Liver Disease in Pregnancy

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Hepatobiliary Disease in Pregnancy

- Physiologic changes
- Hepatitis
- AFLP
- HELLP
- Cholestasis
- Chronic liver disease
Case

• 31 yo P2002
• Chronic liver disease, cirrhosis
• Portal HTN
• Treatment?
• Delivery Recommendations?
Case

- 38 yo P2002
- IVF pregnancy
- New onset pruritis, LFTs 300s at 20 weeks
- Evaluation?
- Treatment?
Physiologic Changes

- Elevated alkaline phosphatase, palmar erythema, spider angiomas, which might suggest liver disease, are commonly found during normal pregnancy.
- Metabolism - altered expression of the cytochrome P450 system that is mediated by higher levels of estrogen, progesterone, and other hormones.
- Hepatic CYP1A2 expression is decreased, whereas that of CYP2D6 and CYP3A4 is increased.
- Importantly, cytochrome enzymes are expressed in many organs besides the liver, most notably the placenta.
- No major hepatic histological changes are induced by normal pregnancy.
• 50-1. Of the following findings that can be associated with liver dysfunction, which is a normal physiologic change in pregnancy?

- Elevation of hepatic transaminases
- Spider angiomas *****
- Esophageal varices
- Asterixis
<table>
<thead>
<tr>
<th>Feature</th>
<th>Hep A</th>
<th>Hep B</th>
<th>Hep C</th>
<th>Hep D</th>
<th>Hep E</th>
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<tbody>
<tr>
<td>Viral type</td>
<td>RNA</td>
<td>DNA</td>
<td>RNA</td>
<td>RNA</td>
<td>RNA</td>
</tr>
<tr>
<td>Inc period</td>
<td>14-50d</td>
<td>30-180d</td>
<td>30-160d</td>
<td>30-180d</td>
<td>14-63d</td>
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<td>Transmission</td>
<td>Fecal/oral</td>
<td>Parenteral</td>
<td>Parenteral</td>
<td>Parenteral</td>
<td>Fecal/oral</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>IgM anti HAV ab</td>
<td>HBsAg, anti-HBs, anti-HBc, HBeAg, HBV DNA</td>
<td>Hep C ab</td>
<td>Delta Ag, IgM-specific Ab</td>
<td>IgM anti-HEV Ab</td>
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<td>Carrier risk of chronic infection</td>
<td>0</td>
<td>10-15%</td>
<td>50-85%</td>
<td>Up to 80% when superinfection with Hep D occurs</td>
<td>0</td>
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<tr>
<td>Vertical transmission risk</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Vaccination available</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
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</table>
Sequence of various antigens and antibodies in acute hepatitis B. ALT = alanine aminotransferase; anti-HBc = antibody to hepatitis B core antigen; anti-HBe = antibody to hepatitis B e antigen; anti-HBs = antibody to hepatitis B surface antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen. (Redrawn from Dienstag, 2012a.)
<table>
<thead>
<tr>
<th>HBsAg</th>
<th>HBsAb</th>
<th>HBcAb</th>
<th>HBeAg</th>
<th>HBeAb</th>
<th>Possible interpretation</th>
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<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Never infected</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-Early acute infxn</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Transient (up to 18d) after vaccination</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Acute HBV infxn, highly infectious</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>IgM</td>
<td>+</td>
<td>-</td>
<td>Chronic HBV infxn, highly infectious</td>
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<tr>
<td>+</td>
<td>-</td>
<td>IgG</td>
<td>+</td>
<td>-</td>
<td>Late acute or chronic HBV infxn, low infectivity</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>IgM</td>
<td>+/-</td>
<td>+/-</td>
<td>Acute HBV infxn</td>
</tr>
<tr>
<td>-</td>
<td>IgG</td>
<td>-</td>
<td>+/-</td>
<td></td>
<td>-Low-level HBsAg carrier or remote past infxn</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Passive transfer to infant of HBsAg-positive mother</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>IgG</td>
<td>-</td>
<td>+/-</td>
<td>Recovery from HBV infxn and immune</td>
</tr>
<tr>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-Immune if concentration &gt;/= 10mIU/mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Passive transfer after hepatitis B immune globulin</td>
</tr>
</tbody>
</table>
Hepatitis B Vaccination Recommendations (CDC, 2005,15)

- Maternal HBsAg Testing - All pregnant women should be tested routinely for HBsAg.
- Vaccination of Infants
- At Birth
  - Infants born to HBsAg-positive mothers should receive hepatitis B vaccine and HBIG within 12 hours of birth.
  - Infants who are born to mothers whose HBsAg status is unknown should receive hepatitis B vaccine within 12 hours of birth.
  - Term infants who weigh 2000 g or more at birth, are medically stable, and are born to HBsAg-negative mothers should receive hepatitis B vaccine before hospital discharge.
  - Preterm infants who weigh 2000 g or less at birth and are born to HBsAg-negative mothers should receive the first dose of hepatitis B vaccine 1 month after birth.
- After the Birth
  - All infants should complete the hepatitis B vaccine series
  - Infants born to HBsAg-apositive mothers should be tested for HBsAg and HBsAb after completion of the hepatitis B vaccine series at age 9 to 18 months

Williams, Creasy
Pregnancy related liver disease

- Hypertensive disease
- HELLP
- AFLP
AFLP

- Most common cause of acute liver failure in pregnancy
- 1 in 10,000 pregnancies
- 3rd trimester
Electron photomicrograph of two swollen hepatocytes containing numerous microvesicular fat droplets (*). The nuclei (N) remain centered within the cells, in contrast to the case with macrovesicular fat deposition.

AFLP - Pathogenesis

- Association with recessively inherited mitochondrial abnormalities of fatty acid oxidation.
- Similar to those in children with Reye-like syndromes.
- Mutations - mitochondrial trifunctional protein enzyme complex that catalyzes the last oxidative steps in the pathway; most common - G1528C and E474Q mutations of the gene on chromosome 2 that code for long-chain-3-hydroxyacyl-CoA-dehydrogenase—known as LCHAD.
50-7. Mutations in enzymes involved in fatty acid oxidation have been classically associated with maternal acute fatty liver of pregnancy when they occur in what pattern?

- Homozygous mutation in the fetus and the mother
- Homozygous mutation in the fetus; heterozygous mutation in the mother
- Heterozygous mutation in the fetus and the mother
- Heterozygous mutation in the fetus; homozygous mutation in the mother
AFLP

- Parkland study – n=51 - 37wk (31-40.9)
- 41% nulliparous, 10-20% multifetal pregnancy
- N/v, malaise, anorexia, epigastric pain, progressive jaundice
- ½ have HTN, unclear overlap
- Elevated LFTs (<1000)
- Hypofibrinogenemia, hypoalbuminemia, hypocholesterolemia, and prolonged clotting times.
- Serum bilirubin levels usually are < 10 mg/dL,
- Hypoglycemia
- Endothelial cell activation with capillary leakage causing hemoconcentration, acute kidney injury, ascites, and sometimes pulmonary permeability edema (Bernal, 2013)
- Severe hemoconcentration, uteroplacental perfusion is reduced, maternal acidosis → can cause fetal death; high CD rate due to NR testing
- Peripheral blood smear – echinocytosis; hemolysis due hypocholesterolemia
A 33-year old G2P1 presents at 35 weeks’ gestation with complaints of nausea and vomiting. Laboratory analysis reveals elevated transaminases and creatinine levels and coagulopathy. A peripheral smear is performed with the results shown.

What is the underlying etiology of these hemolyzed cells found on the blood smear in this patient?

- Increase destruction in the spleen
- Intense vasospasm
- Occlusive pain crisis
- Decreased cholesterol production

50-9
Peripheral smear

Echinoocytes

AFLP - Hemolysis is caused by the effects of hypocholesterolemia on erythrocyte membranes (Cunningham, 1985)

Schistocytes

A schistocyte count of >1% is most often found in thrombotic thrombocytopenic purpura

Target cells – liver disease, etc; http://www.medical-labs.net

http://www.pclv.net/casestudies/mickeybloodsmears.html
AFLP

- Swansea Diagnostic Criteria for Acute Fatty Liver of Pregnancy
- Six or more criteria are required in the absence of another cause:
  - Vomiting
  - Abdominal pain
  - Polydipsia or polyuria
  - Encephalopathy
  - Elevated bilirubin level (>14 µmol/L)
  - Hypoglycemia (<4 mmol/L)
  - Elevated urea level (>340 µmol/L)
  - Leukocytosis (>11 × 10⁹/L)
  - Ascites or bright liver on ultrasound scan
  - Elevated transaminase levels (AST or ALT >42 IU/L)
  - Elevated ammonia level (>47 µmol/L)
  - Renal impairment (creatinine >150 µmol/L)
  - Coagulopathy (PT >14 sec or aPTT >34 sec)
  - Microvesicular steatosis on liver biopsy

AFLP

- Imaging – Not helpful – sonogram, CT, MRI, poor sensitivity (Castro, 1996; Ch’ng, 2002; Knight, 2008; Nelson 2013)
  - Maternal ascites, echogenic hepatic appearance
- Diagnosis – Clinical
- Syndrome worsens – Encephalopathy, DIC, renal failure, liver failure (in 50%), delivery arrests liver deterioration
- Parkland – several women have isolated hemolysis, hypofibrinogenemia as only findings (if LDH is increased, check fibrinogen)
- Cases diagnosed as severe preeclampsia
- Coagulopathy, thrombocytopenia (10-20% with plt <50k)
AFLP - Management

- **Delivery** –
- **Mode** – vaginal preferred; cesarean if remote from delivery, to expedite maternal recovery
- **Blood product replacement**
- **Seizure ppx if unclear diagnosis**
- **N-Acetylcysteine**
- **Regional Anesthetic** – CI/use with caution due to coagulopathy
- **GI consult** – in event that liver failure necessitates orthoptic liver transplantation, so this can be arranged
Postpartum acute pancreatitis occurs in up to what percentage of women who have acute fatty liver of pregnancy?

- 10%
- 25%
- 50% ****
- 75%
• 50-13 All EXCEPT which of the following acute liver diseases of pregnancy can be associated with thrombocytopenia?

• Viral hepatitis
• Preeclampsia
• Acute fatty liver of pregnancy
• Cholestasis of pregnancy ****
Acute fatty liver of pregnancy. Cross section of the liver from a woman who died as the result of pulmonary aspiration and respiratory failure. The liver has a greasy yellow appearance, which was present throughout the entire specimen. Inset: Electron photomicrograph of two swollen hepatocytes containing numerous microvesicular fat droplets (∗). The nuclei (N) remain centered within the cells, in contrast to the case with macrovesicular fat deposition. (Photograph contributed by Dr. Don Wheeler.)
HELPP syndrome

- Hemolysis – peripheral smear, LDH >600
- Elevated LFTs - >70 (mean LFTs of a young healthy pregnant patient – 19-20)
- Low Platelets - <100,000
HELPP Syndrome Management

- Delivery regardless of GA
- Seizure prophylaxis/HTN control
- +/- corticosteroids
  - Increase the chance for a regional anesthetic?
  - Data on improved outcomes otherwise are lacking
HELLP syndrome

For women with HELLP syndrome from the gestational age of fetal viability to 33 6/7 weeks of gestation, it is suggested that delivery be delayed for 24–48 hours if maternal and fetal condition remains stable to complete a course of corticosteroids for fetal benefit.*

Quality of evidence: Low
Strength of recommendation: Qualified

*Corticosteroids have been used in randomized controlled trials to attempt to improve maternal and fetal condition. In these studies, there was no evidence of benefit to improve overall maternal and fetal outcome (although this has been suggested in observational studies). There is evidence in the randomized trials of improvement of platelet counts with corticosteroid treatment. In clinical settings in which an improvement in platelet count is considered useful, corticosteroids may be justified.
Review of studies of steroid ‘rescue’ in HELLP sd

**Table V** Randomized clinical trials of corticosteroids in HELLP syndrome

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Number of subjects</th>
<th>Antepartum</th>
<th>Postpartum</th>
<th>Placebo controlled</th>
<th>Double blind</th>
<th>Benefical effect</th>
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<td>25</td>
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<td>1994</td>
<td>25</td>
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<td>Yes</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Vigil-De Gracia</td>
<td>1997</td>
<td>34</td>
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<td>Yalcin</td>
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<td>30</td>
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<td>Isler</td>
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<td>32</td>
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<td>132</td>
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<td>Yes</td>
<td>Yes</td>
<td>No</td>
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</table>

Fonseca 2005
Katz 2008, n = 145, prospective study, randomized, placebo controlled

**FIGURE 2**
Platelet count behavior according to treatment

**FIGURE 4**
LDH behavior according to treatment

**FIGURE 7**
AST behavior according to treatment

Liver Disease Coincidental to Pregnancy
Liver Disease Coincidental To Pregnancy

- Liver Rupture
Liver Rupture and Infarction

- 95% of cases in pregnancy occur in severe preeclampsia and HELLP syndrome
  - Subcapsular hematoma occurs in <1% of HELLP syndrome patients
- Biliary disease, infection, aneurysm, hepatic neoplasm
- Subcapsular hemorrhage seen commonly in maternal autopsies from preeclampsia
- Diagnosis – CT/MRI
- Lab – Coagulopathy, thrombocytopenia, anemia, hemolysis, elevated LFTs, bilirubin
- DDX for unruptured liver hematoma – AFLP, abruption with coagulopathy, TTP, HELLP, severe pree, cholangitis with sepsis
Liver Rupture and Infarction

- Management
- Unruptured hematoma – hemodynamically stable – conservative, Trauma consult, surveillance in ICU, blood product replacement
- Liver rupture/Ruptured hematoma – Hepatic resection, hepatic artery ligation, embolization of hepatic artery, exploratory laparotomy, digital compression of hepatic artery/portal vein (Pringle); evacuation of hematoma, packing
Chronic Liver Disease
Cirrhosis patients

- Risks – PTB, IUFD, Maternal mortality, anemia, preeclampsia, bleeding from esophageal varices, PPH
- Endoscopy to eval for varices
- Vaginal delivery, shortened second stage, forceps if varices present
- Prep for PPH – blood products, etc
Portal Hypertension

- Normal – 5-10mmHg, increased if >10mmHg
- Diagnosis – Endoscopy, Catheterization of hepatic vein, Pulsed wave Doppler
- Exclude splenic artery aneurysm (Pulsed-wave Doppler and CT imaging) – Rec surgery to ligate before pregnancy if this is present
- Beta blockers, sclerotherapy, TIPS procedure (transjugular intrahepatic protosystemic shunt procedure)
- Propranolol 80mg/d
- Assisted second stage

Cirrhosis & PHT / Pulsatility index of HA
Cirrhotic patients vs controls – Correlation with HVPG

<table>
<thead>
<tr>
<th></th>
<th>20 controls</th>
<th>50 cirrhotic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>PI</td>
<td>0.92 ± 0.1</td>
<td>1.14 ± 0.18</td>
</tr>
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</table>

P< 0.001
Directly correlated with HVPG

Liver Failure

• Hepatomegaly is abnormal in pregnancy

• Labs – LFTs >2000 – liver ischemia, rupture, infarction; hypoglycemia, coagulopathy

• Causes – Viral (hepatitis viruses, CMV, EBV, HIV, HSV), APAP, drug reactions (PTU), pregnancy related (AFLP, HELLP, HTN), Budd-Chiari (hepatic vein thrombosis), ischemic necrosis, Wilson disease, autoimmune hepatitis, toxin, malignancy)

• Management –
  – Exclude pregnancy related causes – HTN, HELLP, AFLP; delivery if these are cause;
  – If viral hepatitis, supportive care is management, delivery is considered if fetus is viable and risks of prematurity are low due to high fetal mortality rate
  – Supportive care, correct coagulopathy, hypoglycemia, PPI, mannitol (cerebral edema tx)

• Acetaminophen overdose – NAC -
Liver Failure - Acetaminophen

- Acetaminophen overdose – NAC – Nomogram
- Tylenol level – 4hr after ingestion – if >120 – Tx
- If unknown tylenol level – est gram ingestion – if >7.5g – Tx
- If unknown ingestion and level – empiric treatment esp if liver failure or dysfunction is noted
- NAC – 140mg/kg load; Maintenance 17 doses of 70mg/kg, q4hr x72hr

Remember:
- The nomogram only applies to acute - not chronic - ingestions.
- The nomogram cannot be applied to ingestions less than 4 hours old.
- Consult a toxicologist for all toxic ingestions: 1-800-222-1222.
Liver transplant patients

- N >200 cases
- Wait 12 months before pregnancy
- Tacrolimus, cyclosporine – monitor drug levels
- Risks – Preeclampsia, PTB, GDM, LBW, SGA
- GDM screening
Tacrolimus (Prograf)

• MOA – Inhibits T-lymphocytes; macrolide antibiotic from streptomycyes
• CI – Hypersensitivity, Kidney disease (relative)
• Pregnancy – Class C – Risk of PTB, neonatal hyperkalemia, renal dysfunction; animal studies show increased risk of anomalies, APO
• Breast feeding – Excreted; Unsafe

Drugs.com
Critical Care Obstetrics, 4th Ed (Dr. Scott)
Cyclosporine

- MOA – inhibits T-lymphocytes
  - Fungal metabolite, inhibits Tcell response by inhibiting IL2, inhibits cell mediated immunity
- CI - Hypersensitivity, Renal dysfunction, liver dysfunction, severe HTN; A/E lymphoma
- Pregnancy – C, PTB, LBW; crosses, no evidence of teratogenicity; levels drop in pregnancy
- Breast feeding – Excreted; unsafe; immunosuppression, neutropenia, growth impairment, carcinogenesis

Drugs.com
Critical Care Obstetrics, 4th Ed (Dr. Scott)
Cholestasis
Intrahepatic cholestasis of pregnancy

- Pruritis and mild jaundice (+/-)
- 3rd trimester (possible earlier)
- Incidence 1 in 1,000-10,000 deliveries
  - Increased in chilean and swedish populations
  - Rare in blacks
- Recurrence risk is significant
  - Gonzalez study of chilean pop was 70% recurrence rate
  - Varying degrees
Cholestasis – risk factors

- Chilean, Swedish descent
- Multiples
- Hepatitis C infection
50-4. Which of the following chronic viral infections has been associated with a marked increased risk for cholestasis of pregnancy?

- Hepatitis B
- Hepatitis C ******
- Human immunodeficiency virus (HIV)
- Cytomegalovirus (CMV)
Natural history

• Initial symptom is nocturnal pruritus followed by continual pruritus

• Clinical jaundice 2 weeks later in 50%
  – Mild, constant until delivery
  – Pruritus can worsen, excoriation possible

• Symptoms resolve quickly after delivery (~2 days)
Differential diagnoses

- Viral hepatitis (cholestasis usually does not have fevers, abdominal pain or as high of an elevation of transaminases)
- Gallbladder disease (cholestasis usually is not associated with nausea or vomiting)
Differential diagnoses

- Acute hepatitis B (AST/ALT>1,000; Bili>5; no coagulopathy; hepatocellular necrosis; perinatal transmission possible)
- Acute fatty liver (AST/ALT<500; Bili<5; coagulopathy frequent; fatty infiltration; coma, renal failure, hypoglycemia possible)
- Intrahepatic cholestasis (AST/ALT<300; bili<5 mostly direct; no coagulopathy; dilated bile canaliculi; pruritus, increased bile acids)
- HELLP (AST/ALT>500; bili<5; coagulopathy common; variable periportal necrosis; hypertension, edema, thrombocytopenia, hemolysis)
50-3. Which of the following clinical features are characteristic of intrahepatic cholestasis?

- Serum transaminases
- Maculopapular rash
- Generalized pruritus
- Nausea and vomiting
Lab findings

- Alkaline phosphatase levels 5-10x normal elevation of pregnancy
  - Normally increased b/c of placental production
  - Fractionation reveals increased hepatic source
- 5’-nucleotidase increased?
- Urinary excretion of total sulfated progesterone metabolites are increased
  - Primary changes in reductase metabolism of progesterone
- Bilirubin is elevated, usually <5mg/dl (mostly direct, conjugated form)
- If chronic, liver dysfunction leads to decreased vit K reabsorption, decreased prothrombin production, prolonged prothrombin time
- Transaminases normal or moderately elevated, well below viral hepatitis levels
- Elevated cholesterol, triglyceride levels
Lab findings

• Serum bile acids (chenodeoxycholic acid, deoxycholic acid, cholic acid) increased 10x normal
  – Deposited in skin, cause of pruritis
  – Variable levels and symptoms
  – To diagnose – fasting levels of serum bile acids elevated 3x upper limit of normal (random levels should not be used alone) + symptoms

• Copper and selenium increased

• CHO metabolism impaired (screen or re-screen for gestational diabetes)
Histologically

• Periportal, hepatocellular architecture unchanged
• Centrilobular areas with dilated bile canaliculi with bile plugs
  – destruction, atrophy of microvilli of bile canaliculi
• Regress PP
• 50-5. Liver biopsy in women who suffer from cholestasis of pregnancy would be expected to show which of the following findings?
  • Bile plugs in hepatocytes ****
  • Inflammatory changes
  • Periportal necrosis
  • All of the above
Perinatal outcome

- **Risk of preterm birth, IUFD increased**
- **Fisk study of 10 yr period**
  - Meconium staining - 45%
  - Spontaneous PTL - 44%
  - Intrapartum fetal distress - 22%
  - Of 86 infants
    - 2 iufds, 1 neonatal death
  - Overall perinatal mortality 35 per 1,000
  - Nsts, serial sonograms for fluid volume, estriol levels failed to predict fetal distress
  - Early intervention (delivery) indicated in 49 pregnancies (12 b/c of fetal distress)
  - Reason for increased fetal surveillance
  - Induction at term, +FLM
Perinatal outcome

- Heinonen study of 91 cases
  - CD rate 10% higher in cholestasis pregnancies
  - risk of preterm delivery (OR 2.73)
  - risk of NICU admission (OR 2.15)

- Case report of intracerebral hemorrhage in pt with cholestasis (b/c delayed PT and vit K factor production of mother?)
Management

• Reduce pruritus – start as soon as diagnosis is made
• Antihistamines (diphenhydramine, hydroxizine) help little
• Anion-binding resin (cholestyramine)
• Corticosteroids (dexamethasone)
• S-adenyl-methionine (sam-e)
• Ursodeoxycholic acid (UDCA)
Cholestyramine

- Interrupts enterohepatic circulation, reduces reabsorption of bile acids
- Dose of 8-16g/d divided QID helpful
- 2 weeks to work
- Interferes with vit K absorption, ck PT weekly?; If prolonged PT, give vit K parenterally
- A/E – bloating, constipation
- Interferes with absorption of prenatal vitamin
- Other ‘binders’ are aluminum containing antacids
Other meds

- Phenobarbital can increase bile salt secretion and increase bile flow
  - No change in bile acid concentration
- Guar gum – gel forming fiber increases fecal elimination of bile acids
  - Finland study RCT showed stabilization of bile acids and symptoms
- SAMe (Sadenosyl methionine) - Reverses estrogen-induced impairment of bile secretion
Corticosteroids

• Dexamethasone
  – suppresses fetal/placental estrogen production (out of balance in cholestasis pregns)
SAM-e

• Reverses estrogen-induced impairment of bile secretion
Ursodeoxycholic acid (UCDA)

- Natural occurring hydrophilic bile acid that replaces other more cytotoxic bile acids
- Palma study compared 1g/d of UDCA with placebo over 3 weeks; significant decrease in lfts and pruritus
- Dose 14-16 mg/kg/d
Management (cont)

- Delivery at term or + FLM to impact perinatal outcome/mortality
- Symptoms abate 2 d PP
- Recurrence risk in subsequent pregnancies, variable severity
- Possible to see cholestasis when pt takes oral contraceptives
Conclusions

- AFLP – LFTs, coagulopathy – supportive care, delivery
- Chronic liver disease/cirrhosis – check for portal HTN, if present – beta blockers, avoid valsalva efforts
- Cholestasis – elevated bile acids, >40 (worse prognosis) – ursodiol, delivery at 37 weeks (36 weeks per UTD)
Misc

- ANCS at 34-36 weeks
- No rescue courses
- Dispositioned for delivery at 34-36 weeks
- PPROM – OK
- Severe preeclampsia – per ACOG, ANCS administration with delivery; per late preterm steroid trial ~1/3 had severe preeclampsia as indication for delivery (completed ANCS course, followed by delivery)
- No tocolysis
End
Add the following for the resident question session
Objectives for Resident Sessions

- AFLP
- HELLP
- Cholestasis
Creasy
Williams Questions – Ch 50
• See notes, ppt –
• See notes from previous Williams Review
Physiologic Changes

- Elevated alkaline phosphatase, palmar erythema, spider angiomas, which might suggest liver disease, are commonly found during normal pregnancy.
- Metabolism - altered expression of the cytochrome P450 system that is mediated by higher levels of estrogen, progesterone, and other hormones.
- Hepatic CYP1A2 expression is decreased, whereas that of CYP2D6 and CYP3A4 is increased.
- Importantly, cytochrome enzymes are expressed in many organs besides the liver, most notably the placenta.
- No major hepatic histological changes are induced by normal pregnancy.
Pregnancy related liver disease
Liver Disease Coincidental to Pregnancy
Chronic Liver Disease
Pancreatitis
Pancreatitis

• 1 in 1000-3000 pregnancies

• Etiology –
  – Gallstones (pregnancy),
  – ETOH (nonpregnant)
  – Hyperlipidemia
  – Familial hypertriglyceridemia
  – AFLP (complication in ½)
  – Hyperparathyroidism
    • Primary – Hypercalcemia
    • Secondary – Initially low calcium
      – Hypercalcemia
  – CF
  – Malignancy

• 20% have severe pancreatitis
• 25% mortality rate
Pancreatitis

• Diagnosis / Symptoms
  • N/v, pain, fever, tachycardia, SIRS
  • Lab – Amylase, lipase (level does not correlate with severity)
  • Cholesterol
  • Triglycerides
  • Leukocytosis
  • Hyperbilirubinemia, elevated LFTs (Gall stone disease)
  • Hypocalcemia
Pancreatitis

• Predictive risk factors
  - Shock
  - Need for massive colloid replacement
  - Hypocalcemia (<8mg/dL)
  - Dark hemorrhagic fluid on paracentesis

If 3 of 4 present – 30% survival
Pancreatitis - Management

- NPO
- IV fluids
- Pain control
- ERCP/removal of gall stones if indicated
- Insulin
- Antibiotics
- Oral/enteral nutrition if pain improves, ileus resolves
- Severe necrotizing pancreatitis – Laparotomy, drainage, debridement
- If hyperlipid/TG emia - Gemfibrozil
Chronic Liver Disease

- Primary Biliary Cirrhosis –
- AI liver disease
- UCDA
- Cholestyramine
- Vitamin K 100mg BID
- Fetal surveillance
Primary Sclerosing Cholangitis

- Chronic cholestatic disease, unclear origin, fibrosis/inflammation of intrahepatic and extrahepatic bile ducts
- Biliary cirrhosis > hepatic failure > death
- Ulcerative colitis pts increased risk of PSC (Crohn disease less)
- UCDA
- Liver failure > transplant
- Increased fetal bile acids
- Meconium passage
- Increased rate of fetal death – Similar to ICP
Wilson Disease

- Rare disease of copper metabolism (excess copper accumulation), decreased ceruloplasmin levels (increased with advanced liver disease)
  - Kayser-Fleischer corneal rings
- Liver failure, Neurologic dysfunction
- Consider in reproductive age women with advanced liver disease of unclear origin
- Tx with penicillamine or trientine
  - Copper deficiency in fetus
  - No clear teratogenic risk
- Continue in pregnancy
Budd Chiari Syndrome

• Hepatic vein occlusion, portal HTN is major complication
• Managed as portal HTN
• Screen for APLS, thrombophilias
• Beta blocker
• Assisted second stage
Hepatobiliary Diseases in Pregnancy

• April 2015

• END END END END END END
Pulmonary edema
Cardiac Manifestations of Preeclampsia

- Wedge and CVP Do Not Correlate
- SVR is Low Initially, and then Becomes Very High (along with BP)
- Pulmonary Artery Catheter Findings
  - Elevated SBP, SVR
  - Hyperdynamic LV Function
  - Normal to Increased PCWP
  - Low CVP
  - High Wedge with Low CVP May be Due to Increased Afterload with Volume Depletion
Pulmonary Edema in Preeclampsia

- Occurs in 3% of Women with Preeclampsia
- 70% Occurs Postpartum (Fluid Overload)
- Antepartum Pulmonary Edema Associated with Chronic HTN in 90% Cases
- Risk Factors: Older Women, Multigravidas, Chronic Hypertension
- Associated with Fluid Overload, either Colloid or Crystalloid
Pulmonary Edema in Preeclampsia

- **Pathophysiology of Pulmonary Edema**
  - Reduced COP
  - Alteration of Capillary Membrane Permeability and Integrity
  - Elevated Pulmonary Vascular Hydrostatic Pressures

- **Extravasation of Fluids in Pulmonary Interstitium**
Pulmonary Edema in Preeclampsia

- Etiology of Pulmonary Edema
  - Abnormal COP-Wedge Gradient
  - Capillary Leak
  - LV Failure

- Non-hydrostatic Forces can Cause Pulmonary Edema

- Fluid Overload is Common, Presenting with Preeclampsia in Pulmonary Edema is Not (If you see it, think LV failure and know that you are in trouble)
Pulmonary Edema in Preeclampsia

- Risk factors – fluid overload, preeclampsia, tocolysis, uncontrolled hypertension
- Diagnosis of Pulmonary Edema
  - Clinical Diagnosis: Progressive Dyspnea and Chest Discomfort
  - Tachypnea, Tachycardia, Bilateral crackles
  - Confirm with CXR and ABG
  - Don’t Forget about Pulmonary Embolism
Case

- 34 yo P0, admitted for preeclampsia
  - IVF pregnancy
- HD #3, developed progressive dyspnea, crackles on physical exam, oxygen requirements
  - CXR revealed bilateral pleural effusions
- Fluid restriction, diuretics (Lasix 20mgIV), delivery, seizure prophylaxis
CXR of pulmonary edema
Pulmonary Edema in Preeclampsia

• Management
  – Oxygen, Fluid Restriction, Semi-Fowler
  – Accurate intake/output
  – If Fluid Overload, then Lasix, Increasing Doses as Needed
  – Consider PA Catheter: Fluid Overload vs. LV Dysfunction vs. Nonhydrostatic Pulmonary Edema
Indications for PA Catheter in Hypertensive Disease

- Severe preeclampsia with refractory oliguria or pulmonary edema
- Ineffective IV antihypertensive therapy
- Intraoperative or intrapartum cardiac failure
Pulmonary Edema in Preeclampsia – 3 subsets

• Management
  – Intravascular volume depletion (oliguria), low PCWP, high CO, high SVR, low CVP –
    • fluids
  – Renal Vasoconstriction (High PCWP, Normal CO and SVR, uroconcentration):
    • Dopamine – 1-5µg/kg/min; furosemide
  – LV Dysfunction/Failure with Vasospasm (high PCWP, high SVR, low CO <5 L/min) :
    • Needs Afterload Reduction (Sodium nitroprusside 0.25-0.5µg/kg/min IV infusion)
    • Volume Restriction
    • Diuretics (max acute dose of furosemide is 120mg, start with 20-40mg)
  – Mechanical Ventilation for Respiratory Failure (If still Pregnant, Intubate Early rather than Late)
Medications
NSAIDS

- NSAIDS – inhibits cyclooxygenase, lipoxygenase, reduces prostaglandin synthesis
- Class D
- Avoid especially in 3\textsuperscript{rd} 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 3\textsuperscript{rd} 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
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
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
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 arteriosis, 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
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- Chloroquine possible teratogenic in initial studies
  - Ototoxicity, eye development

Buchanan, 1996; Khamashta 1996
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- 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
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  - Use if chronic steroids (>5mg/day for >2-4 weeks prior to delivery)
Azathioprine

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- 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
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- Methotrexate (inhibits dihydrofolate reductase; inhibits lymphocyte proliferation) (folate antagonist)
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- 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
Which of the following drugs would be a choice of last resort in the treatment of lupus during pregnancy?

- Aspirin
- Corticosteroids
- Azathioprine
- Cyclophosphamide****
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
Med list – good from GI – complete remicade
Medications
Immunosuppressants (Scott CC OB)

- All drugs cross placenta, diffuse to fetus
- No convincing evidence that prednisone, azathioprine, cyclosporine, tacrolimus produce congenital abnormalities;
- Drugs of choice in preg transplant pts
- A/e IUGR, PTB, o/w neonates do well
  - Short term ‘prematurity issues of infection, hypoglycemia, bone marrow hypoplasia, leukopenia, reduced IGM, IGG, elevated serum cr’ hard to know if it’s the drug or prematurity
- Long term – poss infertility, autoimmune disease, neoplasia – need for long term f/u
Medication

- MOA –
- CI -
- Pregnancy -
- Breast feeding -
Sulfasalazine (Azulfidine)

- **MOA** – Sulfasalazine, metabolites (5-ASA, sulfapyridine) - anti-inflammatory and/or immunomodulatory properties, main effect in UC is from 5-ASA

- **CI** – Intestinal or urinary obstruction, patients with porphyria, allergy to sulfasalazine, metabolites, sulfonamides, salicylates

- **Pregnancy** – Class B, crosses placenta;; no increased rate of defects
  - Impairs folate absorption/metabolism – so take 1-4mg folate /day, esp periconceptionally

- **Breastfeeding** – Excreted; unsafe, especially if infant is preterm, <1month old, or FHX of G6PD deficiency

Drugs.com

Critical Care Obstetrics, 4th Ed (Dr. Scott)
Azathioprine (Imuran)

- MOA – inhibits T-lymphocytes; More toxic metabolite 6-mercaptopurine- purine analog that decreases delayed hypersensitivity and cellular cytotoxicity

- CI – Hypersensitivity, relative (pregnancy), increased risk of cancer, esp if previously used alkylating agents (eg, chlorambucil, cyclophosphamide, melphalan), liver disease, need to follow CBC, CMP

- Pregnancy – Class D - D b/c increased anomaly rate of 9 and 6.4%, not found in recent series, no specific pattern, possible bone marrow suppression in fetus, with anemia, leukopenia, thrombocytopenia
  - 64-90% of azathioprine crosses the placenta, majority is inactive thiouric acid

- Breast feeding – Excreted; UK, unsafe; US – Caution is rec ; Relative CI – Neutropenia, unknown risk of carcinogenesis; Women with decreased activity of enzyme that detoxifies azathioprine metabolites may pass on higher levels of drug to their infants via breast milk; if used, check CBC/diff, CMP in exclusively breastfed infants; wait to breastfeed 4-6hr after dose

Drugs.com
Critical Care Obstetrics, 4th Ed (Dr. Scott)
Tacrolimus (Prograf)

- **MOA** – Inhibits T-lymphocytes; macrolide antibiotic from streptomyces
- **CI** – Hypersensitivity, Kidney disease (relative)
- **Pregnancy** – Class C – Risk of PTB, neonatal hyperkalemia, renal dysfunction; animal studies show increased risk of anomalies, APO
- **Breast feeding** – Excreted; Unsafe

Drugs.com
Critical Care Obstetrics, 4th Ed (Dr. Scott)
Cyclosporine

• MOA – inhibits T-lymphocytes
  – Fungal metabolite, inhibits T cell response by inhibiting IL2, inhibits cell mediated immunity

• CI - Hypersensitivity, Renal dysfunction, liver dysfunction, severe HTN; A/E lymphoma

• Pregnancy – C, PTB, LBW; crosses, no evidence of teratogenicity; levels drop in pregnancy

• Breast feeding – Excreted; unsafe; immunosuppression, neutropenia, growth impairment, carcinogenesis
Infliximab (Remicade)

- MOA –
- CI –
- Pregnancy –
- Breastfeeding
Prednisone

- MOA – inhibit humoral and cell mediated immune response
- CI – Uncontrolled DM, hypersensitity
- Pregnancy – C; Prolonged courses of fluorinated steroids (dexa, beta) may cause decreased brain, somatic growth, adrenal suppression, neonatal sepsis, CLD, psychomotor delay, behavioral prob; metabolized by 11B HSD, fetus exposed to 10%
  - Vitamin D/calcium
  - Stress dosing at delivery
- Breast feeding – Risks increased

Drugs.com
Critical Care Obstetrics, 4th Ed (Dr. Scott)
Glucocorticoids

- Glucocorticoids (antiinflammatory, glucocorticoid, mineralocorticoid)
- Preg class C
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- 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)
Cyclophosphamide – MOA – alkylating agent; D
- Cancer chemotherapy and as an immunosuppressant
- In human pregnancies, cyclophosphamide exposures that occurred during the first trimester have been associated with skeletal and palate defects, as well as malformations of the limbs and eyes
- Cyclophosphamide is excreted into human milk (34). Two reports indicate that the platelet and leukocyte counts of a nursing infant were reversibly depressed during maternal cyclophosphamide therapy (35, 48). Cyclophosphamide was classified among the cytotoxic drugs that may interfere with cellular metabolism of a nursing infant by the American Academy of Pediatrics (36).
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
• Which is not safe to use in pregnancy for reflux esophagitis?
  • Cimetidine, PPIs, calcium carbonate – OK
  • NO misoprostol – –

• What is constellation of defects that misoprostol is associated with if it does not cause SAB? – Moebius sequence –
Pregnancy - FDA classes

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- 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
References

- Email – dfarley@awhobgyn.com
- Provided on request
- Friedman 2008 PRIDE study
- Izmirly 2010 Hydroxychloroquine study
- Creasy – Resnik Maternal Fetal Medicine, Principles and Practice
Liver Disease in Pregnancy

Darren Farley, MD
Clinical Assistant Professor
Division of Maternal-Fetal Medicine
Dept. of Obstetrics and Gynecology
University of Kansas School of Medicine – Wichita
Objectives for Resident Sessions

- AFLP
- HELLP
- Cholestasis
Hepatobiliary Disease in Pregnancy

• April 2015

• Physiologic changes
• Hepatitis
• Chronic liver disease
• AFLP
• Pancreatitis
• Gall bladder
• Cholestasis
Physiologic Changes

- Elevated alkaline phosphatase, palmar erythema, spider angiomas, which might suggest liver disease, are commonly found during normal pregnancy.
- Metabolism - altered expression of the cytochrome P450 system that is mediated by higher levels of estrogen, progesterone, and other hormones.
- Hepatic CYP1A2 expression is decreased, whereas that of CYP2D6 and CYP3A4 is increased.
- Importantly, cytochrome enzymes are expressed in many organs besides the liver, most notably the placenta.
- No major hepatic histological changes are induced by normal pregnancy.
50-1. Of the following findings that can be associated with liver dysfunction, which is a normal physiologic change in pregnancy?

- Elevation of hepatic transaminases
- Spider angiomas
- Esophageal varices
- Asterixis
<table>
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<tr>
<th>Feature</th>
<th>Hep A</th>
<th>Hep B</th>
<th>Hep C</th>
<th>Hep D</th>
<th>Hep E</th>
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<td>DNA</td>
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<td>14-50d</td>
<td>30-180d</td>
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<td>Parenteral</td>
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<td>Parenteral</td>
<td>Fecal/oral</td>
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<td>Diagnosis</td>
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<td>HBsAg, anti-HBs, anti-HBc, HBeAg, HBV DNA</td>
<td>Hep C ab</td>
<td>Delta Ag, IgM-specific Ab</td>
<td>IgM anti-HEV Ab</td>
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<td>Carrier risk of chronic infection</td>
<td>0</td>
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<td>50-85%</td>
<td>Up to 80% when superinfection with Hep D occurs</td>
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<td>Vertical transmission risk</td>
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<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td>No</td>
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</table>
Sequence of various antigens and antibodies in acute hepatitis B. ALT = alanine aminotransferase; anti-HBc = antibody to hepatitis B core antigen; anti-HBe = antibody to hepatitis B e antigen; anti-HBs = antibody to hepatitis B surface antigen; HBeAg = hepatitis B e antigen; HBsAg = hepatitis B surface antigen. (Redrawn from Dienstag, 2012a.)
## Interpretations of serologic testing in patients with hepatitis B virus

### Creasy – MFM

<table>
<thead>
<tr>
<th>HBsAg</th>
<th>HBsAb</th>
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<th>HBeAg</th>
<th>HBeAb</th>
<th>Possible interpretation</th>
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<td>Never infected</td>
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<td>Early acute infxn</td>
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<td>Transient (up to 18d) after vaccination</td>
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<td>IgM</td>
<td>Acute HBV infxn, highly infectious</td>
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<td>IgG</td>
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<td>Chronic HBV infxn, highly infectious</td>
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<td>+</td>
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<td>IgG</td>
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<td>Late acute or chronic HBV infxn, low infectivity</td>
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<td>IgM</td>
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<td>Acute HBV infxn</td>
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<td>IgG</td>
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<td>+/-</td>
<td>Low-level HBsAg carrier or remote past infxn</td>
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<td>Passive transfer to infant of HBsAg-positive mother</td>
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<td>+</td>
<td>IgG</td>
<td>-</td>
<td>+/-</td>
<td>Recovery from HBV infxn and immune</td>
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<td>-</td>
<td>Immune if concentration &gt;/= 10mIU/mL</td>
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<td>Passive transfer after hepatitis B immune globulin</td>
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</table>
Hepatitis B Vaccination Recommendations (CDC, 2005)

• Maternal HBsAg Testing - All pregnant women should be tested routinely for HBsAg.

• Vaccination of Infants

• At Birth
  – Infants born to HBsAg-positive mothers should receive hepatitis B vaccine and HBIG within 12 hours of birth.
  – Infants who are born to mothers whose HBsAg status is unknown should receive hepatitis B vaccine within 12 hours of birth.
  – Term infants who weigh 2000 g or more at birth, are medically stable, and are born to HBsAg-negative mothers should receive hepatitis B vaccine before hospital discharge.
  – Preterm infants who weigh 2000 g or less at birth and are born to HBsAg-negative mothers should receive the first dose of hepatitis B vaccine 1 month after birth.

• After the Birth
  – All infants should complete the hepatitis B vaccine series
  – Infants born to HBsAg-positive mothers should be tested for HBsAg and HBsAb after completion of the hepatitis B vaccine series at age 9 to 18 months

Williams, Creasy
Pregnancy related liver disease

- Hypertensive disease
- HELLP
- AFLP
AFLP

• Most common cause of acute liver failure in pregnancy
• 1 in 10,000 pregnancies
• 3rd trimester
Electron photomicrograph of two swollen hepatocytes containing numerous microvesicular fat droplets (*). The nuclei (N) remain centered within the cells, in contrast to the case with macrovesicular fat deposition.

AFLP - Etiopathogenesis

- Association with recessively inherited mitochondrial abnormalities of fatty acid oxidation.
- Similar to those in children with Reye-like syndromes.
- Mutations - mitochondrial trifunctional protein enzyme complex that catalyzes the last oxidative steps in the pathway; most common - G1528C and E474Q mutations of the gene on chromosome 2 that code for long-chain-3-hydroxyacyl-CoA-dehydrogenase—known as LCHAD.
50-7. Mutations in enzymes involved in fatty acid oxidation have been classically associated with maternal acute fatty liver of pregnancy when they occur in what pattern?

- Homozygous mutation in the fetus and the mother
- Homozygous mutation in the fetus; heterozygous mutation in the mother
- Heterozygous mutation in the fetus and the mother
- Heterozygous mutation in the fetus; homozygous mutation in the mother
AFLP

- Parkland study – n=51 - 37wk (31-40.9)
- 41% nulliparous, 10-20% multifetal pregnancy
- N/v, malaise, anorexia, epigastric pain, progressive jaundice
- ½ have HTN, unclear overlap
- Elevated LFTs (<1000)
- Hypofibrinogenemia, hypoalbuminemia, hypocholesterolemia, and prolonged clotting times.
- Serum bilirubin levels usually are < 10 mg/dL,
- Hypoglycemia
- Endothelial cell activation with capillary leakage causing hemoconcentration, acute kidney injury, ascites, and sometimes pulmonary permeability edema (Bernal, 2013)
- Severe hemoconcentration, uteroplacental perfusion is reduced, maternal acidosis → can cause fetal death; high CD rate due to NR testing
- Peripheral blood smear – echinocytosis; hemolysis due hypocholesterolemia
A 33-year old G2P1 presents at 35 weeks’ gestation with complaints of nausea and vomiting. Laboratory analysis reveals elevated transaminases and creatinine levels and coagulopathy. A peripheral smear is performed with the results shown.

50-9. What is the underlying etiology of these hemolyzed cells found on the blood smear in this patient?
- Increase destruction in the spleen
- Intense vasospasm
- Occlusive pain crisis
- Decreased cholesterol production
Peripheral smear

Echinocytes
AFLP - Hemolysis is caused by the effects of hypocholesterolemia on erythrocyte membranes (Cunningham, 1985)

Schistocytes
A schistocyte count of >1% is most often found in thrombotic thrombocytopenic purpura

Target cells – liver disease, etc; http://www.medical-labs.net

Normal smear
http://library.med.utah.edu/WebPath/TUTORIAL/IRON/IRON002.html

http://www.pclv.net/casestudies/mickeybloodsmears.html
AFLP

- Swansea Diagnostic Criteria for Acute Fatty Liver of Pregnancy
- Six or more criteria are required in the absence of another cause:
  - Vomiting
  - Abdominal pain
  - Polydipsia or polyuria
  - Encephalopathy
  - Elevated bilirubin level (>14 µmol/L)
  - Hypoglycemia (<4 mmol/L)
  - Elevated urea level (>340 µmol/L)
  - Leukocytosis (>11 × 10^9/L)
  - Ascites or bright liver on ultrasound scan
  - Elevated transaminase levels (AST or ALT >42 IU/L)
  - Elevated ammonia level (>47 µmol/L)
  - Renal impairment (creatinine >150 µmol/L)
  - Coagulopathy (PT >14 sec or aPTT >34 sec)
  - Microvesicular steatosis on liver biopsy

AFLP

- Imaging – Not helpful – sonogram, CT, MRI, poor sensitivity (Castro, 1996; Ch’ng, 2002; Knight, 2008; Nelson 2013)
  - Maternal ascites, echogenic hepatic appearance
- Diagnosis – Clinical
- Syndrome worsens – Encephalopathy, DIC, renal failure, liver failure (in 50%), delivery arrests liver deterioration
- Parkland – several women have isolated hemolysis, hypofibrinogenemia as only findings (if LDH is increased, check fibrinogen)
- Cases diagnosed as severe preeclampsia
- Coagulopathy, thrombocytopenia (10-20% with plt <50k)
A 33-year old G2P1 presents at 35 weeks’ gestation with complaints of nausea and vomiting. Laboratory analysis reveals elevated transaminases and creatinine levels and coagulopathy. A peripheral smear is performed with the results shown.

As a part of the evaluation, you want to confirm the suspected diagnosis with imaging. Which of the following modalities is most appropriate?

- Sonography
- Computed tomography
- Magnetic resonance imaging
- None of the above
A 33-year old G2P1 presents at 35 weeks’ gestation with complaints of nausea and vomiting. Laboratory analysis reveals elevated transaminases and creatinine levels and coagulopathy. A peripheral smear is performed with the results shown.

After you stabilize the patient and correct her coagulopathy, you induce labor and she has a vaginal delivery. On postpartum day 2, she appears to be doing well, but you notice that her urine output has increased to approximately 800 cc per hour. What is the most likely cause of this condition?

- Hypothalamic dysfunction
- Elevated serum vasopressinase concentrations
- Acute tubular necrosis
- Pituitary tumor
AFLP - Management

- Delivery –
- Mode – vaginal preferred; cesarean if remote from delivery, to expedite maternal recovery
- Blood product replacement
- Seizure ppx if unclear diagnosis
- N-Acetylcysteine
- Regional Anesthetic – CI/use with caution due to coagulopathy
- GI consult – in event that liver failure necessitates orthoptic liver transplantation, so this can be arranged
Postpartum acute pancreatitis occurs in up to what percentage of women who have acute fatty liver of pregnancy?

- 10%
- 25%
- 50% *****
- 75%
All EXCEPT which of the following acute liver diseases of pregnancy can be associated with thrombocytopenia?

- Viral hepatitis
- Preeclampsia
- Acute fatty liver of pregnancy

Cholestasis of pregnancy *****
Acute fatty liver of pregnancy. Cross section of the liver from a woman who died as the result of pulmonary aspiration and respiratory failure. The liver has a greasy yellow appearance, which was present throughout the entire specimen. Inset: Electron photomicrograph of two swollen hepatocytes containing numerous microvesicular fat droplets (*). The nuclei (N) remain centered within the cells, in contrast to the case with macrovesicular fat deposition. (Photograph contributed by Dr. Don Wheeler.)
Liver Disease Coincidental to Pregnancy
Liver Disease Coincidental To Pregnancy

- Liver Rupture
Liver Rupture and Infarction

- 95% of cases in pregnancy occur in severe preeclampsia and HELLP syndrome
  - Subcapsular hematoma occurs in <1% of HELLP syndrome patients
- Biliary disease, infection, aneurysm, hepatic neoplasm
- Subcapsular hemorrhage seen commonly in maternal autopsies from preeclampsia
- Diagnosis – CT/MRI
- Lab – Coagulopathy, thrombocytopenia, anemia, hemolysis, elevated LFTs, bilirubin
- DDX for unruptured liver hematoma – AFLP, abruption with coagulopathy, TTP, HELLP, severe pree, cholangitis with sepsis
Liver Rupture and Infarction

- Management
- Unruptured hematoma – hemodynamically stable – conservative, Trauma consult, surveillance in ICU, blood product replacement
- Liver rupture/Ruptured hematoma – Hepatic resection, hepatic artery ligation, embolization of hepatic artery, exploratory laparotomy, digital compression of hepatic artery/portal vein (Pringle); evacuation of hematoma, packing
Chronic Liver Disease
Cirrhosis patients

- Risks – PTB, IUFD, Maternal mortality, anemia, preeclampsia, bleeding from esophageal varices, PPH
- Endoscopy to eval for varices
- Vaginal delivery, shortened second stage, forceps if varices present
- Prep for PPH – blood products, etc
Portal Hypertension

- Normal – 5-10mmHg, increased if >10mmHg
- Diagnosis – Endoscopy, Catheterization of hepatic vein, Pulsed wave Doppler
- Exclude splenic artery aneurysm (Pulsed-wave Doppler and CT imaging) – Rec surgery to ligate before pregnancy if this is present
- Beta blockers, sclerotherapy, TIPS procedure (transjugular intrahepatic protosystemic shunt procedure)
- Propranolol 80mg/d
- Assisted second stage

Cirrhosis & PHT / Pulsatility index of HA
Cirrhotic patients vs controls – Correlation with HVPG

\[
\begin{align*}
\text{20 controls} & : & \text{PI} = 0.85 & : & \text{0.92 ± 0.1} \\
\text{50 cirrhotic patients} & : & \text{PI} = 1.22 & : & \text{1.14 ± 0.18}
\end{align*}
\]

\[P< 0.001\]

Directly correlated with HVPG

Liver Failure

- Hepatomegaly is abnormal in pregnancy
- Labs – LFTs >2000 – liver ischemia, rupture, infarction; hypoglycemia, coagulopathy
- Causes – Viral (hepatitis viruses, CMV, EBV, HIV, HSV), APAP, drug reactions (PTU), pregnancy related (AFLP, HELLP, HTN), Budd-Chiari (hepatic vein thrombosis), ischemic necrosis, Wilson disease, autoimmune hepatitis, toxin, malignancy)

- Management –
  - Exclude pregnancy related causes – HTN, HELLP, AFLP; delivery if these are cause;
  - If viral hepatitis, supportive care is management, delivery is considered if fetus is viable and risks of prematurity are low due to high fetal mortality rate
  - Supportive care, correct coagulopathy, hypoglycemia, PPI, mannitol (cerebral edema tx)
- Acetaminophen overdose – NAC -
Liver Failure - Acetaminophen

- Acetaminophen overdose – NAC – Nomogram
- Tylenol level – 4hr after ingestion – if >120 – Tx
- If unknown tylenol level – est gram ingestion – if >7.5g – Tx
- If unknown ingestion and level – empiric treatment esp if liver failure or dysfunction is noted
- NAC – 140mg/kg load; Maintenance 17 doses of 70mg/kg, q4hr x72hr
Liver transplant patients

- N >200 cases
- Wait 12 months before pregnancy
- Tacrolimus, cyclosporine – monitor drug levels
- Risks – Preeclampsia, PTB, GDM, LBW, SGA
- GDM screening
Tacrolimus (Prograf)

- **MOA** – Inhibits T-lymphocytes; macrolide antibiotic from streptomyces
- **CI** – Hypersensitivity, Kidney disease (relative)
- **Pregnancy** – Class C – Risk of PTB, neonatal hyperkalemia, renal dysfunction; animal studies show increased risk of anomalies, APO
- **Breast feeding** – Excreted; Unsafe

Drugs.com
Critical Care Obstetrics, 4th Ed (Dr. Scott)
Cyclosporine

- MOA – inhibits T-lymphocytes
  - Fungal metabolite, inhibits T-cell response by inhibiting IL2, inhibits cell-mediated immunity
- CI - Hypersensitivity, Renal dysfunction, liver dysfunction, severe HTN; A/E lymphoma
- Pregnancy – C, PTB, LBW; crosses, no evidence of teratogenicity; levels drop in pregnancy
- Breast feeding – Excreted; unsafe; immunosuppression, neutropenia, growth impairment, carcinogenesis
Immunosuppressants

per Dr. Scott in CC in OB book 4th ed

- **Tacrolimus** – MOA – inhibits T-lymphocytes; C
  - FK506 – macrolide abx from streptomyces;
  - Incidence of post transplant DM with tacrolimus is 11-20%; median time to onset is 68d; 50% reversible
  - Nephrotoxicity, hyperkalemia in 1/3; HA, tremor, motor fxn, sensory fxn are neuro a/e
  - Cord blood concentrations 50% of maternal levels, no proven association with anomalies to date
Immunosuppressants -

**Cyclosporine** per Dr. Scott in CC in OB book 4th ed

- Cyclosporine – MOA – inhibits T-lymphocytes; C
  - Fungal metabolite, inhibits Tcell response by inhibiting IL2
  - Improved survival in transplant pt, in most regimen
  - a/e – nephrotoxicity, HTN; others hirsutism, tremor, gingival hyperplasia, hepatotoxicity, risk of lymphomas
  - Cyclosporine levels drop in pregnancy, but graft function remains stable in most pts (Bumgardner Matas 1992)
  - Readily crosses placenta, no evidence of teratogenicity
Chronic Liver Disease

- Primary Biliary Cirrhosis –
- AI liver disease
- UCDA
- Cholestyramine
- Vitamin K 100mg BID
- Fetal surveillance
Primay Sclerosing Cholangitis

- Chronic cholestatic disease, unclear origin, fibrosis/inflammation of intrahepatic and extrahepatic bile ducts
- Biliary cirrhosis > hepatic failure > death
- Ulcerative colitis pts increased risk of PSC (Crohn disease less)
- UCDA
- Liver failure > transplant
- Increased fetal bile acids
- Meconium passage
- Increased rate of fetal death – Similar to ICP
Wilson Disease

- Rare disease of copper metabolism (excess copper accumulation), decreased ceruloplasmin levels (increased with advanced liver disease)
  - Kayser-Fleischer corneal rings
- Liver failure, Neurologic dysfunction
- Consider in reproductive age women with advanced liver disease of unclear origin
- Tx with penicillamine or trientine
  - Copper deficiency in fetus
  - No clear teratogenic risk
- Continue in pregnancy
Budd Chiari Syndrome

- Hepatic vein occlusion, portal HTN is major complication
- Managed as portal HTN
- Screen for APLS, thrombophilias
- Beta blocker
- Assisted second stage
Pancreatitits
Pancreatitis

- 1 in 1000-3000 pregnancies

Etiology –
- Gallstones (pregnancy),
- ETOH (nonpregnant)
- Hyperlipidemia
- Familial hypertriglyceridemia
- AFLP (complication in ½)
- Hyperparathyroidism
  - Primary – Hypercalcemia
  - Secondary – Initially low calcium
  - Hypercalcemia
  - CF
  - Malignancy

- 20% have severe pancreatitis
- 25% mortality rate
Pancreatitis

- **Diagnosis / Symptoms**
- N/v, pain, fever, tachycardia, SIRS
- Lab – Amylase, lipase (level does not correlate with severity)
- Cholesterol
- Triglycerides
- Leukocytosis
- Hyperbilirubinemia, elevated LFTs (Gall stone disease)
- Hypocalcemia
Pancreatitis

- Predictive risk factors
  - Shock
  - Need for massive colloid replacement
  - Hypocalcemia (<8mg/dL)
  - Dark hemorrhagic fluid on paracentesis
If 3 of 4 present – 30% survival
Pancreatitis - Management

- NPO
- IV fluids
- Pain control
- ERCP/removal of gall stones if indicated
- Insulin
- Antibiotics
- Oral/enteral nutrition if pain improves, ileus resolves
- Severe necrotizing pancreatitis – Laparotomy, drainage, debridement
- If hyperlipid/TGemia - Gemfibrozil
Cholestasis
Intrahepatic cholestasis of pregnancy

- Pruritis and mild jaundice (+/-)
- 3rd trimester (possible earlier)
- Incidence 1 in 1,000-10,000 deliveries
  - Increased in chilean and swedish populations
  - Rare in blacks
- Recurrence risk is significant
  - Gonzalez study of chilean pop was 70% recurrence rate
  - Varying degrees
Cholestasis – risk factors

- Chilean, swedish descent
- Multiples
- Hepatitis C infection
50-4. Which of the following chronic viral infections has been associated with a marked increased risk for cholestasis of pregnancy?

- Hepatitis B
- Hepatitis C ****
- Human immunodeficiency virus (HIV)
- Cytomegalovirus (CMV)
Natural history

- Initial symptom is nocturnal pruritus followed by continual pruritus
- Clinical jaundice 2 weeks later in 50%
  - mild, constant until delivery
  - pruritus can worsen, excoriation possible
- Symptoms resolve quickly after delivery (~2 days)
Differential diagnoses

• Viral hepatitis (cholestasis usually does not have fevers, abdominal pain or as high of an elevation of transaminases)

• Gallbladder disease (cholestasis usually is not associated with nausea or vomiting)
Differential diagnoses

- Acute hepatitis B (AST/ALT>1,000; Bili>5; no coagulopathy; hepatocellular necrosis; perinatal transmission possible)
- Acute fatty liver (AST/ALT<500; Bili<5; coagulopathy frequent; fatty infiltration; coma, renal failure, hypoglycemia possible)
- Intrahepatic cholestasis (AST/ALT<300; bili<5 mostly direct; no coagulopathy; dilated bile canaliculi; pruritus, increased bile acids)
- HELLP (AST/ALT>500; bili<5; coagulopathy common; variable periportal necrosis; hypertension, edema, thrombocytopenia, hemolysis)
50-3. Which of the following clinical features are characteristic of intrahepatic cholestasis?

- Serum transaminases
- Maculopapular rash
- Generalized pruritus
- Nausea and vomiting
Lab findings

- Alkaline phosphatase levels 5-10x normal elevation of pregnancy
  - normally increased b/c of placental production
  - fractionation reveals increased hepatic source
- 5’-nucleotidase increased?
- urinary excretion of total sulfated progesterone metabolites are increased
  - primary changes in reductase metabolism of progesterone
- bilirubin is elevated, usually <5mg/dL (mostly direct, conjugated form)
- if chronic, liver dysfunction leads to decreased vit K reabsorption, decreased prothrombin production, prolonged prothrombin time
- transaminases normal or moderately elevated, well below viral hepatitis levels
- elevated cholesterol, triglyceride levels
Lab findings

- serum bile acids (chenodeoxycholic acid, deoxycholic acid, cholic acid) increased 10x normal
  - deposited in skin, cause of pruritis
  - variable levels and symptoms
  - to diagnose – fasting levels of serum bile acids elevated 3x upper limit of normal (random levels should not be used alone) + symptoms
- copper and selenium increased
- CHO metabolism impaired (screen or re-screen for gestational diabetes)
Histologically

- periportal, hepatocellular architecture unchanged
- centrilobular areas with dilated bile canaliculi with bile plugs
  - destruction, atrophy of microvilli of bile canaliculi
- regress PP
50-5. Liver biopsy in women who suffer from cholestasis of pregnancy would be expected to show which of the following findings?

- Bile plugs in hepatocytes ******
- Inflammatory changes
- Periportal necrosis
- All of the above
Perinatal outcome

- risk of preterm birth, IUFD increased
- Fisk study of 10 yr period
  - meconium staining - 45%
  - spontaneous PTL - 44%
  - intrapartum fetal distress - 22%
  - of 86 infants
    - 2 IUFDs, 1 neonatal death
  - overall perinatal mortality 35 per 1,000
  - NSTs, serial sonograms for fluid volume, estriol levels failed to predict fetal distress
  - early intervention (delivery) indicated in 49 pregnancies (12 b/c of fetal distress)
  - reason for increased fetal surveillance
  - induction at term, +FLM
Perinatal outcome

• Heinonen study of 91 cases
  – CD rate 10% higher in cholestasis pregnancies
  – risk of preterm delivery (OR 2.73)
  – risk of NICU admission (OR 2.15)

• case report of intracerebral hemorrhage in pt with cholestasis (b/c delayed PT and vit K factor production of mother?)
Management

- Reduce pruritus – start as soon as diagnosis is made
- Antihistamines (diphenhydramine, hydroxizine) help little
- Anion-binding resin (cholestyramine)
- Corticosteroids (dexamethasone)
- S-adenyl-methionine (SAM-e)
- Ursodeoxycholic acid (UDCA)
Cholestyramine

- Interrupts enterohepatic circulation, reduces reabsorption of bile acids
- Dose of 8-16g/d divided QID helpful
- 2 weeks to work
- Interferes with vit K absorption, ck PT weekly?; if prolonged PT, give vit K parenterally
- A/E – bloating, constipation
- Interferes with absorption of prenatal vitamin
- Other ‘binders’ are aluminum containing
Other meds

• phenobarbital can increase bile salt secretion and increase bile flow
  – no change in bile acid concentration

• guar gum – gel forming fiber increases fecal elimination of bile acids
  – Finland study ?RCT showed stabilization of bile acids and symptoms
Corticosteroids

• Dexamethasone
  - suppresses fetal/placental estrogen production (out of balance in cholestasis pregns)
SAM-e

- reverses estrogen-induced impairment of bile secretion
ursodeoxycholic acid (UCDA)

• natural occurring hydrophilic bile acid that replaces other more cytotoxic bile acids
• Palma study compared 1g/d of UDCA with placebo over 3 weeks; significant decrease in LFTs and pruritus
• dose 14-16 mg/kg/d
Management (cont)

• delivery at Term or + FLM to impact perinatal outcome/mortality
• symptoms abate 2 d PP
• Recurrence risk in subsequent pregnancies, variable severity
• Possible to see cholestasis when pt takes oral contraceptives
Gallbladder disease
This sonogram shows multiple hyperechoic gallstones filling an anechoic gallbladder.

Legend:
Cholelithiasis

- Et of 7% of jaundice in pregnancy
- Present in 12% of all pregnancies
- Increased development of cholelithiasis in pregnancy, but not choleycystitis
- GB function altered
  - After 14 weeks
    - Fasting GB volume 2x normal
    - Rate of GB emptying is delayed
    - % Of emptying is delayed
    - Higher residual compared to nonpregnant state
    - Cholecystokinin major stimulus for GB contractions
    - Estrogen/progesterone make CTX less effective, increased residual
Diagnosis

- H&P
- ultrasound
Management

- Medical
  - IV hydration
  - analgesics
  - NG suction
  - antibiotics
  - TPN

- Surgical
  - if possible, postpone until PP
  - cholecystectomy, cholangiography
  - common bile duct exploration sometimes needed
Indications For Cholecystectomy

- Ascending cholangitis
- Common bile duct obstruction
- Severe pancreatitis
- Acute abdomen
- Cholecystectomy in 2\textsuperscript{nd}/3\textsuperscript{rd} trimester associated with fetal mortality of < 5\%
  - If pancreatitis secondary to biliary tract stones remains untreated, fetal mortality approaches 60\%
    (Printen et al)
- Laparoscopic cholecystectomy safe in pregnancy
  - Studies note insufflation pressures of 8-10mmHg
Liver disease

END of ppt slides, notes are f/u slides
Creasy
• See notes, ppt –
• See notes from previous Williams Review
Physiologic Changes

• Elevated alkaline phosphatase, palmar erythema, spider angiomas, which might suggest liver disease, are commonly found during normal pregnancy.

• Metabolism - altered expression of the cytochrome P450 system that is mediated by higher levels of estrogen, progesterone, and other hormones.

• Hepatic CYP1A2 expression is decreased, whereas that of CYP2D6 and CYP3A4 is increased.

• Importantly, cytochrome enzymes are expressed in many organs besides the liver, most notably the placenta.

• No major hepatic histological changes are induced by normal pregnancy
Pregnancy related liver disease
Liver Disease Coincidental to Pregnancy
Chronic Liver Disease
Hepatobiliary Diseases in Pregnancy

• April 2015

• END END END END END END
Pulmonary edema
Cardiac Manifestations of Preeclampsia

- Wedge and CVP Do Not Correlate
- SVR is Low Initially, and then Becomes Very High (along with BP)
- Pulmonary Artery Catheter Findings
  - Elevated SBP, SVR
  - Hyperdynamic LV Function
  - Normal to Increased PCWP
  - Low CVP
  - High Wedge with Low CVP May be Due to Increased Afterload with Volume Depletion
Pulmonary Edema in Preeclampsia

- Occurs in 3% of Women with Preeclampsia
- 70% Occurs Postpartum (Fluid Overload)
- Antepartum Pulmonary Edema Associated with Chronic HTN in 90% Cases
- Risk Factors: Older Women, Multigravidas, Chronic Hypertension
- Associated with Fluid Overload, either Colloid or Crystalloid
Pulmonary Edema in Preeclampsia

• **Pathophysiology of Pulmonary Edema**  
  – Reduced COP  
  – Alteration of Capillary Membrane Permeability and Integrity  
  – Elevated Pulmonary Vascular Hydrostatic Pressures

• **Extravasation of Fluids in Pulmonary Interstitium**
Pulmonary Edema in Preeclampsia

• Etiology of Pulmonary Edema
  – Abnormal COP-Wedge Gradient
  – Capillary Leak
  – LV Failure

• Non-hydrostatic Forces can Cause Pulmonary Edema

• Fluid Overload is Common, Presenting with Preeclampsia in Pulmonary Edema is Not (If you see it, think LV failure and know that you are in trouble)
Pulmonary Edema in Preeclampsia

• Risk factors – fluid overload, preeclampsia, tocolysis, uncontrolled hypertension

• Diagnosis of Pulmonary Edema
  – Clinical Diagnosis: Progressive Dyspnea and Chest Discomfort
  – Tachypnea, Tachycardia, Bilateral crackles
  – Confirm with CXR and ABG
  – Don’t Forget about Pulmonary Embolism
Case

• 34 yo P0, admitted for preeclampsia
  – IVF pregnancy

• HD #3, developed progressive dyspnea, crackles on physical exam, oxygen requirements
  – CXR revealed bilateral pleural effusions

• Fluid restriction, diuretics (Lasix 20mgIV), delivery, seizure prophylaxis
CXR of pulmonary edema
Pulmonary Edema in Preeclampsia

- **Management**
  - Oxygen, Fluid Restriction, Semi-Fowler
  - Accurate intake/output
  - If Fluid Overload, then Lasix, Increasing Doses as Needed
  - Consider PA Catheter: Fluid Overload vs. LV Dysfunction vs. Nonhydrostatic Pulmonary Edema
Indications for PA Catheter in Hypertensive Disease

- Severe preeclampsia with refractory oliguria or pulmonary edema
- Ineffective IV antihypertensive therapy
- Intraoperative or intrapartum cardiac failure
Pulmonary Edema in Preeclampsia – 3 subsets

• Management
  – Intravascular volume depletion (oliguria), low PCWP, high CO, high SVR, low CVP –
    • fluids
  – Renal Vasoconstriction (High PCWP, Normal CO and SVR, uroconcentration):
    • Dopamine – 1-5µg/kg/min; furosemide
  – LV Dysfunction/Failure with Vasospasm (high PCWP, high SVR, low CO <5 L/min):
    • Needs Afterload Reduction (Sodium nitroprusside 0.25-0.5µg/kg/min IV infusion)
    • Volume Restriction
    • Diuretics (max acute dose of furosemide is 120mg, start with 20-40mg)
  – Mechanical Ventilation for Respiratory Failure (If still Pregnant, Intubate Early rather than Late)
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
Lupus meds - NSAIDS

- used outside of pregnancy – most common anti-inflammatory agent
- inhibits cyclooxygenase, lipoxygenase, reduces prostaglandin synthesis
- Preg class B
- Avoid in 3\textsuperscript{rd} trimester
  - cross placenta, blocks prostaglandin synthesis in fetal tissue
  - premature closure of ductus arteriosis, fetal pulmonary hypertension, NEC, fetal renal insufficiency
  - ASA crosses placenta and can affect fetal platelet function and is associated with intracranial fetal hemorrhage in 3\textsuperscript{rd} 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
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
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)
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• 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
Which of the following drugs would be a choice of last resort in the treatment of lupus during pregnancy?

- Aspirin
- Corticosteroids
- Azathioprine
- Cyclophosphamide****
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
Med list – good from GI – complete remicade
Medications
Immunosuppressants (Scott CC OB)

• All drugs cross placenta, diffuse to fetus
• No convincing evidence that prednisone, azathioprine, cyclosporine, tacrolimus produce congenital abnormalities;
• Drugs of choice in preg transplant pts
• A/e IUGR, PTB, o/w neonates do well
  – Short term ‘prematurity issues of infection, hypoglycemia, bone marrow hypoplasia, leukopenia, reduced IGM, IGG, elevated serum cr’ hard to know if it’s the drug or prematurity
• Long term – poss infertility, autoimmune disease, neoplasia – need for long term f/u
Medication

• MOA –
• CI -
• Pregnancy -
• Breast feeding -
Sulfasalazine (Azulfidine)

- **MOA** – Sulfasalazine, metabolites (5-ASA, sulfapyridine) - anti-inflammatory and/or immunomodulatory properties, main effect in UC is from 5-ASA

- **CI** – Intestinal or urinary obstruction, patients with porphyria, allergy to sulfasalazine, metabolites, sulfonamides, salicylates

- **Pregnancy** – Class B, crosses placenta; no increased rate of defects
  - Impairs folate absorption/metabolism – so take 1-4mg folate /day, esp periconceptionally

- **Breastfeeding** – Excreted; unsafe, especially if infant is preterm, <1month old, or FHX of G6PD deficiency

Drugs.com

Critical Care Obstetrics, 4th Ed (Dr. Scott)
Azathioprine (Imuran)

- MOA – inhibits T-lymphocytes; More toxic metabolite 6-mercaptopurine- purine analog that decreases delayed hypersensitivity and cellular cytotoxicity
- CI – Hypersensitivity, relative (pregnancy), increased risk of cancer, esp if previously used alkylating agents (eg, chlorambucil, cyclophosphamide, melphalan), liver disease, need to follow CBC, CMP
- Pregnancy – Class D - D b/c increased anomaly rate of 9 and 6.4%, not found in recent series, no specific pattern, possible bone marrow suppression in fetus, with anemia, leukopenia, thrombocytopenia
  - 64-90% of azathioprine crosses the placenta, majority is inactive thiouric acid
- Breast feeding – Excreted; UK, unsafe; US – Caution is rec ;Relative CI – Neutropenia, unknown risk of carcinogenesis; Women with decreased activity of enzyme that detoxifies azathioprine metabolites may pass on higher levels of drug to their infants via breast milk; if used, check CBC/diff, CMP in exclusively breastfed infants; wait to breastfeed 4-6hr after dose

Drugs.com
Critical Care Obstetrics, 4th Ed (Dr. Scott)
Tacrolimus (Prograf)

• MOA – Inhibits T-lymphocytes; macrolide antibiotic from streptomyces
• CI – Hypersensitivity, Kidney disease (relative)
• Pregnancy – Class C – Risk of PTB, neonatal hyperkalemia, renal dysfunction; animal studies show increased risk of anomalies, APO
• Breast feeding – Excreted; Unsafe

Drugs.com
Critical Care Obstetrics, 4th Ed (Dr. Scott)
Cyclosporine

- MOA – inhibits T-lymphocytes
  - Fungal metabolite, inhibits T-cell response by inhibiting IL2, inhibits cell mediated immunity
- CI - Hypersensitivity, Renal dysfunction, liver dysfunction, severe HTN; A/E lymphoma
- Pregnancy – C, PTB, LBW; crosses, no evidence of teratogenicity; levels drop in pregnancy
- Breast feeding – Excreted; unsafe; immunosuppression, neutropenia, growth impairment, carcinogenesis
Infliximab (Remicade)

• MOA –
• CI –
• Pregnancy –
• Breastfeeding
Prednisone

- **MOA** – inhibit humoral and cell mediated immune response
- **CI** – Uncontrolled DM, hypersensitivity
- **Pregnancy** – C; Prolonged courses of fluorinated steroids (dexa, beta) may cause decreased brain, somatic growth, adrenal suppression, neonatal sepsis, CLD, psychomotor delay, behavioral prob; metabolized by 11B HSD, fetus exposed to 10%
  - Vitamin D/calcium
  - Stress dosing at delivery
- **Breast feeding** – Risks increased

Drugs.com
Critical Care Obstetrics, 4th Ed (Dr. Scott)
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  - Use if chronic steroids (>5mg/day for >2-4 weeks prior to delivery)
Immunosuppressants - Cyclophosphamide per Dr. Scott in CC in OB book 4th ed

- Cyclophosphamide – MOA – alkylating agent; D
  - cancer chemotherapy and as an immunosuppressant
  - In human pregnancies, cyclophosphamide exposures that occurred during the first trimester have been associated with skeletal and palate defects, as well as malformations of the limbs and eyes
  - Cyclophosphamide is excreted into human milk (34). Two reports indicates that the platelet and leukocyte counts of a nursing infants were reversibly depressed during maternal cyclophosphamide therapy (35,48). Cyclophosphamide was classified among the cytotoxic drugs that may interfere with cellular metabolism of a nursing infant by the American Academy of Pediatrics (36).
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
• Which is not safe to use in pregnancy for reflux esophagitis?
• Cimetidine, PPIs, calcium carbonate – OK
  NO misoprostol - -
• What is constellation of defects that misoprostol is associated with if it does not cause SAB? – Moebius sequence –

Williams Obstetrics
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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
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- Monitor creatinine, K, fasting blood glucose, serum drug levels
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