Collagen Vascular Diseases in Pregnancy

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Educational objectives

- Discuss the two most common CV diseases as “models”
  - SLE
  - APLS
- Review clinical manifestations and diagnosis, pregnancy implications, and treatment
SLE: diagnostic criteria

- Malar rash
- Discoid rash
- Photosensitivity
- Oral ulcers
- Arthritis (>1 joint)
- Serositis
  - Pleuritis
  - Pericarditis
- Renal disorder
  - Proteinuria > 500 mg/d
  - Cellular casts
- Neuro disorder
  - Seizures
  - Psychosis
- Hematologic disorder
  - Hemolytic anemia
  - ...penia
- Immunologic disorder
  - Anti-DNA
  - Anti-Sm
  - APL Abs
- ANA

Dx if ≥ 4 of 11 criteria observed

Am Coll Rheum, updated 1997
SLE: laboratory testing

*connect the related items*

- ANA
- $\alpha$-DS-DNA
- $\alpha$-SSA (Ro)
- $\alpha$-SSB (La)
- ESR
- C3 and C4

- Disease activity
- Correlates with neonatal lupus and CCHB
- Normal < 50 for pregnancy
- Neg assoc’d with nephritis in anti-SSA pts
- Diagnosis (present in 98%)
- Inversely related to disease activity
Case 1: another day on the antepartum service, another MFT

- 36 yo SAAF
- 342 pounds
- PMH: CHTN, “arthritis in knees”
- Transferred @ 25 wks EGA for HTN
- Exam: nonfocal
- Labs: 3+ prot, h/h 9/27, plts 148, VDRL positive

D/Dx ???
Differential diagnosis

**SLE**
- HTN
- Proteinuria; $S_{Cr}$
- Headache
- Transaminase
- C3, C4
- ESR
- Course

**Preeclampsia**
# Differential diagnosis

<table>
<thead>
<tr>
<th></th>
<th>SLE</th>
<th>Preeclampsia</th>
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<tr>
<td>HTN</td>
<td>±</td>
<td>+</td>
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<tr>
<td>Proteinuria; $S_{Cr}$</td>
<td>±; nl or ↑</td>
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<td>C3, C4</td>
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<tr>
<td>ESR</td>
<td>↑</td>
<td>nl</td>
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<tr>
<td>Course</td>
<td>Indolent; improves with steroids</td>
<td>progressive</td>
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Counseling regarding the impact of pregnancy on SLE

- Does pregnancy impact the long-term prognosis of SLE?
  - Not usually – 10% chance of permanent renal insufficiency

- Incidence of exacerbation during pregnancy?
  - 40% (including 20% chance of renal flare)

- Does pregnancy induce exacerbations?
  - perhaps post-partum

- What about course of subsequent pregnancies?
  - unpredictable
Impact of SLE on pregnancy

* increases risk of iatrogenic PTD

SLE: risk of fetal loss

- Overall
- Urine prot > 300 mg/d
- CrCl < 100 ml/min
- High prot, low CrCl
- Remission

%
SLE: neonatal risks

- Hematologic: *transient* hemolytic anemia, leukopenia, and thrombocytopenia
- Cutaneous: *transient* skin lesions
- Cardiac: *permanent* complete congenital heart block
- PATHOLOGY of heart lesions (related to soluble antibodies & ?? microchimerism)
  - absent AV node
  - AV bundle fibrosis
  - ± endomyocardial fibrosis or fibroelastosis
Case 2 (same pt as case 1)

- P1001 – prior baby healthy since birth
- Nephrologist ordered wide lab panel; positives include ANA and SS-A

Significance of lab results?
Congenital heart block

- 5% risk of CHB if mother has $\alpha$-SSA
- 33% risk for recurrent CHB
- $HR \approx 60$ bpm (AV dissociation can be confirmed by US) typically tolerated (without need for pacing) if no structural defects
- 30-60% of mothers of infants with CHB have or develop connective tissue disease
- 20-50% of infants with CHB have structural heart defect
- Maternal microchimerism (maternal cells in fetal heart) may be cause or reparative effect …it may be more than a passive Ab effect

Stevens. Lancet 2003;362:1617
Steroid treatment for CCHB

Lit review
- 30 fetuses with CCHB
  - 16 (53%) with hydrops

Case 3: Discoid lupus

- 32 yo P2002 presents for PNC @ 13 wks
- Asx’ic except recent recurrence of cutaneous lesions (self d/c’d chloroquin after (+) hCG)
- Hx of “discoid lupus”

Management?
Discoid lupus

- Erythematous plaques on head & face become depigmented scars
- May be only SLE manifestation, or …
- Activity of cutaneous lesions may correlate with systemic disease, so …
- Get comprehensive ROS and evaluate for systemic disease (esp renal)
- If no other evidence of active systemic disease, topical steroids may be effective (if not, use chloroquin or oral steroids)
Predictors for optimal pregnancy outcome for SLE

- Remission $\geq$ 6 months
- Serum creatinine $\leq$ 1.5 mg/dL
- Creatinine clearance $\geq$ 65 mL/min
- Proteinuria < 2.4 g/d
Treatment for SLE during pregnancy

- BEST
  - acetaminophen
  - prednisone

- ACCEPTABLE
  - azathioprine
  - chloroquine

- BEST AVOIDED
  - NSAID
  - aspirin
Obstetric management for SLE

- Prenatal counseling
- Optimize status before pregnancy
- Team approach
- Secure dating
- Baseline CrCl, 24 hr proteinuria, complement levels
- Screen for lupus anticoagulant (10% incidence)
- Maternal surveillance: BP, proteinuria, symptoms
- Low threshold for serial US, antenatal testing
Antiphospholipid syndrome (APS)

- Antibodies to negatively charged phospholipids and
- Clinical manifestations, which may include these non-obstetric conditions:
  - thrombosis (venous or arterial [1/3 of total]) *
  - thrombocytopenia
  - lymphopenia
  - hemolytic anemia
- LA and ACL independently associated with APS: test for both

* Prospective risk = 2%/yr  
  
  Rheum Dis Clin 2001;27:525
APS: obstetric risks

- SAb, unrx'd, prior SAb
- PIH
- severe PIH
- IUGR
- FHRA
- PTD
Incidence of $\alpha$PL antibodies in obstetric conditions

- Recurrent SAb
- PIH, severe, <34 wks
- PIH, term
- IUGR

%
APS: laboratory testing for ACL

- Anticardiolipin (ACL): antibodies to diphosphatidylglycerol
- Standardized ELISA reported as binding units: GPL, MPL, APL
- Only medium or hi levels of GPL likely clinically significant
APS: laboratory testing for LA

- Lupus anticoagulant (LA): functional PL-dependent clotting assays
  - aPTT, KCT, RVVT
- In vitro, LA inhibitor binds to PL, interfering with clotting factor interactions
- Confirmatory mixing study: normal plasma corrects a clotting factor deficiency but not the effect of an inhibitor (like LA)
- Secondary confirmatory test: platelet neutralization
  - preincubation of plasma with plt PL removes LA and normalizes clotting time
“Lupus Anticoagulant”
double misnomer

- NOT specific for LUPUS (present in <1/3 patients with SLE)
- NOT an ANTICOAGULANT *in vivo* (thrombogenic risk)
Indications for $\alpha$PL antibody testing

- SLE
- Recurrent miscarriage
- Unexplained 2nd, 3rd TM fetal death
- Autoimmune thrombocytopenia or hemolytic anemia
- Unexplained severe IUGR
- Unexplained thrombosis
- Unexplained stroke, TIA, or amaurosis fugax
- False positive serologic test for syphilis
- Severe PIH < 34 wks EGA
Pathogenesis of APS

- Placental thrombosis and infarcts
- Decidual vasculopathy
  - atherosis
  - intimal thickening
  - fibrinoid necrosis
- Induction of thrombogenic mediators
  - tissue factor
  - platelet-activating factor
  - vascular cell adhesion molecule 1
  - inhibition of protein S, protein C, and thrombomodulin
  - inhibition of annexin 1 (placental anticoagulant protein 1)
Case 4: Pregnancy in pt with APLS

- 26 yo P0131 presents @ 8 wks for PNC
- 1st preg was 8 yrs ago, c/b severe PIH @ 26 wks
- SAbs: 8-12 wks at demise
- PMH o/w neg
- Labs: neg LAC; ACL 36 GPL and 24 MPL

Diagnosis?

Management?
APS: proposed treatments and their rationale

- Prednisone: immunosuppression of $\alpha$PL Ab’s
- Heparin: interfere with thrombogenesis
- Aspirin: selective inhibition of platelet thromboxane production, improving placental blood flow
- IVIG: immunosuppression of $\alpha$PL Ab’s
APS treatment: prednisone ± ASA vs heparin + ASA

* Median of multiple studies
APS treatment options
Meta-analysis

- 10 RCTs
- n=627
- 3 trials of ASA alone showed no reduction in pregnancy loss
- Only heparin + ASA reduces recurrent pregnancy loss

Obstet Gynecol 2002;99:135
Primary APLS: 10 year pt status

- Organ damage: 40%
- Fxn impaired: 20%
- CNS: 35%
- MI: 10%
- Pulm infarct: 5%
- ESRD: 5%

n=39; F=35

J Rheum 2000; 27:2817
APS: pregnancy management

- Preconception counseling
- Selection of appropriate medical mgmt based on risk factors
- Serial $\alpha$-PL Ab testing NOT beneficial
- Maternal surveillance for preeclampsia and thrombosis
- Fetal surveillance for growth and well-being (using 3rd TM objective biophysical testing)