Lupus in Pregnancy

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• No financial interests to disclose.
Objectives

- Physiologic changes
- Lupus overview
- Care in pregnancy
- Congenital heart block
  - Hydroxychloroquine
- Lupus flares
Maternal Physiology

Pathogens, allergens, self-antigens

Maternal Immune System

Fetoplacental tissues/Pregnancy-associated hormones

<table>
<thead>
<tr>
<th>↑ Anti-inflammatory factors</th>
<th>↓ Proinflammatory factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-4</td>
<td>IL-12</td>
</tr>
<tr>
<td>IL-10</td>
<td>IL-2</td>
</tr>
<tr>
<td>TGF-β</td>
<td>IFN-γ</td>
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<tr>
<td>PIBF</td>
<td>TNF-α</td>
</tr>
<tr>
<td>Tolerogenic DCs</td>
<td>NK cells</td>
</tr>
<tr>
<td>M2 Macrophages</td>
<td>M1 Macrophages</td>
</tr>
<tr>
<td>Th2 Cells</td>
<td>Th1 Cells</td>
</tr>
<tr>
<td>Regulatory T cells</td>
<td>Th17 Cells</td>
</tr>
<tr>
<td>Antibody</td>
<td></td>
</tr>
</tbody>
</table>

↑ Successful Pregnancy
↓ Susceptibility to Inflammatory Diseases
↑ Susceptibility to Infectious Diseases

Robinson, 2012
Maternal Physiology

- Estrogens upregulate T-cell responses, immunoglobulin synthesis, and leukocyte production of IL 1, 2, 6, TNFα
- Cell-mediated immunity is depressed
  - Decreased ratio of T cells to B cells
  - Increased ratio of suppressor T cells to helper T cells
  - Decreased ratio of lymphocytes to monocytes

- Inhibition of complement activation in the placenta may be essential for fetal survival
- Trophoblast may be a target of autoimmunity.
Maternal Physiology

- AFP suppresses lymphocyte function
- IL-1, IL-3, TNF-α, IFN γ, Granulocyte-macrophage colony-stimulating factor are critical in sustaining pregnancy.
- IL-3 levels - low in women with RPL
- Pregnancy - Total C3, C4, and hemolytic (CH₅₀) complement levels – unchanged / increased
  - Increase in classic pathway complement activation
  - Complement activation can result in excess soluble vascular endothelial growth factor receptor type 1 (sFlt-1), which has implications for placental development and the risk for preeclampsia.
SLE

• Chronic autoimmune d/o with disease flares and remissions

• Can affect all organs
  – Mild cases – skin, musculoskeletal system
  – More severe – kidney, brain
  – Possible manifestations are arthralgias, rashes, renal abnormalities, neurologic complications, thromboemboli, myocarditis, serositis
Epidemiology

• Prevalence of lupus varies with population
• 5-125/100,000 people
• Affects 1% of pregnancies
• Lifetime risk of developing lupus is 1/700
  – peaks at 30 y/o
• Women : Men – 9:1
• Ethnic groups
  – African Americans
  – Hispanics
Etiology

• Unknown

• Genetic linkage
  – 5-12% of affected individuals have an affected relative
  – 25-50% of monozygotic twins are concordant for the disease

• Alterations in HLA system
  – HLA-B8, HLA-DR3, HLA-DR2

• Abnormal B and T cell biology and immune clearance mechanisms
Pathophysiology

- Damage due to immune complex deposition, complement activation, inflammation, fibrosis
  - Renal, MSK, hepatic, platelets
- Autoantibodies
  - Antinuclear antibody – most common, ‘lab is open’
    - Increased in pregnancy – 10% of asymptomatic pregnant women without autoimmune disease have ANA ab compared to 2% of nonpregnant controls
    - Screening for lupus b/c of high prevalence in gen pop
  - Anti-dsDNA antibody and anti-Smith Ab - more specific for lupus; dsdna ab correlates with disease activity
  - Antiphospholipid antibodies
    - Anti – Ro/SSA, anti- La/SSB more often associated with sjogrens sd, but seen in 20-40% of females with lupus
      - Associated with neonatal lupus syndrome
Symptom frequency

- Fatigue – 80-100%
- Fever – 80-100%
- Arthritis – 95%
- Myalgia – 70%
- Weight loss – 60%
- Photosensitivity – 60%
- Malar rash – 50%
- Nephritis – 50%
- Pleurisy – 50%
- Lymphadenopathy – 50%
- Pericarditis – 30%
- Neuropsychiatric – 20%
Criteria for Diagnosis

- Per American College of Rheumatology
- Need 4 of 11 (serially or at one time)
  - Malar rash (erythema over malar eminences)
  - Discoid rash (erythematous raised patches)
  - Photosensitivity (unusual rxn to sunlight)
  - Oral ulcers (oral, nasopharyngeal)
  - Arthritis (nonerosive, 2+ peripheral joints)
  - Serositis (pleuritis, pericarditis)
  - Nephritis (>500mg/d proteinuria or cellular casts)
  - Neurologic disorder (seizures, psychosis, stroke with other causes r/o)
  - Hematologic disorder (hemolytic anemia with reticulocytosis, thrombocytopenia <100k, leukopenia <4000 2 occasions, lymphopenia <1500 2 occasions)
  - Immunologic disorder (anti-dsDNA, anti-Sm, positive LAC ACA, false pos RPR or other serologic test for syphilis for 6 months confirmed by treponema pallidum immobilization or fluorescent treponemal ab absorption test)
  - Antinuclear antibodies (without being on drugs associated with drug induced lupus syndrome)
- <4 of 11 = lupus-like syndrome
General Morbidity/Mortality

- Renal and cardiovascular disease
- Thrombosis
- Infection
- Survival rates
  - 5y – 93%
  - 10y – 85%
  - 15y – 79%
  - 20y – 68%
- Risk factors for death from lupus
  - Lupus nephritis
  - Thrombocytopenia
  - Lung involvement
  - High disease activity at time of diagnosis
Pregnancy Outcomes

• **Effect of SLE on pregnancy**
  - Increased stillbirth rate 25x (150/1000)
    - Esp with antiphospholipid antibodies
  - Increased preeclampsia rate to 20-30% (7-10%)
  - Increased IUGR rate to 12-32%
  - Increased preterm delivery rate to 50-60% (12-15%)
  - Increased PPROM rate
  - Neonatal lupus only in Ro/La antibody positive patients

• **Effect of pregnancy on SLE**
  - Worsening renal status if nephropathy (Cr 1.5) present
  - Increased flares if active disease at start of pregnancy
Chronic Renal Insufficiency and Pregnancy Outcomes (vs serum creatinine mg/dL)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Cr&lt;1.5</th>
<th>Cr 1.5-3</th>
<th>Cr &gt;3</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTB</td>
<td>13%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Perinatal death</td>
<td>5%</td>
<td>17%</td>
<td>33%</td>
</tr>
<tr>
<td>IUGR</td>
<td>10%</td>
<td>20%</td>
<td>100%</td>
</tr>
<tr>
<td>Abortion</td>
<td>11%</td>
<td>21%</td>
<td>25%</td>
</tr>
<tr>
<td>Surviving infants</td>
<td>84%</td>
<td>62%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Queenan 2007
Renal Biopsies in Pregnancy

- Complications -
  - Hematoma formation
  - Bleeding
  - Death
- Usually do not help change management
- If steroids are the change in management, then steroid administration is of lower risk than a renal biopsy
Evaluation & Management
Goals of Management

• Disease control/remission before pregnancy
• Avoid drugs that harm the fetus
• Prompt detection of preeclampsia and placental insufficiency
• Discern between lupus exacerbations and preeclampsia
• Appropriate detection and treatment of lupus flares
Preconception counseling

- Potential complications – preeclampsia, preterm labor, miscarriage, fetal death, fetal growth restriction, and neonatal lupus
- Evaluate lupus activity – delay pregnancy until remission
- Evaluate for nephritis (24 hr urine), hematologic abnormalities (CBC), antiphospholipid abnormalities
- Discontinue NSAIDS and cytotoxic agents
Medications
NSAIDS

- NSAIDS – inhibits cyclooxygenase, lipoxygenase, reduces prostaglandin synthesis
- Class D
- Avoid especially in 3rd trimester
  - Cross placenta, blocks prostaglandin synthesis in fetal tissue
  - Premature closure of ductus arteriosus, fetal pulmonary hypertension, NEC, fetal renal insufficiency
  - Occurs with selective COX-II inhibitors
  - ASA crosses placenta and can affect fetal platelet function and is associated with intracranial fetal hemorrhage in 3rd trimester; avoid in pregnancy
- Used outside of pregnancy – most common anti-inflammatory agent
Hydroxychloroquine

- Hydroxychloroquine (antimalarial/antirheumatic; binds DNA, interferes with vesicle functions, inhibits phospholipid metabolism; immunosuppressive by inhibiting rheumatoid factor, acute phase reactants, enzymes)
  - Stopping this in pregnancy is associated with increased risk of lupus flares, continuing this drug is recommended if needed to control lupus (prospective study by cortes-hernandez showed the increased risk)
  - Large series show no increased risk of anomalies
  - Used in prevention of malaria with increase of fetal anomalies
  - Not associated with increased r/o fetal malformations

- Class C

- Chloroquine possible teratogenic in initial studies
  - Ototoxicity, eye development

Buchanan, 1996; Khamashta 1996
Klinger 2001; Motta 2002
Glucocorticoids

- Glucocorticoids (antiinflammatory, glucocorticoid, mineralocorticoid)
- Preg class C
- Avoid fluorinated glucocorticoids b/c they cross the placenta
  - Hydrocortisone, prednisone, prednisolone inactivated by 11-beta hydroxysteroid dehydrogenase in the placenta allowing <10% of active drug to reach fetus
- High dose associated with maternal/fetal A/E
  - Osteoporosis (tx with vit D, ca2+); glucose intolerance, sodium, h2o retention; hypertension, infection; avascular necrosis
  - Preg complications – GDM, preeclampsia, PPROM, IUGR
  - Incidence of fetal adrenal suppression with maternal tx is low
- Avoid empiric treatment, use at lowest possible dose
- Stress dose steroids (hydrocortisone 100mg IV q8hr in labor and for 24 hr PP)
  - Use if chronic steroids (>5mg/day for >2-4 weeks prior to delivery)
Azathioprine

- Azathioprine (inhibits T lymphocytes)
- Class D
- Teratogenic in animals, appears safe in humans
- Associated with IUGR
- Neonatal immunosuppression
- Indicated in pregnancy if chronic high doses of steroids is not controlling symptoms or to lower steroid dose
Cyclophosphamide

- Cyclophosphamide (alkylates and cross links DNA)
- Preg class D
  - Cleft palate, skeletal abnormalities, abnormal renal function
  - Avoid, esp in first trimester
  - May be needed in cases of severe proliferative nephritis (drug of choice in nonpregnant patients with proliferative lupus nephritis)
  - Crosses placenta
Methotrexate

- Methotrexate (inhibits dihydrofolate reductase; inhibits lymphocyte proliferation) (folate antagonist)
- Preg class X
- Avoid
- Embryolethal, IUFD
- Congenital anomalies
Cyclosporine

- Cyclosporine A (inhibits T lymphocytes)
- Preg class C
- Data comes from use in renal transplant patients, not an animal teratogen, appears safe in humans, long term follow up studies are limited
Tacrolimus

- Tacrolimus (inhibits T lymphocyte activation, immunosuppressant)
- Dose in liver transplant
  - 0.1-0.15mg/kg/d po divide q12 hr
- Preg class C
- Therapeutic drug levels 5-20 ng/ml just before next dose; time to steady state 3 days
- Monitor creatinine, K, fasting blood glucose, serum drug levels
Pregnancy - FDA classes

- **A** – controlled studies show no fetal risk in any trimester, probability of fetal harm is remote
- **B** – animal studies, no risk; if risk in animal studies, controlled human studies do not confirm harm
- **C** – harm in animal studies with no controlled human studies; no available human or animal studies
- **D** – human studies show fetal risk but r/b relative to medical state of mother may support use
- **X** – animal/human studies show fetal risk or abnormalities, use is contraindicated during pregnancy or in women who may become pregnant
Pregnancy Care
Pregnancy

- Labs/Evaluation
  - CBC, CMP, 24hr UA for TP/CC
  - Antiphospholipid antibodies
  - Anti-Ro and anti-La antibodies
  - Anti-dsDNA antibody
  - Complement (C3 and C4 or CH₅₀)
  - Monthly CBC, Platelet count, Complement and anti-dsDNA antibody
  - Maternal echocardiogram if disease present
  > 3-5 yrs, cardiac complications, associated CHTN, lupus nephritis
Lupus and Presence of Antiphospholipid Antibodies

- 1/3 of lupus patients
- Risks – thrombosis, fetal loss
- + APA and history of fetal loss = APLS
  - Heparin/lovenox is recommended
- Thromboprophylaxis
  - Due to increased thrombosis risk
- Data is lacking that reveals improved outcomes (less SABs, IUFDs, etc) unless APLS is diagnosed
Antenatal care

- **Frequent visits to assess lupus status, screen for hypertension**
- **Continue hydroxychloroquine**
  - Depends on control as to whether to initiate it if patient is not medicated
- **Monitor for exacerbations/flares**
- **If chronic hypertension – monitor as such**
- **APLS – see above**
Antenatal care

- Between 18 and 25 weeks (mothers with anti-ro/la antibodies)
  - *Screening fetal echocardiogram
  - Fetal electrocardiogram through echocardiography
  - Vs. *weekly FHR checks
  - +/- Dexamethasone
- Serial ultrasounds to evaluate fetal growth
- Antenatal surveillance at 32 weeks or earlier if indicated
Neonatal Lupus

• Rash, thrombocytopenia, hepatitis, hemolytic anemia
  – Transient

• Complete heart block – Permanent

• Only if +SSA/B antibodies
  – 25% risk of rash (recurrence risk 25%)
  – <3% risk of heart block (RR 18%)
Congenital Heart Block

- SSA/B + increases risk
- Prior history of child with heart block increases risk
- Dexamethasone – limited data that shows clear benefit
- Hydroxychloroquine  Izmirly, 2010
Fetal PR Interval

Wojakowski 2009
Table 1. Outcomes in 98 Prospectively Followed Pregnancies in 95 Women With Anti-SSA/Ro-SSB/La Antibodies Correlated With the Mothers’ Pregnancy Histories*

<table>
<thead>
<tr>
<th>PRIDE Outcome</th>
<th>First Pregnancy (n=44)</th>
<th>Previous Children Healthy (n=30)</th>
<th>Previous Child With Rash (n=8), n</th>
<th>Previous Child With CHB (n=16), n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal sinus rhythm</td>
<td>38</td>
<td>27</td>
<td>8</td>
<td>13</td>
</tr>
<tr>
<td>First-degree block</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Second-degree block</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Third-degree block</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Rash/normal sinus rhythm</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Isolated cardiomypathy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Died (non-CHB)</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Poor outcome unrelated to neonatal lupus</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Three of the 95 mothers had 2 evaluable pregnancies during the course of the study; all 3 appear in the First Pregnancy column. The second pregnancies of 2 are tabulated in the Previous Children Healthy column, and the second pregnancy of the third subject is tabulated in the Previous Child With Rash column.
PRIDE Study

• 127 women evaluated, 95 completed course – all had Ro or La Ab
• Fetal echo, weekly 16-26 weeks
• PR >150msec – 1\textsuperscript{st} degree
  – 92 - Normal PR intervals
  – 3 with complete heart block, without prolonged PR interval preceding it
  – Tricuspid regurgitation, atrial echodensity
  – 2 had PR intervals >150msec, 22 weeks
    • Dexamethasone initiated, reported to prevent progression and resolved the 1\textsuperscript{st} degree
• Recurrence – 19% with previous heart block
  – 3% without previous heart block
Evaluation Of The Risk Of Anti-ssa/Ro-ssb/La Antibody-associated Cardiac Manifestations Of Neonatal Lupus In Fetuses Of Mothers With Systemic Lupus Erythematosus Exposed To Hydroxychloroquine

- TLR signaling in pathogenesis of neonatal heart block
- Hydroxychloroquine is a TLR inhibitor
- A TLR inhibitor, might reduce the risk of anti-SSA/Ro/SSB/La antibody associated cardiac manifestations of NL
- Cardiac-NL children (N=50) and controls (N=151) were drawn from the following overlapping pregnancy studies: Research Registry for NL; PR Interval and Dexamethasone Evaluation in Cardiac-NL; and Predictors of Pregnancy Outcomes: Biomarkers in Antiphospholipid Syndrome and SLE
- Ro/La +; SLE dx
- Results Seven (14%) of the cardiac-NL children were exposed to HCQ compared with 56 (37%) of the controls (p=0.002; OR 0.28; 95% CI 0.12 to 0.63).
- Concluded – in mothers with SLE with anti-SSA/Ro/SSB/La antibodies, exposure to HCQ during pregnancy may decrease the risk of fetal development of cardiac-NL

Izmirly, 2010
Maternal Autoantibody Levels In Congenital Heart Block And Potential Prophylaxis With Antiinflammatory Agents

• Retrospective, 2007-2011, Ro/La +
• N = 33
• Higher Anti La titers in pregnancies c/b heart block; no difference if Ro Ab
• Did not have to have SLE, etc
• 94% of fetuses maintained normal conduction when the mother was treated with hydroxychloroquine or daily prednisone therapy throughout pregnancy, compared to 59% in the untreated group (odds ratio, 0.1; \( P = .04 \)).
• Maternal treatment with either hydroxychloroquine or daily low-dose prednisone throughout pregnancy may provide a protective effect.

Tunks 2013
Lupus Flares

• Incidence in pregnancy 15-63%
  – Studies support and refute that pregnancy increases the incidence of flares

• Risk factors
  – Active disease at conception (50% vs 20%)
  – Active nephritis
  – Abrupt discontinuation of hydrochloroquine
Diagnosis Of Flare

• Symptoms
  – Fatigue, fever, arthralgias/myalgias, weight loss, rash, renal deterioration, serositis, LAD, CNS symptoms

• Titers of antibodies

• Rising titers of dsDNA Ab with falling complement levels suggest impending flare
Lupus Vs Preeclampsia

- Lupus flare
  - Arthritis, leukopenia, thrombocytopenia, rashes, pleuritis, fevers
  - Htn, proteinuria, coagulopathy possible
  - Rising antidsdna titer, active urinary sediment, low complement levels suggest lupus flare
  - Complement levels (C3, C4, CH50) generally rise in pregnancy and are unaffected by uncomplicated preeclampsia
  - Normal uric acid
  - Differentiation near term likely not worthwhile, deliver for suspected preeclampsia and initiate tx for lupus flare if patient does not get better
# Lupus Flare vs. Preeclampsia

<table>
<thead>
<tr>
<th>Finding/test</th>
<th>Preeclampsia</th>
<th>SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased complement</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Increased anti-ds DNA Ab</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Antithrombin III decreased</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Microangiopathic hemolytic anemia (Ab screen -)</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Coombs positive hemolytic anemia (Ab screen +)</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Hematuria</td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td>Cellular casts</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Increased serum creatinine</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Hypocalciuria</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Increased liver transaminases</td>
<td>++</td>
<td>+/-</td>
</tr>
</tbody>
</table>
Uterine Artery Notching – Present in Preeclampsia
Renal Biopsies in Pregnancy

- Complications -
  - Hematoma formation
  - Bleeding
  - Death

- Usually do not help change management

- If steroids are the change in management, then steroid administration is of lower risk than a renal biopsy
Renal Biopsy

• Risks in pregnancy
  – Hematoma formation
  – Renal dysfunction

• Lupus Nephritis
  – Increased mesangial matrix and mesangial hypercellularity (increased leukocytes)

• Preeclampsia - Endotheliosis
Renal Biopsy

- **Preeclampsia**
  - **A** – endothelial swelling
  - **B** – Glomerular necrosis
  - **C** – sloughing of tubular epithelial cells
Treatment Of Lupus Exacerbations

- Mild to moderate
  - Hydroxychloroquine
  - Start prednisone 15-20mg/day or increase dose to 20-30mg/day if already on glucocorticoids

- Severe exacerbations without renal/CNS manifestations
  - Rheumatology consult, hospitalize
  - Glucocorticoid treatment (prednisone 1-1.5mg/kg/d; expect improvement in 5-10 days)
  - Taper once significantly improving
  - If patient cannot be tapered off high dose steroids – add cyclosporine or azathioprine

- Severe, life threatening disease – with renal/CNS involvement – Plasmapharesis, IVIG
Lupus Nephritis

- 50% of patients with lupus develop renal disease
- Pathophysiology
  - Immune complex deposition
  - Complement activation
  - Inflammation in kidney
- Retrospective review (Burkett, 1985)
  - 242 pregnancies in 156 women with lupus nephritis
    - 59% no change in renal function
    - 30% with transient decrease in function
    - 7% with permanent renal insufficiency
    - Critical creatinine level is 1.5mg/dl
      - Above this - risk is increased of decreased renal function
      - Below this – risk is not increased
- Cyclophosphamide in extreme cases, would try IVIG, plasmapheresis first
Delivery

• Consider delivery at 39 weeks to avert ongoing risks of fetal loss, development of preeclampsia
• Cesarean for obstetrical indications
• Stress dose steroids if indicated
• Thromboprophylaxis IP/PP management
Conclusions

- Goal is control at conception
- Continue hydroxychloroquine
- Rheumatologic evaluation – the Obstetrical version
- APA - +/- thromboprophylaxis
  - Esp if true APLS
- Fetal surveillance
- Hydroxychloroquine 200mg BID may be preventative of fetal heart block in Ro/La patients
• ??

• OMNY

End
References

- Email – dfarley@awhobgyn.com
- Provided on request
- Friedman 2008 PRIDE study
- Izmirly 2010 Hydroxychloroquine study
Maternal Physiology

• Inhibition of complement activation in the placenta may be essential for fetal survival
• Trophoblast may be a target of autoimmunity.
Lupus Exacerbations

• Severe exacerbation with renal or CNS involvement
  – Hospitalize, rheumatology consult
  – IV methylprednisolone 10-30mg/kg/day for 3-6 days
  – Maintain on oral prednisone 1-1.5mg/kg/day
  – When patient responds, taper steroids
  – If no response, add cyclophosphamide, or move to plasmapheresis
The Lupus Placenta

- Reduction in size
- Placental infarctions
- Intraplacental hemorrhage
- Deposition of immunoglobulin and complement
- Thickening of trophoblast basement membrane
- Above are reasons for pregnancy complications (later) – pree, IUGR, preterm delivery)
Figure 1. A, pulsed Doppler sample volume placed in the left ventricle at the junction of the anterior leaflet of the mitral valve and left ventricular outflow tract. B, fetal heart displaying the pulsed Doppler sample volume at the junction of the anterior leaflet of the mitral valve and the left ventricular outflow tract.
Figure 2. Time intervals were measured from the onset of the mitral A wave (atrial systole) to the onset of the aortic pulsed Doppler (ventricular systole), representing the mechanical PR interval.
Neonatal Lupus

- Occurs in 1-2% of women with antissA or antissB regardless of whether pt has SLE
- Immune mediated damage of fetus by transplacental passage of autoab that affect the fetus
- Congenital heart block, skin lesions, thrombocytopenia, anemia, hepatitis
- CHB permanent
  - AntissA and SSB maternal ab cross placenta and damage AV conducting system; varying degrees of heart block, poss myocarditis
    - 1st
    - 2nd
    - 3rd
  - Typically dx at 18-24 weeks
  - Ab act by apoptosis or directly interfere with cardiac conduction through calcium channels
  - R/o CHB in women with antissA ab and no previous affected infants is 1-2%
  - ~50% of women with fetus/infant with CHB are asymptomatic but more than 85% are antissA or antissB +
    - ½ of these women develop sx of rheumatic disease, typically sjogren’s sd with dry eyes and mouth; <50% chance of developing SLE
Neonatal Lupus; CHB

- Cardiac lesions – heart block from endocardial fibroelastosis from anti SSA-52 binding to myocardial tissue
- Histo – mononuclear cell infiltration, fibrin deposition, calcification of conduction system (AV, SA nodes, diffuse fibroelastosis t/o myocardium)
- Typically seen as FHR of 60-80 bpm at 16-25 wks gestation with structurally normal heart with AV dissociation, hydrops possible
- 3rd degree heart block; complete
  - Permanent
- 1st or 2nd degree (defs???)
  - Reversed with antenatal fluorinated (crosses placenta) steroid therapy b/c of prevention of progression to more severe forms +/-
    - Rationale of steroids is that cardiac histo has diffuse inflammation, igg, fibrin, complement deposition
    - Risk of chronic steroids without any proven benefit especially in a condition that is permanent once it is diagnosed
    - M/f risks osteoporosis, glucose intolerance, fetal growth restriction, development delay
    - Reversal of hydrops case reports?
- No evidence supporting use of ppx steroid tx in women with antissa or antissb ab to prevent onset of chb
- 1/3 of fetuses with heart block die within 3 yrs of age
  - Remaining 2/3 require permanent pacemakers
Heart Block
Pathophysiology Of NLE

• Autoantibodies alone are insufficient to cause NLE
• 30% of SLE pt have antissa ab and 15-20% have antissb ab
• Incidence of CHB in infants of SLE mothers is 2%
• Recurrence risk 5-25%; reports of twins discordant for NLE
• Therefore antissa alone does not always lead to NLE
• Maternal SLE is NOT a prerequisite for NLE
  – 50% of NLE cases occur in healthy pregnant women with circulating autoantibodies
  – Some develop connective tissue d/o
NLE

- 1 in 20,000 live births
- Heart block 50%
- Skin lesions 50% - erythematous scaling plaques on scalp or face, typically resolve within first few months like hematologic changes as the maternal autoantibodies disappear
- Both 10%
- Most cases from maternal autoantibodies
  - Antibodies to cytoplasmic ribonucleo-proteins SSA (ro) more specifically the 5 anti-ss2-kda epitope of SSA
  - And SSB (la) – detected 50-75% of the time
  - Rare to have just SSB antibodies
Multidisciplinary Prenatal Diagnosis Conference

8/7/08-SLE
Case

- 27 y/o G5 P3 with good prenatal care
- PMH –
  - SLE dx 2005 (rheumatology); 4 of 11
    - Arthritis, malar rash, pericardial effusion, leukopenia
  - Medications
    - Hydroxychloroquine 200mg BID
    - Prednisone 10mg daily
    - Azathioprine 150mg up to 6 weeks (d/c w/+hcg)
- POB history – 3 term deliveries (1 CD, 2 VBAC); h/o GDM, gestational hypertension; h/o first trimester loss
- Social and family history (-)
Systemic Lupus Erythematosus

- Autoimmune d/o (need 4 of 11 Rheum criteria)
- Prevalence 5-125/100,000
- 1% of pregnancies
- Survival rates decrease with duration of disease
Criteria for diagnosis

- Per American College of Rheumatology
- Need 4 of 11 (serially or at one time)
  - Malar rash (erythema over malar eminences)
  - Discoid rash (erythematous raised patches)
  - Photosensitivity (unusual reaction to sunlight)
  - Oral ulcers (oral, nasopharyngeal)
  - Arthritis (nonerosive, 2+ peripheral joints)
  - Serositis (pleuritis, pericarditis)
  - Nephritis (>500mg/d proteinuria or cellular casts)
  - Neurologic disorder (seizures, psychosis, stroke with other causes ruled out)
  - Hematologic disorder (hemolytic anemia with reticulocytosis, thrombocytopenia <100k, leukopenia <4000 2 occasions, lymphopenia <1500 2 occasions)
  - Immunologic disorder (anti-dsDNA, anti-Sm, positive LAC ACA, false positive RPR or other serologic test for syphilis for 6 months confirmed by treponema pallidum immobilization or fluorescent treponemal antibody absorption test)
  - Antinuclear antibodies (without being on drugs associated with drug induced lupus syndrome)
- <4 of 11 = lupus-like syndrome
Pregnancy outcomes

• effect of SLE on pregnancy
  – increased stillbirth rate 25x
  – increased preeclampsia rate - 20-30%
  – increased IUGR rate - 12-32%
  – increased preterm delivery rate to 50-60%
  – increased PPROM rate
  – Neonatal lupus (1-2% if anti SSA/SSB present)

• effect of pregnancy on SLE
  – worsening renal status if nephropathy (cr 1.5) present
  – increased flares if active disease at start of pregnancy
Case

- Physical exam - obese, no evidence of lupus flare at initial visit

- Lab findings
  - Rh +; negative RPR, HepBsAg, HIV, GBS
  - 24hr urine analysis revealed normal renal function
  - ECG normal
  - Rheumatologic labs
    - ESR - slightly elevated
    - Complement levels normal t/o pregnancy
    - ANA antibodies not available
    - -dsDNA antibodies negative (high spec; 75% sens)
    - Anti-cardiolipin antibodies negative
    - + SSA, - SSB
Case

- **Lupus meds –**
  - **Hydroxycholorquine continued**
    - Immunosuppressive
    - class C
    - stopping this in pregnancy - increased risk of lupus flares,
    - continue if needed for control
    - no increased r/o fetal malformations
  - **Prednisone continued**
    - Immunosuppressive
    - class B
    - use non-fluorinated like prednisone that do not cross placenta
    - M/F side effects with high dose steroids > 20mg prednisone/day;
    - stress dose in labor if high dose used
  - **Azathioprine not restarted, unless needed for control**
    (inhibits T lymphocytes; class D; possible IUGR)
Case – pregnancy course

- Ultrasound findings
  - Anatomy normal at 20 weeks, no heart block
    - EFW 382g
  - Growth at 30 weeks, no heart block
    - EFW 1541g (48\textsuperscript{th} percentile)

- Delivered b/c of 3\textsuperscript{rd} trimester bleeding occurred at 34 weeks (repeat CD for suspected abruption)
  - Female, birth weight 2373gm, APGAR scores 9/9

- Placenta – ? Abruptio placentae; 435g; villous edema, dystrophic calcification seen
Fetal complete heart block (CHB)

- Cardiac anatomy is normal up to 50% of cases
- Most common bradyarrhythmia
- 1 in 20-25,000 live births

**Ultrasound**
- Structure
- Cord doppler (immune deposits in placenta can precipitate heart failure)
- EFW (? IUGR)
- Cardiothoracic ratio (pulm hypoplasia/heart failure)

**Differential diagnosis**
- Structural heart disease
- Immunologic/SSA/B disease
- Sinus brady in premorbid fetus
CHB – Antenatal natural history

- Mean GA of 26 weeks
- Nonimmune hydrops - 25%
- Survival 14-15% if + hydrops or structural disease
  - AV valve incompetence preceede NI hydrops
- Structurally normal heart and CHB = SSA/B uniformly
  - Fetal/neonatal heart - highest concentration of Ro antigen (SSA binds)
  - In vitro studies - SSA/B binds newborn (not adult) myocardium
    - this binding inhibits repolarization
  - ? Cofactor
    - b/c while mothers of infants with CHB almost uniformly have SSA/B, the majority of pt with these antibodies have normal pregnancies; suggest cofactor that is triggered for some reason (viruses being immunogenic?); increased incidence of CMV antibodies in some reports
    - Generalized myocarditis from Ab deposition and inflammatory response
    - Subendocardial fibroelastosis – marker of endstage myocardial injury
      - Sonographically = echogenic papillary muscles or areas of subendocariddial myocardium
- Heart rate <55 – 14% survival; no survivors reported <50bpm
CHB – fetal intervention

- Medical
  - Lessen immunologic injury
    - maternal IVIG, plasmapharesis
    - No reversal of heart block
  - Increase ventricular rate (beta-mimetics doses too high
  - Prophylaxis?
    - Maternal risk > benefit
    - Steroids in CHB - avert further immunologic damage from evolving myocarditis? (rec from Fetology)
  - PERMANENT
    - Surgical – inutero pacing (transcutaneous, open fetal surgery) described in hydropic fetuses; pacing accomplished, but fetal death was result
    - Newborn treatment…
Fetal complete heart block

- Pregnancy management
  - Rheumatology evaluation
  - Fetal echo
  - If rate <65bpm, increased surveillance to detect AV valve incompetence or early signs of NI hydrops
    - 2x weekly scans, dopplers (deposition of immune complexes in placental bed can ppt heart failure), cardiothoracic ratios
    - NSTs not helpful b/c of AV node dissociation
  - Indications for delivery
    - Deteriorating cardiac status
    - NI hydrops
  - CD for fetuses >30 weeks with CHB and hemodynamic compromise, ventricular rate <55, AV valve insufficiency, poor contractility
  - CD for all cases? Intrapartum monitoring with scalp pH, echo difficult but have been reported
Fetal CHB

- **Outcome**
  - Mortality rate – 25%
  - 90% survival after neonatal period?
  - Monitor for autoimmune disease

- **Genetics, recurrence risk**
  - No genetic predisposition
  - Previous baby with CHB has a recurrence risk range of 25-64%
  - Autoimmune d/o, +SSA 7.6% rate of CHB vs 0.6% rate of Autoimmune disease and NO SSA Ab
  - Healthy women with SSA/B Ab are majority of cases, but difficult to ID

- **Risk factors**
  - Previous child with CHB
  - High titer of SSA Ab (>1:16)
  - + SSA and + SSB
  - Maternal HLA DR3
Neonatal lupus erythmatosus

• Neonatal lupus (NLE)
  – 1 in 20,000 live births
  – occurs in 1-2% of women with antiSSA or antiSSB regardless of whether pt has SLE
  – congenital heart block, skin lesions, thrombocytopenia, anemia, hepatitis
    • heart block 50%
    • skin lesions 50% - erythematous scaling plaques on scalp or face, typically resolve within first few months like hematologic changes as the maternal autoantibodies disappear
  • both 10%
• most cases from maternal autoantibodies that cause immune mediated damage of fetus by transplacental passage of autoantibodies
  – antibodies to cytoplasmic ribonucleo-proteins SSA (Ro) more specifically the 5 anti-SS2-kDa epitope of SSA
  – and SSB (La) – detected 50-75% of the time
  – rare to have just SSB antibodies
Congenital heart block

- Pathophysiology of autoantibody mediated disease
  - SSA and SSB Ab cross placenta,
  - damage AV conducting system;
    - Apoptosis
    - Direct interference with cardiac conduction through calcium channels
  - varying degrees of heart block,
  - Myocarditis possible

- Histology - heart block from endocardial fibroelastosis from anti SSA-52 binding to myocardial tissue, mononuclear cell infiltration, fibrin deposition, calcification of conduction system (AV, SA nodes, diffuse fibroelastosis t/o myocardium)

- Typically dx at 18-28 weeks
  - typically seen as FHR of 60-80 bpm at 16-25 wks gestation with structurally normal heart with AV dissociation, hydrops possible

- Conduction system (affected AV node- delayed, intermittent, absent)
  - first degree (slowed conduction without missed beats),
  - second degree (missed beats, often in a regular pattern, eg, 2:1, 3:2, or higher degrees of block),
  - third degree or complete AV block (permanent) CHB = complete heart block

- Recurrence
  - r/o CHB in women with antiSSA ab and no previous affected infants is 1-2%
Prevention/Treatment of CHB?

- 3rd degree heart block; complete
  - permanent
- 1st or 2nd degree (def? def??.
  - reversed with antenatal fluorinated (crosses placenta) steroid therapy b/c of prevention of progression to more severe forms +/-
    - rationale of steroids is that cardiac histo has diffuse inflammation, IgG, firbrin, complement deposition
    - risk of chronic steroids without any proven benefit especially in a condition that is permanent once it is diagnosed
    - m/f risks osteoporosis, glucose intolerance, fetal growth restriction, development delay
    - reversal of hydrops case reports?
- no evidence supporting use of ppx steroid tx in women with antiSSA or antiSSB ab to prevent onset of CHB

- 1/3 of fetuses with heart block die within 3 yrs of age
  - remaining 2/3 require permanent pacemakers
end

• Refs
  – Fetology
  – Creasy MFM
  – Uptodate
  – High risk pregnancy – epi approach
  – Foley ICU manual
Symptom frequency

- Fatigue – 80-100%
- Fever – 80-100%
- Arthritis – 95%
- Myalgia – 70%
- Weight loss – 60%
- Photosensitivity – 60%
- Malar rash – 50%
- Nephritis – 50%
- Pleurisy – 50%
- Lymphadenopathy – 50%
- Pericarditis – 30%
- Neuropsychiatric – 20%
Autoantibodies
- antinuclear antibody – most common, so good screening antibody for autoimmune syndromes
  - increased in pregnancy – 10% of asymptomatic pregnant women without autoimmune disease have ANA ab compared to 2% of nonpregnant controls
  - screening for lupus b/c of high prevalence in gen pop
- dsDNA ab and Sm ab are more specific for lupus; dsDNA ab correlates with disease activity?
- AntiSSA/Ro and antiSSB/La more often associated with Sjogrens sd, but seen in 20-40% of females with lupus
  - associated with neonatal lupus sd (more later)

renal damage secondary to immune complex deposition, complement activation, inflammation, fibrosis
Management

• Preconception counseling
  – Potential complications – preeclampsia, preterm labor, miscarriage, fetal death, fetal growth restriction, and neonatal lupus
  – Evaluate lupus activity – delay pregnancy until remission
  – Evaluate for nephritis (24 hr urine), hematologic abnormalities (CBC), antiphospholipid abnormalities
  – Discontinue NSAIDS and cytotoxic agents
Antenatal care

• Frequent visits to assess lupus status, screen for hypertension
• Serial ultrasounds to evaluate fetal growth
• Antenatal surveillance at 32 weeks or earlier if indicated
Goals of management

- Avoid drugs that harm the fetus
- Prompt detection of preeclampsia and placental insufficiency
- Discern between lupus exacerbations and preeclampsia
- Appropriate detection and treatment of lupus flares
Lupus meds - NSAIDs

- Used outside of pregnancy – most common anti-inflammatory agent
- Inhibits cyclooxygenase, lipoxygenase, reduces prostaglandin synthesis
- Preg class B
- Avoid in 3rd trimester
  - Cross placenta, blocks prostaglandin synthesis in fetal tissue
  - Premature closure of ductus arteriosus, fetal pulmonary hypertension, NEC, fetal renal insufficiency
  - ASA crosses placenta and can affect fetal platelet function and is associated with intracranial fetal hemorrhage in 3rd trimester; avoid in pregnancy
Lupus meds - Hydroxychloroquine

- Hydroxychloroquine (antimalarial/antirheumatic; binds DNA, interferes with vesicle functions, inhibits phospholipid metabolism; immunosuppressive by inhibiting rheumatoid factor, acute phase reactants, enzymes)
  - stopping this in pregnancy - increased risk of lupus flares, continue if needed for control
  - limited data
  - not associated with increased r/o fetal malformations

- Preg class C
- Chloroquine is teratogenic
Lupus meds - steroids

- Preg class B
- Avoid fluorinated glucocorticoids b/c they cross the placenta
  - Hydrocortisone, prednisone, prednisolone inactivated by 11-beta hydroxysteroid dehydrogenase in the placenta allowing <10% of active drug to reach fetus
- High dose associated with maternal/fetal side effects
  - Maternal
    - Osteoporosis, glucose intolerance, sodium/water retention, hypertension, infection
  - Adverse pregnancy outcomes - GDM, preeclampsia, PPROM, IUGR
  - Incidence of fetal adrenal suppression with maternal tx is low
- Avoid empiric treatment, use at lowest possible dose
- Stress dose steroids (hydrocortisone 100mg IV q8hr in labor and for 24 hr PP)
  - Use if chronic steroids (20mg or more of prednisone for >= 3 weeks during last 6 mos)
Lupus meds - Azathioprine

- Azathioprine (inhibits T lymphocytes)
- Preg class D
- teratogenic in animals, appears safe in humans
- associated with IUGR
- indicated in pregnancy if chronic high doses of steroids is not controlling symptoms or to lower steroid dose
Lupus meds

- cyclosporine A (inhibits T lymphocytes)
- preg class C
- data comes from use in renal transplant patients, not an animal teratogen, appears safe in humans, long term follow up studies are limited
Lupus meds

- cyclophosphamide (alkylates and cross links DNA)
- preg class D
  - cleft palate, skeletal abnormalities; avoid if possible
  - may be needed in cases of severe proliferative nephritis (drug of choice in nonpregnant patients with prolif lupus nephritis)
  - crosses placenta
Lupus meds

- methotrexate (inhibits dihydrofolate reductase; inhibits lymphocyte proliferation (folate antagonist)
- preg class X
- avoid, embryo-lethal, congenital anomalies
Lupus flares

- Incidence in pregnancy 15-63%
  - Studies support and refute that pregnancy increases the incidence of flares
- Regardless they are common
- Risk factors
  - Active disease at conception (50% vs 20%)
  - Active nephritis
  - Abrupt discontinuation of hydrochloroquine
Diagnosis of flare

- sx include fatigue, fever, arthralgias/myalgias, weight loss, rash, renal deterioration, serositis, LAD, CNS sx
- titers of ab
- rising titers of dsDNA Ab with falling complement levels suggest impending flare
lupus vs preeclampsia

• Lupus flare
  – arthritis, leukopenia, thrombocytopenia, rashes, pleuritis, fevers
  – htn, proteinuria, coagulopathy possible
  – rising antidsDNA titer, active urinary sediment, low complement levels suggest lupus flare
  – complement levels (C3, C4, CH50) generally rise in pregnancy and are unaffected by uncomplicated pree
  – normal uric acid
  – differentiation near term likely not worthwhile, deliver for suspected preeclampsia and initiate tx for lupus flare if patient does not get better
Treatment of lupus exacerbations

- Mild to moderate
  - hydroxychloroquine
  - Start prednisone 15-20mg/day or increase dose to 20-30mg/day if already on glucocorticoids

- Severe exacerbations without renal/CNS manifestations
  - Rheumatology consult, hospitalize
  - Glucocorticoid treatment (prednisone 1-1.5mg/kg/d; expect improvement in 5-10 days)
  - Taper once significantly improving
  - If patient cannot be tapered off high dose steroids – add cyclosporine or azathioprine
Lupus exacerbations

- Severe exacerbation with renal or CNS involvement
  - Hospitalize, rheumatology consult
  - IV methylprednisolone 10-30mg/kg/day for 3-6 days
  - Maintain on oral prednisone 1-1.5mg/kg/day
  - When patient responds, taper steroids
  - If no response, add cyclophosphamide, or move to plasmapheresis
Lupus nephritis

- 50% of patients with lupus develop renal disease
- Pathophys
  - Immune complex deposition
  - Complement activation
  - Inflammation in kidney
- Retrospective review (Burkett, 1985)
  - 242 preg in 156 women with lupus nephritis
    - 59% no change in renal function
    - 30% with transient decrease in function
    - 7% with permanent renal insufficiency
    - Critical creatinine level is 1.5mg/dL
      - Above this - risk is increased of decreased renal function
      - Below this – risk is not increased
the lupus placenta

- reduction in size
- placental infarctions
- intraplacental hemorrhage
- deposition of immunoglobulin and complement
- thickening of trophoblast basement membrane
- above are reasons for pregnancy complications (later) – preE, IUGR, Preterm delivery
preg FDA classes

• A – controlled studies show no fetal risk in any trimester, probability of fetal harm is remote
• B – animal studies, no risk; if risk in animal studies, controlled human studies do not confirm harm
• C – harm in animal studies with no controlled human studies; no available human or animal studies
• D – human studies show fetal risk but r/b relative to medical state of mother may support use
• X – animal/human studies show fetal risk or abnormalities, use is contraindicated during pregnancy or in women who may become pregnant
tacrolimus

- tacrolimus (inhibits T lymphocyte activation, immunosuppressant)
- dose in liver transplant
  - 0.1-0.15mg/kg/d po divide q12 hr
- preg class C
- therapeutic drug levels 5-20 ng/mL just before next dose; time to steady state 3 days
- monitor creatinine, K, fasting blood glucose, serum drug levels
NLE

- 1 in 20,000 live births
- heart block 50%
- skin lesions 50% - erythematous scaling plaques on scalp or face, typically resolve within first few months like hematologic changes as the maternal autoantibodies disappear
- both 10%
- most cases from maternal autoantibodies
  - antibodies to cytoplasmic ribonucleo-proteins SSA (Ro) more specifically the 5 anti-SS2-kDa epitope of SSA
  - and SSB (La) – detected 50-75% of the time
  - rare to have just SSB antibodies
CHB

- Cardiac lesions – heart block from endocardial fibroelastosis from anti SSA-52 binding to myocardial tissue
- Histo – mononuclear cell infiltration, fibrin deposition, calcification of conduction system (AV, SA nodes, diffuse fibroelastosis t/o myocardium
- Typically seen as FHR of 60-80 bpm at 16-25 wks gestation with structurally normal heart with AV dissociation, hydrops possible
- 3rd degree heart block; complete
  - Permanent
- 1st or 2nd degree (defs???) reversed with antenatal fluorinated (crosses placenta) steroid therapy b/c of prevention of progression to more severe forms +/-
  - Rationale of steroids is that cardiac histo has diffuse inflammation, IgG, fibrin, complement deposition
  - Risk of chronic steroids without any proven benefit especially in a condition that is permanent once it is diagnosed
  - M/f risks osteoporosis, glucose intolerance, fetal growth restriction, development delay
  - Reversal of hydrops case reports?
- No evidence supporting use of ppx steroid tx in women with antiSSA or antiSSB ab to prevent onset of CHB

- 1/3 of fetuses with heart block die within 3 yrs of age
  - Remaining 2/3 require permanent pacemakers
Following is slides, notes, long version of above shortened for PNDX conf
Case

- 27 y/o G5 P3
- PMH –
  - systemic lupus erythematosus diagnosed in 2005 by rheumatology
  - Diagnosed based on arthritis, malar rash, pericardial effusion, leukopenia
  - NKDA
- Medications
  - Hydroxychloroquine 200mg BID
  - Prednisone 10mg daily
  - Azathioprine 150mg up to 6 weeks (d/c w/+hcg)
  - Fish oil, iron, calcium, prenatal vitamins
- POB history – 3 term deliveries (1 CD, 2 VBAC); h/o GDM, gestational hypertension; h/o first trimester loss
- Social and family history unremarkable
Case

• Physical exam
  – Normotensive, obese, vitiligo, no evidence of lupus flare at initial visit

• Lab findings
  – Rh +; negative RPR, HepBsAg, HIV, GBS
  – 24hr urine analysis revealed normal renal function
  – ECG normal
  – Rheumatologic labs
    • Sedimentation rate slightly elevated
    • Complement levels (C3, C4) normal t/o pregnancy
    • ANA antibodies not available
    • -dsDNA antibodies negative (high spec; 75% sens)
    • Anti-cardiolipin antibodies negative
    • + SSA, - SSB
Case

- Plan for pregnancy (Avoid harmful drugs; detection of preeclampsia, placental insufficiency; detection, treatment of lupus flares)

- Lupus meds –
  - Hydroxychloroquine continued (immunosuppressive; class C; stopping this in pregnancy - increased risk of lupus flares, continue if needed for control; no increased r/o fetal malformations)
  - Prednisone continued (immunosuppressive; class B; use non-fluorinated like prednisone that do not cross placenta; M/F side effects with high dose steroids > 20mg prednisone/day; stress dose in labor if high dose used
  - Azathioprine not restarted, unless needed for control (inhibits T lymphocytes; class D; possible IUGR)
  - Follow with rheumatology
  - Low dose aspirin started
Case – pregnancy course

- Maternal serum screen for aneuploidy and neural tube defects was normal
- Ultrasound findings
  - Anatomy normal at 20 weeks, no heart block
    - EFW 382g
  - Growth at 30 weeks, no heart block
    - EFW 1541g (48th %ile)
- Diabetes screen – abnormal 1-hr test, 3-hr test normal
- Fetal testing reassuring
Case – pregnancy course

- 3rd trimester bleeding occurred at 34 weeks
  - Patient delivered by repeat C-section (with sterilization) for suspected abruption
  - Female, birth weight 2373gm, APGAR scores 9/9

- Placenta – 435g; villous edema, dystrophic calcification seen

- Postoperative course uncomplicated

- Repeat anti-cardiolipin antibodies?

- Avoid estrogen containing medications
Systemic Lupus Erythematosus

- chronic autoimmune d/o with disease flares and remissions
- can affect all organs
  - mild cases – skin, musculoskeletal system
  - more severe – kidney, brain
  - possible manifestations are arthralgias, rashes, renal abnormalities, neurologic complications, thromboemboli, myocarditis, serositis
Epidemiology

- prevalence of lupus varies with population
- 5-125/100,000 people
- affects 1% of pregnancies
- lifetime risk of developing lupus is 1/700
  - peaks at 30 y/o
- affects women 3-10x more than men
- Ethnic groups
  - African Americans (prevalence -
  - Hispanics (prevalence -
General morbidity/mortality

• Survival rates
  – 5y – 93%
  – 10y – 85%
  – 15y – 79%
  – 20 y – 68%

• Risk factors for mortality – renal damage, thrombocytopenia, lung involvement, high disease activity at dx, >50 y/o at dx
Criteria for diagnosis

• Per American College of Rheumatology
• Need 4 of 11 (serially or at one time)
  – Malar rash (erythema over malar eminences)
  – Discoid rash (erythematous raised patches)
  – Photosensitivity (unusual rxn to sunlight)
  – Oral ulcers (oral, nasopharyngeal)
  – Arthritis (nonerosive, 2+ peripheral joints)
  – Serositis (pleuritis, pericarditis)
  – Nephritis (>500mg/d proteinuria or cellular casts)
  – Neurologic disorder (seizures, psychosis, stroke with other causes r/o)
  – Hematologic disorder (hemolytic anemia with reticulocytosis, thrombocytopenia <100k, leukopenia <4000 2 occasions, lymphopenia <1500 2 occasions)
  – Immunologic disorder (anti-dsDNA, anti-Sm, positive LAC ACA, false pos RPR or other serologic test for syphilis for 6 months confirmed by treponema pallidum immobilization or fluorescent treponemal ab absorption test)
  – Antinuclear antibodies (without being on drugs associated with drug induced lupus syndrome
• <4 of 11 = lupus-like syndrome
Significance of SSA, SSB antibodies

- Antibodies to extractable nuclear antigens
- 52, 60 kD
- SSA
  - Found in 10-60% of SLE patients
  - Of these patient’s, 50% will have antibodies positive for SSB
- ‘ANA negative SLE’
  - Occasionally SSA (Ro) is positive in patients whose negative ANA - SLE patients
Neonatal lupus erythematosus

- Neonatal lupus (NLE)
  - 1 in 20,000 live births
  - occurs in 1-2% of women with antiSSA or antiSSB regardless of whether pt has SLE
  - congenital heart block, skin lesions, thrombocytopenia, anemia, hepatitis
    - heart block 50%
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  - antibodies to cytoplasmic ribonucleo-proteins SSA (Ro) more specifically the 5 anti-SS2-kDa epitope of SSA
  - and SSB (La) – detected 50-75% of the time
  - rare to have just SSB antibodies
CHB - fetology

- Bradyarrhythmias - 9% of all arrhythmias
  - Cardiac anatomy is normal up to 50% of cases; severe congenital heart disease up to 53% of cases
  - Most common is complete (3rd degree, complete disassociation of A-V conduction
    - 1st – prolonged P-R interval (hard to see)
    - 2nd – progressive lengthening of P-R interval with dropped beats (Wenckebach); fixed P-R interval with ratio of transmission of atrial beats to ventricular beats
- CHB 1 in 20-25,000 live births
- Ck for structure, doppler cord to detect resistance, EFW to detect IUGR; cardiothoracic ratio to detect pulm hypoplasia/ cardiomeg/heart failure
- DDX- structural heart disease; immunologic/SSA/B disease; sinus brady in premorbid fetus
- Antenatal natural history (presents at mean GA of 26 weeks)
  - Nonimmune hydrops develops in 25% due to cardiac decompensation (IUFD or neonatal death)
    - Survival is 15% when hydrops is present; 14% if structural heart dz is present
    - AV valve incompetence tends to precede devel of NI hydrops
  - Structurally normal heart and CHB = SSA/B uniformly
  - Fetal/neonatal heart contains body’s highest concentration of Ro antigen (SSA binds)
  - In vitro studies show SSA/B binds to newborn myocardium (and not adult); this binding inhibits repolarization
  - ? Cofactor b/c while mothers of infants with CHB almost uniformly have SSA/B, the majority of pt with these antibodies have normal pregnancies; suggest cofactor that is triggered for some reason (viruses being immunogenic?); increased incidence of CMV antibodies
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  - Subendocardial fibroelastosis – marker of endstage myocardial injury
    - Sono = echogenic papillary muscles or areas of subendocardial myocardium
  - Heart rate <55 – 14% survival; no survivors reported <50bpm
Fetal complete heart block

- **Pregnancy management**
  - Rheumatology evaluation
  - Fetal echo
  - If rate <65bpm, increased surveillance to detect AV valve incompetence or early signs of NI hydrops
    - 2x weekly scans, dopplers (deposition of immune complexes in placental bed can ppt heart failure), cardiothoracic ratios
    - NSTs not helpful b/c of AV node dissociation
  - Indications for delivery
    - Deteriorating cardiac status
    - NI hydrops
  - CD for fetuses >30 weeks with CHB and hemodynamic compromise, ventricular rate <55, AV valve insufficiency, poor contractility
  - CD for all cases? Intrapartum monitoring with scalp pH, echo difficult but have been reported
CHB – fetal intervention

• Medical
  – Lessen immunologic injury (maternal IVIG to bind Ab to prevent placental passage; plasmapharesis to remove Ab directly)
    • No reversal of heart block
  – Increase ventricular rate (beta-mimetics in doses large enough to have an effect on fetus are not tolerated by mother)
  – Prophylaxis?
    • Maternal risk > benefit
    • Steroids in CHB to avert further immunologic damage from evolving myocarditis? (rec from Fetology)
      • PERMANENT
• Surgical – inutero pacing (transcutaneous, open fetal surgery) described in hydropic fetuses; pacing accomplished, but fetal death was result
• Newborn treatment...
Fetal CHB

- **Outcome**
  - Mortality rate – 25%
  - 90% survival after neonatal period?
  - Monitor for autoimmune disease
- **Genetics, recurrence risk**
  - No genetic predisposition
  - Previous baby with CHB has a recurrence risk range of 25-64%
  - Autoimmune d/o, +SSA 7.6% rate of CHB vs 0.6% rate of Autoimmune disease and NO SSA Ab
  - Healthy women with SSA/B Ab are majority of cases, but difficult to ID
- **Risk factors**
  - Previous child with CHB
  - High titer of SSA Ab (>1:16)
  - + SSA and + SSB
  - Maternal HLA DR3
Structural heart defects most commonly associated with complete heart block

- Left atrial isomerism
- Transposition of the great arteries
- Atrioventricular septal defect
- Pulmonic atresia
- Anomalous pulmonary venous connection
- Double outlet right ventricle
- Atrioventricular discordance
- Absent right atrioventricular connection
- Double-inlet ventricle
- Right atrial isomerism
- Pulmonic stenosis
Congenital heart block

• Pathophysiology of autoantibody mediated disease
  – SSA and SSB Ab cross placenta,
  – damage AV conducting system;
    • Apoptosis
    • Direct interference with cardiac conduction through calcium channels
  – varying degrees of heart block,
  – Myocarditis possible
• Histology - heart block from endocardial fibroelastosis from anti SSA-52 binding to myocardial tissue, mononuclear cell infiltration, fibrin deposition, calcification of conduction system (AV, SA nodes, diffuse fibroelastosis t/o myocardium)
• Typically dx at 18-28 weeks
  – typically seen as FHR of 60-80 bpm at 16-25 wks gestation with structurally normal heart with AV dissociation, hydrops possible
• Conduction system (affected AV node- delayed, intermittent, absent)
  – first degree (slowed conduction without missed beats),
  – second degree (missed beats, often in a regular pattern, eg, 2:1, 3:2, or higher degrees of block),
  – third degree or complete AV block (permanent) CHB = complete heart block
• Recurrence
  – r/o CHB in women with antiSSA ab and no previous affected infants is 1-2%
Neonatal lupus (NLE) and congenital heart block

- Neonatal lupus (due to maternal antibodies that cross the placenta) is responsible for 60-90% of cases of complete heart block (CHB) overall.
- Presence of maternal lupus or autoantibodies (SSA or SSB Ab) does not always lead to NLE or complete heart block:
  - ~50% of women with fetus/infant with CHB are asymptomatic but more than 85% are antiSSA or antiSSB +
    - ½ of these women develop sx of rheumatic disease, typically Sjogren’s sd with dry eyes and mouth; <50% chance of developing SLE
  - 50% of NLE cases occur in healthy pregnant women with circulating autoantibodies
  - Women that give birth to children with CHB almost uniformly test positive to SSA or SSB; BUT most do not have lupus or Sjogren’s syndrome
  - 30% of SLE patients have anti-SSA Ab and 15-20% have anti-SSB Ab
- Incidence of CHB in infants of SLE mothers is 2%
- Among women with SSA or SSB Ab, 2% develop CHB
Prevention/Treatment of CHB?

- 3rd degree heart block; complete
  - permanent
- 1st or 2nd degree (def??)
  - reversed with antenatal fluorinated (crosses placenta) steroid therapy b/c of prevention of progression to more severe forms +/-
  - rationale of steroids is that cardiac histo has diffuse inflammation, IgG, fibrin, complement deposition
  - risk of chronic steroids without any proven benefit especially in a condition that is permanent once it is diagnosed
  - m/f risks osteoporosis, glucose intolerance, fetal growth restriction, development delay
  - reversal of hydrops case reports?
- no evidence supporting use of ppx steroid tx in women with antiSSA or antiSSB ab to prevent onset of CHB

- 1/3 of fetuses with heart block die within 3 yrs of age
  - remaining 2/3 require permanent pacemakers
Pregnancy outcomes

• effect of SLE on pregnancy
  – increased stillbirth rate 25x (150/1000); esp w/ APLS
  – increased preeclampsia rate to 20-30% (7-10%)  
  – increased IUGR rate to 12-32%  
  – increased preterm delivery rate to 50-60% (12-15%)  
  – increased PPROM rate  
  – Neonatal lupus (1-2% if anti SSA/SSB present)

• effect of pregnancy on SLE
  – worsening renal status if nephropathy (cr 1.5) present  
  – increased flares if active disease at start of
end

• Refs
  – Fetology
  – Creasy MFM
  – Uptodate
  – High risk pregnancy – epi approach
  – Foley ICU manual