American College of Rheumatology

The Lupus Initiative

Session 3
Pregnancy & SLE

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Disclosures & Reminders

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REMINDER

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PHARMACISTS: This program has been reviewed by the Oregon Board of Pharmacy and is acceptable for up to 1 Therapeutic CE Credit Hour. For assistance, please contact Karen Kruger, M.Ed., CME Event Coordinator, Office: 541-706-2603 X2603, kmkruger@stcharleshealthcare.org

Objectives

1. Introduce important considerations for fertility and family planning in patients with lupus including medications, lupus activity, and hypercoagulability.
2. Discuss antiphospholipid antibody syndrome and its implications in pregnancy.
3. Discuss the role of SSA/SSB antibodies in neonatal congenital disease
4. Recognize neonatal lupus

Why is this important?

- Estimated 4500 pregnancies to women with SLE each year in the United States
- Wide debate in literature whether patients who are pregnant flare more than non-pregnant females
- Hopkins Lupus Pregnancy Cohort (1987-2002)
  - 265 pregnancies to SLE patients: risk for significant SLE activity was 7.25 fold higher if patient had recently active lupus prior to conception (58% vs 8%, $p<0.001$)

Clowse et al. National Study of medical complication in SLE pregnancies. Arthritis Rheum Sept 2006: S63.
Clowse et al. The impact of increased lupus activity on obstetric outcomes. Arthritis Rheum Feb; 2005 52 (2): 514-521.

What is the relationship between connective tissue diseases and pregnancy?

1. **Pregnancy-induced changes in immune system function may affect connective tissue disease**
   - Increased risk of lupus flare and RA remission
2. **CTD autoimmune effects may affect maternal/fetal outcome**
   - Antiphospholipid antibodies and increased fetal loss
3. **Transplacental autoantibodies may directly affect fetus**
   - e.g. SSA/Ro and SSB/La antibodies and neonatal lupus
4. **Severe maternal illness activity or damage may affect maternal/fetal outcome**
   - CKD, severe disease activity
5. **Medications for CTD may affect pregnancy outcomes**

Fertility and Contraception

- Medications used for SLE can affect fertility
- Timing of pregnancy in SLE is important
  - Disease control
  - Medication exposure
- Dr. Ramsey-Goldman's Pregnancy Module addressed
  - Fertility preservation
  - Contraception methods

Case #1

- 29 yo G2P1132 at 6 weeks gestation presents for care. She has chronic pain in her wrists and knees, takes Tylenol.
- 1st child was born at term w/o problems.
- (3) 1st trimester miscarriages.
- Last pregnancy she developed severe early onset (26 weeks) preeclampsia.
- Her PCP found a (+) ANA
- Her exam is unremarkable

Case #1

- What are the possible problems?
- What is the significance of a (+) ANA?
- What further workup does she need?

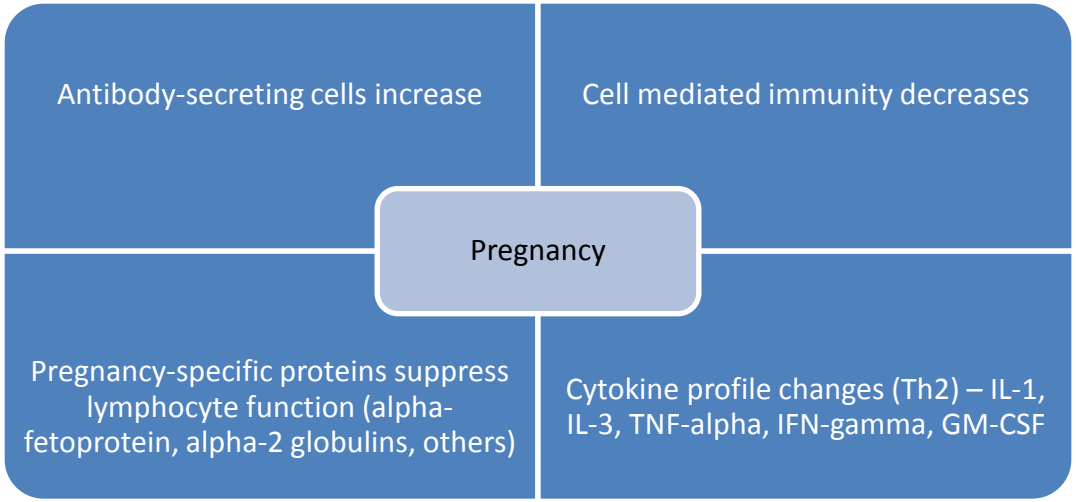
Positive ANA

- Anti-nuclear antibodies (ANA) are sensitive, but not specific, for autoimmune disease
- ~5% of multiparous women will have (+) ANA
- (+) ANA does NOT diagnose lupus

Common pregnancy symptoms

- Low back pain
- Carpal tunnel
- Fatigue/lassitude
- Chloasma/facial and palmar erythema
- Constipation
- Breathlessness
- Dizziness/ near syncope
- Pedal edema
- Urinary frequency/increased thirst
- Postpartum hair loss

Physiologic changes in pregnancy



- Increased cardiac output
- Decreased blood pressure
- Increased GFR
- Increased RR and tidal volume
- Cardiomegaly/prominent pulmonary vascular
- Dilation of renal pelvis and gallbladder
- Relaxin induced joint changes
- “Physiologic” anemia

Lab results:
Changes in pregnancy

Hb/Hct	11 g±1/33%±3
WBC	9,000-13,000
Platelets	Same
Creatinine	0.4-0.6 mg/dL
Alk phos	100-300 U/L
ESR and CRP	Elevated
Complement	Elevated
Urinalysis	Contaminated (wbcs/rbcs)
Urine protein	Up to 300 mg/24-hr

Case #1 – lab results

ANA	Positive 1:80, nucleolar
Anti-dsDNA	Negative
Anti-Smith	Negative
Anti-RNP	Negative
SSA/SSB	Negative
Lupus anticoagulant	Positive
Anticardiolipin IgG/IgM	Negative
Urine protein	269 mg/24-hour
Creatinine	0.5 mg/dL

Diagnostic criteria

- Must have ≥ **1 clinical** and ≥ **1 laboratory** criterion
- Clinical criteria
  - Unequivocal evidence of venous, arterial or small vessel **thrombosis** in any organ
  - Unexplained IUFD >= 10 weeks
  - Preterm birth < 34 weeks for eclampsia, preeclampsia, or placental insufficiency
  - 3 or more unexplained SAB < 10 weeks

2006 revised Sapporo criteria: Miyakis S et al. J Thromb Haemost 2006;4:295.

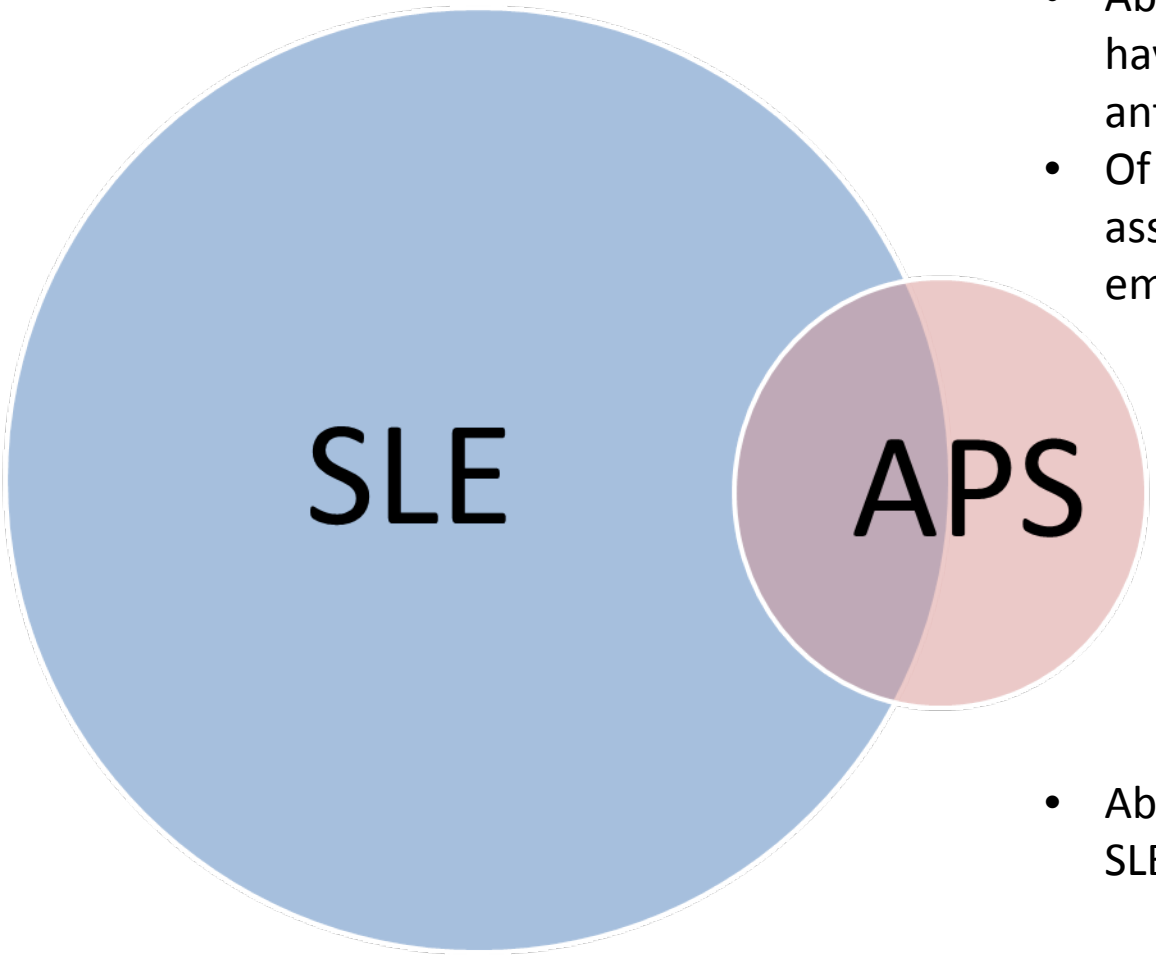
Diagnostic criteria

Lab criteria must be present on **2 or more occasions at least 12 weeks apart** by at least one of these tests:

- **Anticardiolipin Ab** (IgG or IgM in moderate or high titer, > 40 GPL or MPL)
- **Anti-β2 glycoprotein 1 antibodies** (IgG or IgM at titer above 99th percentile for lab)
- **Lupus anticoagulant** presence

2006 revised Sapporo criteria: Miyakis S et al. J Thromb Haemost 2006;4:295.

How are APS and lupus related?



- About 1/3 of SLE patients have anti-phospholipid antibodies present.
- Of those, about 1/3 are associated with thrombo-embolism (11% of SLE)

- About ½ of APS patients have SLE and the other half do not.

Antiphospholipid Antibodies in Pregnancy

- aPL antibodies associated with:
  - Pregnancy loss, premature births, pre-eclampsia, HELLP
  - HELLP can occur early at 15-20 weeks and progress rapidly
  - Increased learning disabilities age 7-16 y/o.
    - Dyslexia is commonly associated with maternal Ro and aPL.

Izmirly P. Arthritis Rheum 2010; 62 (4): 1153-37. Doria A. Rheumatology (2008) 47; iii9-iii12.
Brucato A. Rheumatology (2008) 47; iii35-iii37.

Antiphospholipid antibodies in pregnancy

- Management in pregnancy:
  - No single best recommendation.
  - Suggested that healthy women or those with SLE and 2 or fewer losses before 10 weeks and no fetal loss, should have close maternal monitoring
  - Aspirin? Start during preconception or with positive pregnancy test
  - Low molecular weight heparin-Start in those with clear aPL related events
    - Start at time of detection of fetal heart activity, which is generally 6 weeks of gestation
    - Prophylaxis of heparin-induced osteoporosis with supplementation of calcium/vitamin D in all patients on heparin.

How should Case #1 be managed? Anticoagulation for APLS?

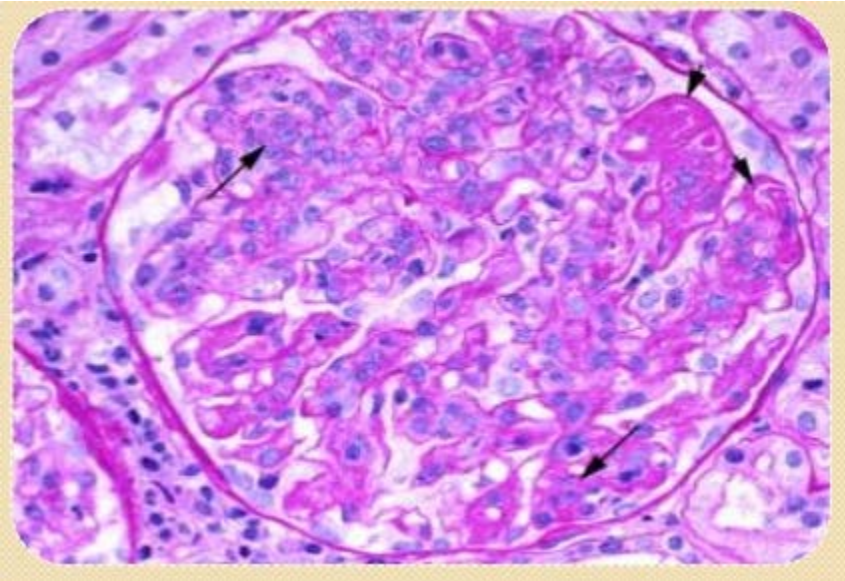
- If h/o VTE-→prophylactic
- If current VTE-→therapeutic
- If REPLs (<10 wks)-→begin preconception
- ASA 81 mg/d
- Steroids NOT helpful
- Anticoagulation – unfractionated vs. LMWH
  - (heparin doesn't cross the placenta)

How to monitor Case #1's fetus?

- Early dating and viability ultrasound
- Detailed fetal anatomy at 18 weeks
- Monthly fetal growth ultrasounds
- Fetal surveillance (NST/BPP/AFI) at 28 wks
- Monitor blood pressure closely
- Delivery for fetal indications or at 37-39 wks

Case #2

- 19 yo G1P0 at 6 weeks gestation
- h/o severe lupus nephritis on cyclophosphamide and high-dose steroids, stopped tx
- BP 142/104
- Urine protein:creatinine ratio = 12.9!
- C'3/C'4 complement markedly decreased
- Declined treatment



Light microscopy shows membranoproliferative pattern in lupus with areas of cellular proliferation (long arrow) and by thickening of glomerular capillary wall due to immune deposits that may be prominent enough to show a wire loop (short arrow)

Case #2

- Pt reappeared at 12 wks gestation
- Serum creatinine = 9.1 mg/dL!
- Admitted to ICU for dialysis
- Developed seizures, myocarditis, pulmonary hemorrhage
- Received IV steroids, cyclophosphamide, rituximab, and plasmapheresis
- Underwent TOP, patient survived

Pregnancy Complications in SLE

	OR	(%)
Preterm birth	2.4	(21)
Preeclampsia	3.0	(23)
IUGR	2.6	(6)
Cesarean	1.7	(36)
APLS	35	(4)
SAB	-	(19)
Maternal death*	20	(0.32)

*From OI, sepsis, lupus nephritis, renal failure

(Clowse – AJOG 2008)

Smyth A et al. A systematic review and metaanalysis of pregnancy outcomes in patients with SLE and lupus nephritis. Clin J Am Soc Nephrol. 2010; 5(11): 2060-8.

Predictors of adverse outcome

- History of nephritis
- Flare during pregnancy
- Non-use of hydroxychloroquine
- Lupus anticoagulant (+)
- Preexisting hypertension
- Active disease, SLEDAI >4, abnormal serologies
- Prior or active nephritis (proteinuria, HTN at first visit)
- Antiphospholipid antibody
- Thrombocytopenia, higher uric acid

Kwok – Lupus 2011

Who shouldn’t be pregnant?

- Severe pulmonary hypertension (estimated systolic PAP > 50 mm Hg symptomatic)
- Severe restrictive lung disease (FVC <1 L)
- Heart failure
- Active nephritis
- Chronic renal failure (Cr >2.8 mg/dL)
- Recent stroke or cerebritis (within the previous 6 months)
- Recent acute flare
- Previous severe preeclampsia or HELLP despite therapy with aspirin and heparin

Who is high risk in pregnancy?

- Develops acute flare
- Develops active nephritis
- Develops preeclampsia
- Develops IUGR
- Has APLS with h/o recurrent losses
- Has anti-SSA or h/o neonatal lupus

How to monitor pregnancy?

- Early dating US
- Monthly growth US after 24 weeks
- Baseline urine protein/creatinine ratio
- Baseline CBC, chemistries, C3/C4, dsDNA
- Weekly fetal surveillance (NST) after 32 wks
- Increase surveillance if PEC, IUGR, flare
- Delivery at term if no complications

Trimester	Labs	Maternal monitoring	Fetal monitoring
First trimester	CBC with diff, CMP, UA with protein:creatinine, c3/c4, dsDNA, anti-cardiolipin, lupus anticoagulant, SSA/SSB	Check BP, Lupus disease activity index Echo (optional)	Routine ultrasound
Monthly thereafter	Repeat labs	Check BP, Lupus disease activity index	First fetal echo at 16 Weeks, Fetal echo every 1-2 weeks after 16 weeks Biophysical profile.

SLE Medications—
let's get prepared for pregnancy!

- Approximately 10% of women between the ages of 15 and 44 become pregnant annually.
- ¼ of all pregnancies in the USA are unintended—hence inadvertent drug exposure during pregnancy is common!
- Comorbidities often require the same drugs before, during, and after pregnancy
- Women take on average 3-5 drugs during pregnancy.
- Postpartum drug exposure (lactation) is common

How about meds?

- Teratogens:
  - Methotrexate, cyclophosphamide, leflunomide, mycophenolate, warfarin
- Non-teratogens:
  - Hydroxychloroquine, prednisone, azathioprine, cyclosporine, rituximab, heparin

Treatment of Lupus Flares in Pregnancy

- Corticosteroids
- Azathioprine or cyclosporine preferred
- IVIG
- Avoid ACE inhibitors
- Furosemide OK
- Bottom line:
  - "Fetuses don't do well if their mother dies…."

How to tell if there's preeclampsia?

- BP 140/90
- Proteinuria (>300 mg/24-hr)
- Symptoms:
  - headache
  - visual changes
  - abdominal pain
  - hyperreflexia
  - edema?

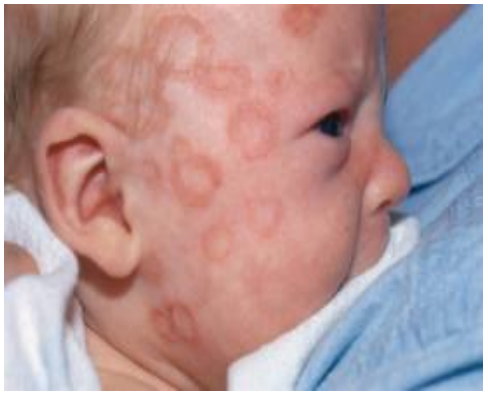
Is it Preeclampsia or Lupus?

HTN, proteinuria, low platelets…. which is it??

	PEC	SLE
Urinary sediment	nl	active
24-hr urine Ca++	<200	>200
C'3/C'4	nl	low
dsDNA titer	neg	rising
Uric acid	nl/high	nl
Timing	>20 wks	anytime

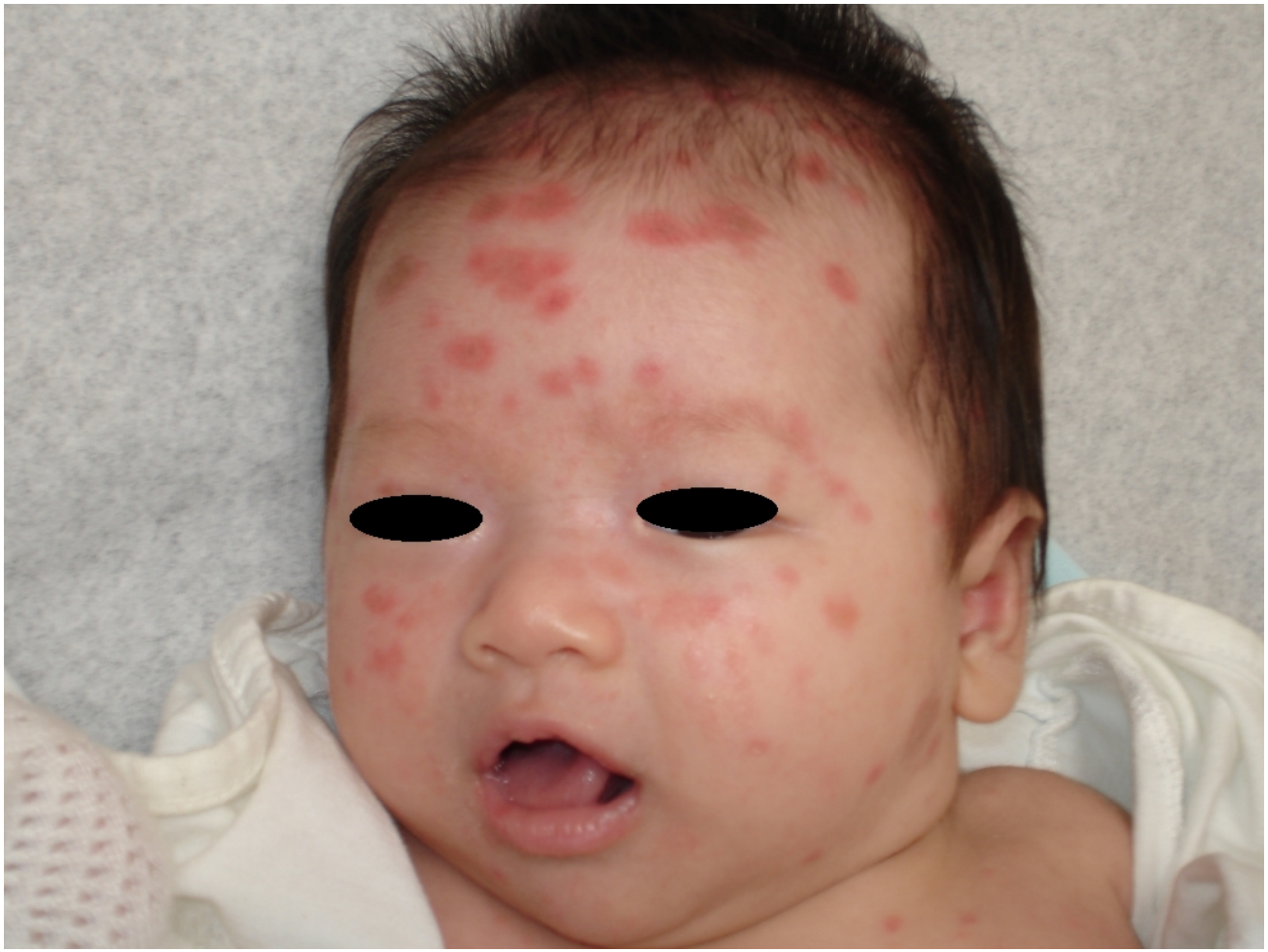
Neonatal Lupus

- Due to transplacental passage of maternal anti-SSA (Ro) +/- anti-SSB (La) antibodies.
- Manifestations
  - Cutaneous
  - Hematologic or Hepatic
  - Cardiac (irreversible)
    - Congenital heart block (1-2 % of offspring)
    - Endocardial fibroelastosis
    - Dilated cardiomyopathy



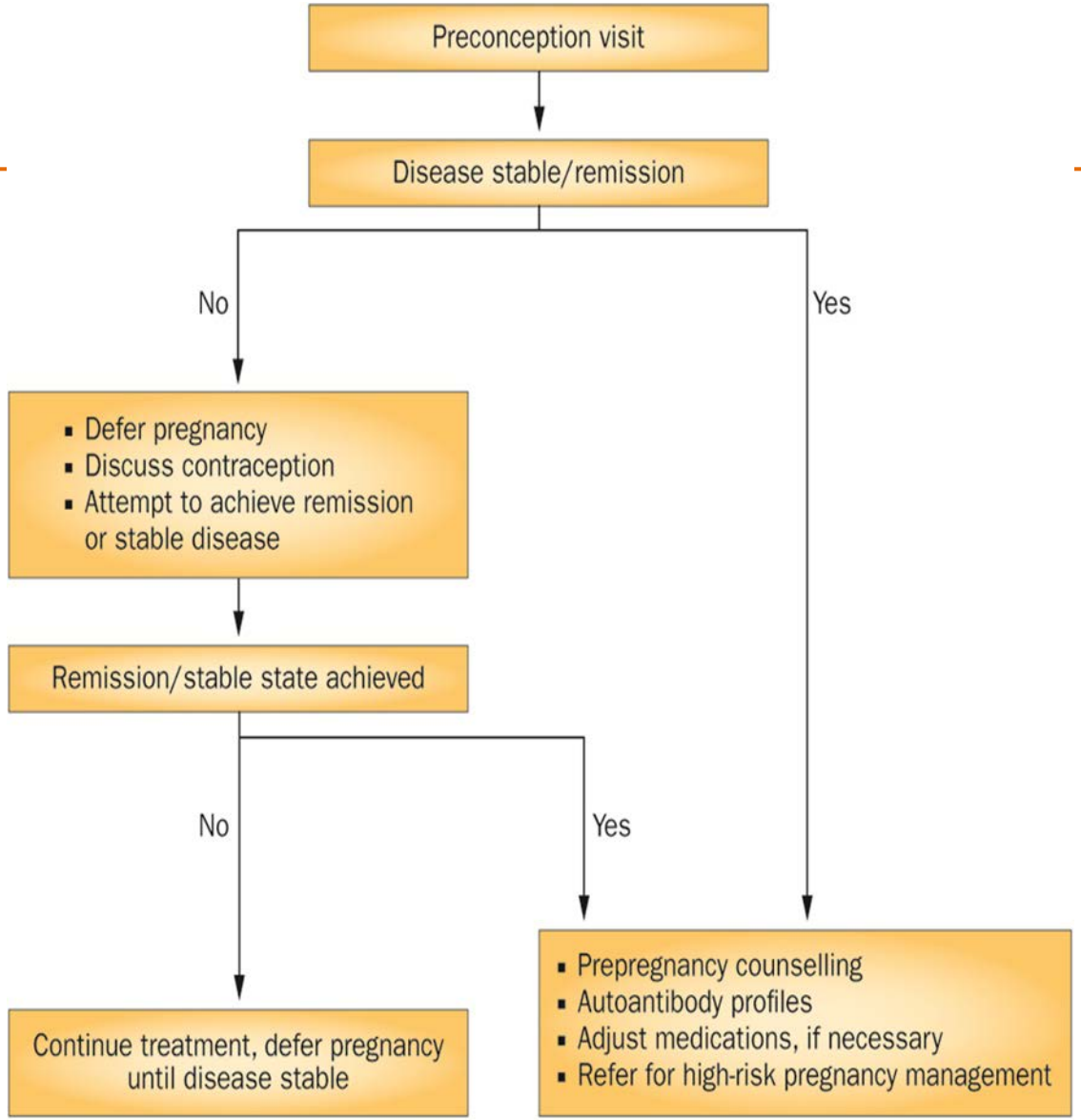
Does **NOT** increase risk of SLE later in life

Neonatal lupus rash



How to counsel patients with anti-SSA/Ro antibodies

- Maternal disease activity does not appear to influence development of CHB in offspring
- Primigravid female risk is 2%
- Risk may be lower in women who take hydroxychloroquine
- Recurrence rate is 18%
- Diagnosis of CHB usually in 18-24 weeks
  - Based on serial echos, fetus can progress from NSR to complete block in 7 days!
  - Time to intervene:
    - 1. When PR interval is prolonged but atrial signals continue to reach the ventricles OR
    - 2. When signs of myocardial dysfunction alone are present.
  - Fetal echo q 2 weeks starting week 16 (to detect PAC, pericardial effusion, that precedes AV block)



Lateef, A. & Petri, M. (2012) Management of pregnancy in systemic lupus erythematosus

Nat. Rev. Rheumatol. doi:10.1038/nrrheum.2012.133

Contraception—many of these pregnancies are *unintended*!

- OCs generally not prescribed for SLE patients due to widely held view that they may activate disease
- Safety of Estrogen in Lupus Erythematosus: National Assessment (SELENA) trial
  - Premenopausal women with SLE and inactive or stable active lupus randomly assigned to take low-estrogen oral contraception or placebo for 1 year.
  - Excluded: women with moderate anti-cardiolipin or lupus anticoagulant
  - Results: No increase in severe flares– or any flares—in oral contraceptive arm.

Do physicians discuss contraception with SLE patients?

- Women receiving teratogenic medications were no more likely to have received contraceptive counseling, to have used contraception consistently, or to have used more effective methods.
- History of aPL or thrombosis did not account for low rates of hormonal methods
- Four women with history of thrombosis or aPL were using estrogen-containing contraceptives.

Yazdany et al. Contraceptive Counseling and Use Among Women with Systemic Lupus Erythematosus: A Gap in Health Care Quality? Arthritis Care and Research. March 2011, 63 (3). p. 358-265.

Postpartum Management

- Postpartum flares common
- Most maternal deaths occur postpartum
- IUD is an ideal contraceptive
- Breast feeding is usually OK (same meds OK for pregnancy)
- Best to avoid pregnancy for 6 months after a flare

Lupus Pregnancy Pearls

- Avoid pregnancy until lupus has been inactive for 6 months
- Pay attention to patient antibodies: LAC, Ro, La, aPL Ab.
- Control hypertension
- Use of hydroxychloroquine improves fetal and maternal outcomes
- Review patient medications and discuss pregnancy at each visit including methods of contraception—remember ¼ of pregnancies are unintended!

Thank you!

This project is part of the American College of Rheumatology's (www.rheumatology.org) The Lupus Initiative (www.thelupusinitiative.org) in partnership with St. Charles Health System.

If you have a **diagnosed lupus patient** in need of case management assistance, please contact Shonta Chambers with the Patient Advocate Foundation (PAF) at (757) 952-2533 or online at **http://bit.ly/LupusReferral.** PAF is providing free case management assistance for up to ten lupus patients as part of this educational series.

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