6 months prior to conception
- Presence of pulmonary HTN, renal disease, other organ involvement
- Medication use
  - Teratogenic/high risk medications
  - Corticosteroids
  - NSAIDs
- Prior adverse pregnancy outcomes
- Other comorbid conditions
- Consider **discouraging** pregnancy in setting of:
  - Creatinine >2 mg/dL, prior arterial thrombosis, pulmonary hypertension, severe organ damage



www.mothertobaby.org

Conclusions

- Autoimmune pregnancies are among us
- Safe pregnancies with good outcomes are possible if disease well-controlled
- Educate your patients on teratogenic medications and be strict about contraception when indicated
- Regular visits to high risk OB and rheumatology are encouraged throughout pregnancy and post-partum
- Use Mother to Baby as a resource and to enroll your patients in studies – mothertobaby.org
- Become a rheumatologist!

Questions?

cjfsmithMD@gmail.com