Disclaimers

- I feel uniquely qualified to give this talk at this time as I have had two children and was recently pregnant!
- I may be biased for that reason 😊!
Overview

- Non-pathologic hepatic changes of pregnancy
- Liver diseases unique to pregnancy
- Liver disease superimposed on pregnancy
- Pregnancy and cholelithiasis
- Chronic liver disease and fertility
- OLT, fertility and pregnancy
Non-pathologic Hepatic Changes

- No change in liver size or blood flow
- Increase of plasma volume
  - Leads to decrease of serum albumin 4.2 g/dl → 3.1 g/dl
- Progressive increase of estrogen and progesterone, peak in 3rd trimester
  - Results in impaired bile flow
  - May exacerbate other cholestatic processes
  - Telangiectasias occur in 60%, but disappear
Non-pathologic Hepatic Changes

- Increase of alkaline phosphatase
  - Progressive from fifth to ninth month
  - Two to four times normal
  - Placental and bone source

- AST, ALT, GGT, bilirubin do not normally change
**Pregnancy Unrelated Diseases that may occur during Pregnancy**

<table>
<thead>
<tr>
<th>Disease \ Symptom</th>
<th>Pruritis</th>
<th>Jaundice</th>
<th>RUQ or Epigastric pain</th>
<th>Nausea / Vomiting</th>
<th>Coagulopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug hepatotoxicity</td>
<td>+</td>
<td>+</td>
<td>-/+</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Cholelithiasis / Choledocholithiasis</td>
<td>-/+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Acute Viral Hepatitis</td>
<td>-/+</td>
<td>+</td>
<td>+/-</td>
<td>-/+</td>
<td>-/+ (severe)</td>
</tr>
<tr>
<td>Exacerbation of chronic liver disease (AIH, Wilson’s, PBC)</td>
<td>- (PBC +)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+/- (severe)</td>
</tr>
<tr>
<td>TTP/HUS</td>
<td>-</td>
<td>+</td>
<td>-/+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Other viral syndromes</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>

Knox TA, Olans LB. NEJM 1996;335:569-575
<table>
<thead>
<tr>
<th>Disease</th>
<th>Symptoms</th>
<th>Jaundice</th>
<th>Trimester</th>
<th>Incidence in Pregnancy</th>
<th>Laboratory Values†</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperemesis gravidarum</td>
<td>Nausea, vomiting</td>
<td>Mild</td>
<td>1 or 2</td>
<td>0.3–1.0%</td>
<td>Bilirubin &lt;4 mg/dl, ALT &lt;200 U/liter</td>
<td>Low birth weight</td>
</tr>
<tr>
<td>Intrahepatic cholestasis of pregnancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary tract disease</td>
<td>Right-upper-quadrant pain, nausea, vomiting, fever</td>
<td>With CBD</td>
<td>Any</td>
<td>Unknown</td>
<td>If CBD stone, increased bilirubin and GGT</td>
<td>Unknown</td>
</tr>
<tr>
<td>Drug-induced hepatitis</td>
<td>None or nausea, vomiting, pruritus</td>
<td>Early (in cholestatic hepatitis)</td>
<td>Any</td>
<td>Unknown</td>
<td>Variable</td>
<td>Unknown</td>
</tr>
<tr>
<td>Acute fatty liver of pregnancy</td>
<td>Upper abdominal pain, nausea, vomiting, pruritus</td>
<td>Common</td>
<td>3</td>
<td>0.008%</td>
<td>ALT &lt;500 U/liter, low glucose, DIC in &gt;75%, increased bilirubin and ammonia late in disease</td>
<td>Increased maternal mortality (≤20%) and fetal mortality (13–18%)</td>
</tr>
<tr>
<td>Preeclampsia and eclampsia</td>
<td>Upper abdominal pain, edema, hypertension, mental-status changes</td>
<td>Late, 5–14%</td>
<td>2 or 3</td>
<td>5–10%</td>
<td>ALT &lt;500 U/liter (unless infarction), proteinuria, DIC in 7%</td>
<td>Increased maternal mortality (~1%)</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>Upper abdominal pain, nausea, vomiting, malaise</td>
<td>Late, 5–14%</td>
<td>3</td>
<td>0.1% (4–12% of women with preeclampsia)</td>
<td>ALT &lt;500 U/liter, platelets &lt;100,000/mm³, hemolysis, increased LDH, DIC in 20–40%</td>
<td>Increased maternal mortality (1–3%) and fetal mortality (35%)</td>
</tr>
<tr>
<td>Viral hepatitis</td>
<td>Nausea, vomiting, fever</td>
<td>Common</td>
<td>Any</td>
<td>Same as general population</td>
<td>ALT greatly increased (&gt;500 U/liter), increased bilirubin, DIC rare</td>
<td>Maternal mortality increased with hepatitis E</td>
</tr>
</tbody>
</table>

*ALT denotes alanine aminotransferase, CBD common bile duct, GGT γ-glutamyl transpeptidase, DIC disseminated intravascular coagulation, and LDH lactate dehydrogenase.

†To convert bilirubin values to micromoles per liter, multiply by 17.1.
Hyperemesis gravidarum (HG)

- Severe nausea and emesis which leads to weight loss, ketosis and dehydration
- Usually in first trimester, but may recur
- May recur in subsequent pregnancies
- Mild ↑ Tbili (<4 mg/dl), mild ↑ ALT (2-3x ULN)
  - Related to malnutrition
- LBx (if done): fatty change
- No adverse outcome on fetus in general
  - Severe HG associated with low birth weight
- Treatment: IVF, if severe TPN
OHSS

- Increase in capillary permeability that results in the leakage or exudation of protein-rich fluid from the ovaries or peritoneal surface to the third space compartments.
- Pharmacological doses of exogenous gonadotropins override the hypothalamic-pituitary-ovarian feedback mechanism, leading to the recruitment of a large number of follicles.
- A mild to moderate increase in ALT and AST (no greater than 1000 IU/L).
  - ALT and AST can remain elevated for up to 2 months,
  - Associated with a lower pregnancy rate
- Significant cholestasis is rare.
Intrahepatic cholestasis of pregnancy (IHCP)

- “Benign” process, begins in 2nd and 3rd trimester
- Causes pruritis and jaundice, dark urine and acholia
- LBx (if done): bland cholestasis
- ↑ Tbili (up to 6 g/dl), ↑ ALT (3-4x ULN), ↑ Alk phos (4x ULN), Elevation in serum bile acids
- Symptoms resolve within hours of delivery
- Commonly recurs in subsequent pregnancy (60%)
- Strong familial predisposition (Chile 15%, Scandinavia)
  - MDR3 gene
- Genetic susceptibility to cholestatic effects of estrogen
- High rates of premature labor (60%), increased fetal mortality (as high as 10-20%), 60% have recurrence
- Treatment: ADEK, cholestyramine (10-12 g/d), ursodiol (also improves fetal outcome), vitamin K near delivery
Pre-eclampsia/Eclampsia

- Frequent: 5-10% of pregnancy
- Late 2nd or 3rd trimester
- Clinical features:
  - Pregnancy-induced HTN
  - Edema
  - Proteinuria
  - Neurologic sequelae: seizure, papilledema, headache, visual abnormalities
- Pathophysiology not clear
  - LBx (if done): often abnormal with sinusoidal fibrin deposition, periportal hemorrhage or necrosis; ? Abn endothelial reactivity
- Risk factors: pre-existing HTN, first pregnancy, multiple gestations, extremes of child-bearing age
- Severe cases: cerebral edema, hepatic infarction or rupture, FHF, ARF, placental abruption, prematurity, IUGR
- Mortality 1% in experienced centers
Hemolysis, Elevated Liver enzymes, Low Platelets (HELLP)

- Infrequent (0.1-0.6% of pregnancies)
- Late 2nd or 3rd trimester
- Clinical features: RUQ pain, jaundice (5%), N/V, headache, HTN
  - ↑ ALT (2-10x ULN), ↓ platelets, ↓ haptoglobin
- Severe cases: cerebral edema, hepatic infarction or rupture, FHF, ARF, placental abruption, prematurity, IUGR
- Treatment - 35-60% perinatal mortality
  - Supportive care and prompt delivery
  - Steroids for 48 hours to mature fetal lung
  - Surgical therapy for hepatic rupture, OLT
- Recurs in 25% of subsequent pregnancies
Acute Fatty Liver of Pregnancy (AFLP)

- Uncommon, usually late 3rd trimester (1:13000 deliveries)
- Primigravida or multiple gestation more likely to be affected
- 40% present with pre-eclamptic symptoms
  - N/V as early as 22nd week (70%)
  - RUQ pain
  - Jaundice then follows
  - Pruritis rare
- Associated with fetal LCHAD deficiency - LCFA build up
- Life threatening
  - Progresses to hepatic failure, encephalopathy, renal failure, DIC, hemorrhage, seizure coma, death
- Treatment:
  - **Immediate delivery**
    - OLT if don’t respond to delivery
  - Liver recovers fully if patient survives
  - Unlikely to recur (only 3 cases in literature) but may be related to high mortality and low rate of subsequent pregnancy
Spontaneous Hepatic Rupture (SHF)

- Rare
- 94% associated with eclampsia/pre-eclampsia
- RUQ pain --> tenderness, diffuse abdominal pain and peritoneal signs
- Therapy is hemodynamic support and then emergency surgery
- 50% mortality for mother
Liver Diseases Superimposed on Pregnancy

- **Viral hepatitis**
  - No higher incidence than in normal population
  - Uncomplicated viral hepatitis does not affect maternal course but increased fetal prematurity except...
  - Hepatitis E - India, Middle East, Mexico, Central Asia - 20% mortality, worse in later trimesters
    - 25% mortality versus 1.9% mortality in non pregnant patients
  - Vertical transmission of hepatitis B
    - HBlg for HBsAg+ mother’s newborns with HBV vaccination at month 1 and 6 (75% efficacy of HBlg, 90% for combination)
  - Vertical transmission of hepatitis C < 5%
  - HSV hepatitis can be severe/fatal for mother and child
Liver Diseases Superimposed on Pregnancy

- **EtOH-related Chronic Liver Disease**
  - Maternal morbidity and mortality similar to other etiologies of cirrhosis
  - Fetus may suffer from fetal alcohol syndrome
  - Fetal liver may have typical changes of ASH

- **Wilson’s Disease**
  - Maternal morbidity and mortality similar to other etiologies of cirrhosis
  - Recommended to continue D-penicillamine at 1/4 to 1/2 of normal dose (0.25-0.5 g/d)
  - Supplementation of pyridoxine
  - Trientine probably safe
Liver Diseases Superimposed on Pregnancy

- **Cirrhosis and portal hypertension**
  - High incidence of infertility
  - 15% maternal mortality if cirrhotic (but may not be significantly different from non-gravid cirrhotic)
  - 30-50% morbidity: HE, ascites, post-partum hemorrhage frequent
  - 18-31% of women will bleed from varices (use beta blockers)
  - ? C-section or ? Abx at time of delivery

- **Hypercoaguable disorders**
  - Budd-Chiari Syndrome, VOD
  - Factor V Leiden, ATIII deficiency, protein C & S deficiency
  - Hyperestrogenemia
Liver Diseases Superimposed on Pregnancy

- **Hepatic neoplasms**
  - FNH - increase in size during pregnancy
  - Hepatocellular adenoma - also increase in size, can rupture; consider resection if identified pre-conception

- **Cholelithiasis**
  - Multiple pregnancy-related changes in biliary secretion
  - Increased cholecystitis and choledocholithiasis
  - Cholecystectomy required in 1:1000 pregnancy
  - ERCP may be option, shielding fetus
Miscellaneous Issues

- **Menstruation**
  - Amenorrhea, oligomenorrhea common

- **Transplantation**
  - Menstruation regained in 90% post-OLT within 1 year
  - Conception delay by 12-24 months recommended
  - OCP use can effect CsA and FK506 levels
  - No increased graft rejection during pregnancy
  - Immunosuppressants - Prednisone, CsA, AZP, Tac; avoid MMF;
  - No breast feeding
  - CMV issues, Genetic counseling
  - ? Abx at time of delivery
Algorithm

Fever, leukocytosis, RUQ pain, +/- jaundice

No
- Exclude Drug-induced liver disease
  - New onset pruritis?
    - Yes
      - Intrahepatic Cholestasis of Pregnancy
    - No
      - RUQ sonography
Another Algorithm

Rule out viral hepatitis (HAV IgM, HBsAg, HBsAb, HCV Ab/PCR, CMV IgM, CMV eAg, HSV IgM, EBV IgM)

HBsAg+  Supportive care

No

Yes

ALT > 1000 U/l

Clinical Picture

Yes

Toxin (e.g. acetaminophen)
Ischemia (hypotension)
Infarction
Acute Budd-Chiari
Severe acute AIH
Rupture

No

Fever, leukocytosis, RUQ pain, +/- jaundice

Suspect hyperemesis, medications

No

Yes

Suspect cholelithiasis, choledocholithiasis, liver abscess

Preeclampsia, hemolysis, thrombocytopenia, DIC

Suspect HELLP

Deliver Promptly

Suspect AFLP

Encephalopathy, Renal Failure, Hypoglycemia, DIC