Pregnancy and the Liver

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Northwestern University Feinberg School of Medicine

Outline

• Liver diseases occurring in pregnancy
• Pregnancy in patients with established liver disease
• Liver disease specific to pregnancy:
  – Hyperemesis gravidarum
  – Pre-ecclampsia/ecclampsia/HELLP
  – Acute fatty liver of pregnancy
  – Intrahepatic cholestasis of pregnancy
### The Liver During Normal Pregnancy

<table>
<thead>
<tr>
<th>Test</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin</td>
<td>Normal; urine bilirubin may be positive in the absence of jaundice</td>
</tr>
<tr>
<td>Albumin</td>
<td>Decreased because of hemodilution</td>
</tr>
<tr>
<td>Serum bile acids</td>
<td>Remain within normal limits</td>
</tr>
<tr>
<td>Aminotransferases</td>
<td>Unchanged or lower</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Elevated in third trimester; placental origin</td>
</tr>
<tr>
<td>5’-nucleotidase</td>
<td>Normal</td>
</tr>
<tr>
<td>γ-Glutamyl transferase</td>
<td>May not rise with hepatic injury</td>
</tr>
</tbody>
</table>

### Jaundice in Pregnancy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Associated Symptoms</th>
<th>Laboratory Abnormalities</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral hepatitis A</td>
<td>Malaise, abdominal pain</td>
<td>Aminotransferases</td>
<td>Generally good</td>
</tr>
<tr>
<td>B</td>
<td></td>
<td>HAV IgM</td>
<td>Transmission likely</td>
</tr>
<tr>
<td>C</td>
<td></td>
<td>HBV serologies</td>
<td>without prophylaxis</td>
</tr>
<tr>
<td>D</td>
<td></td>
<td>HCV Ab, HCV RNA</td>
<td>Low vertical transmission</td>
</tr>
<tr>
<td>E</td>
<td></td>
<td>HDV RNA</td>
<td>Low vertical transmission</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HEV Ab, serum RT-PCR, stool sample</td>
<td>High fetal wastage, high maternal mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>less reliable</td>
<td></td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>Epigastric pain, fever, nausea</td>
<td>Ultrasound</td>
<td>Surgery if needed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ideally in 2nd trimester</td>
</tr>
<tr>
<td>Choledocholithiasis</td>
<td>Epigastric pain, nausea +/− fever</td>
<td>Ultrasound, MRCP</td>
<td>EUS, ERCP if needed</td>
</tr>
<tr>
<td>Choledocholithiasis/</td>
<td></td>
<td></td>
<td>radiation exposure</td>
</tr>
<tr>
<td>Cholangitis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICP</td>
<td>pruritus</td>
<td>High BA, bil&lt;5</td>
<td>Poor fetal</td>
</tr>
</tbody>
</table>
Non-pregnancy Associated Liver Diseases According to Gestational Period

TRIMESTER

1st  2nd  3rd

Gallstones

Acute viral hepatitis (A-E)

Herpetic hepatitis

The Pregnant Cirrhotic

- 50% have maternal or fetal complications
- 24% with stable cirrhosis will decompensate
- Main maternal risk is variceal bleed (20-25%), 2nd TM, delivery
- **Large varices present:** Beta Blockers (FGR) or banding
- **No known varices:** screen initially and in 2nd TM
Hyperemesis Gravidarum

- Incidence: 0.3-2% of pregnancies
- Risk factors
  - Obesity, DM, hypothyroidism, psychiatric d/o
  - Twin pregnancy
  - Nulliparity
  - Molar pregnancy
Hyperemesis Gravidarum - Presentation

• Intractable nausea and vomiting can persist throughout pregnancy in 10%

• Liver chemistries:
  – Abnormal in up to 50%
  – Hepatocellular pattern (mild → 10 x ULN)
  – Cholestasis rare – rule out other causes

• Can lead to severe dehydration and ketosis
  – Increased fetal problems if not controlled

Hyperemesis Gravidarum - Management

• Supportive care

• May require hospitalization
  – Correction of electrolytes
  – Volume repletion
  – Thiamine supplementation to prevent Wernicke’s encephalopathy
  – ? Corticosteroids in refractory cases
Hepatic Disorders Associated with Toxemia of Pregnancy

Toxemia
Preeclampsia/ecclampsia
• 0.6-1.2% of pregnancies

HELLP
• 0.2-0.6% pregnancies
• 10% of all toxemias

AFLP
• 1 in 500-6000 pregnancies
• Up to 50% have toxemia

Toxemia/Pre-eclampsia

• Risk factors
  – Nulliparity (75%)
  – Maternal age > 40 yrs
  – Family history of pregnancy-induced HTN
  – Chronic HTN
  – Chronic renal failure
  – Diabetes
Pre-eclampsia: Common Clinical Features

• **Hallmark:** HTN (140/90 mm Hg), proteinuria, and edema
• Nausea and vomiting
• Abdominal pain
• Sudden increase in body weight

Severe Toxemia

• Severe hypertension (>160/100 mm Hg)
• Proteinuria (> 5 g/24hrs)
• **Organ damage:** oliguria, cerebral or visual problems, pulmonary edema, impaired liver function, thrombocytopenia or fetal growth restriction
• Seizures (Ecclampsia)
  • 25% before labor
  • 50% during labor
  • 25% within 72 hours postpartum
Hepatic Manifestations of Toxemia

- Liver involvement is indicative of severe disease
- Labs:
  - Wide range: Mild abnormalities → ALF (20-30%)
  - AST/ALT (usually < 10 x ULN)
  - Elevated LDH and bili (usually < 3 mg/dl)
- RUQ pain
  - Hepatic infarction
  - Subcapsular hematoma/Hepatic rupture
- *more common in HELLP syndrome

HELLP Syndrome

- Often presenting symptoms nonspecific: malaise, 50% epigastric/RUQ pain
- Hallmarks:
  - (H) hemolysis
  - (EL) elevated liver enzymes (TA>70, LDH>600)
  - (LP) low platelets (<100)
- Microangiopathic hemolytic anemia on smear
- Occurs invariably in the context of toxemia
Toxemia is Associated with Increased Pro-Inflammatory Cytokines


Increased Placental Oxidative Stress

Yang and Walsh, Placenta 1998;19:581-6
Causes of Maternal Mortality in HELLP

Intrahepatic Hemorrhage in HELLP

Common presenting features:
- increasing abdominal pain
- shock
- drop in hemoglobin

Treatment:
- angiography and embolization
- APC coagulation
- hepatic artery ligation
Management

• Fetus:
  – Close monitoring for IUGR and fetal distress
  – Immediate delivery especially after wk 34
  – Use of steroids to improve lung maturity if < 34 weeks
    (Dexamethasone 10mg IV q12)

• Maternal:
  – Management of blood pressure
  – Bed rest, Na restriction
  – Maintain “eu-metabolic state”
  – *High dose steroids
  – *Plasmapheresis
  – *Activated protein c
  – *Liver transplant
  * Very limited data

Use of Steroids

• Benefits:
  – promotes fetal lung maturity
  – reduced blood pressure
  – reduced bleeding complications
  – improvement in maternal morbidity: class 1:
    69 vs 49%, class 2: 54 vs 22% and class 3:
    40% vs 21%
ASA to Prevent Toxemia and HELLP

- N= 22 studies, 33,598 subjects
- 5 trials of low risk subjects (n=16700)
- 17 trials of high risk subjects (n=16898)
- Incidence of toxemia: 6.4% overall with 3.75% in low risk and 9% in high risk
- In high risk group, low dose ASA decreased risk (RR: 0.87 95% CI: 0.79-0.96)

Ruano et al., Clinics 2005;60:407-14

Acute Fatty Liver of Pregnancy (AFLOP)

- Rare (incidence: 1 in 500-6000 pregnancies)
- **Hallmarks:**
  - microvesicular steatosis
  - liver failure
- 28% (up to 50%) of cases occur in those with toxemia/HELLP

Dani et al, Am J Gastroenterol 1996;91:292
Clinical Differentiation between HELLP and AFLOP

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<th>AFLP</th>
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<td>Gestational duration</td>
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<td>36 wks (M fetus 71%)</td>
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<tr>
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<td>15%</td>
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<tr>
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Multiple sources Courtesy of AJS

ACG 2013

ACG Postgraduate Course • October 12-13, 2013
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Lab Evaluation of HELLP and AFLOP

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<th>% with abnormal values (AFLOP)</th>
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<tr>
<td>RBC morphology</td>
<td>90</td>
<td>50</td>
</tr>
<tr>
<td>Platelet count</td>
<td>98</td>
<td>73</td>
</tr>
<tr>
<td>LDH</td>
<td>98 (up to 5000 IU/l)</td>
<td>75</td>
</tr>
<tr>
<td>AST</td>
<td>90 (up to 6000 IU/l)</td>
<td>99</td>
</tr>
<tr>
<td>ALT</td>
<td>65 (up to 750 IU/l)</td>
<td>95</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>20 (up to 20 mg/dl)</td>
<td><strong>95</strong></td>
</tr>
<tr>
<td>INR</td>
<td>13</td>
<td><strong>92</strong></td>
</tr>
<tr>
<td>Creatinine</td>
<td>80 (usually &lt; 5 mg/dl)</td>
<td>87</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td>FSP</td>
<td>40</td>
<td>35</td>
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Role of LCHAD Deficiency in AFLOP

- 62% of mothers carrying a fetus with LCHAD deficiency develop AFLP or HELLP
- Only 20% of babies in setting of AFLOP have LCHAD deficiency

Case control studies:
- Risk of maternal disease 50-fold higher in LCHAD deficient fetus
- Risk of maternal disease 12-fold higher in SCHAD deficient fetus

1 Strauss et al, NEJM, 1999;340:1723-1731
2 Browning et al, Obstet Gynecol 2006;107:115-20
Recurrent AFLOP Depends Largely on LCHAD Status

- + fetal fatty acid oxidation defect
  Risk of AFLOP next pregnancy 20-70%

- No fetal fatty acid oxidation defect
  Risk of AFLOP next pregnancy Rare

Browning et al, Obstet Gynecol 2006;107:115-20
Strauss et al, NEJM 1999;340:1723-1731

Maternal Hepatic Consequences of Fetal FAO Defect

- Microvesicular hepatic steatosis
- Mitochondrial dysfunction:
  - low ATP (energy failure)
  - low ketone levels in heterozygous mother
  - high ammonia
- Hypoglycemia
- Functional failure (↑INR, bilirubin)
Management

• Fetus:
  – Close monitoring for IUGR and fetal distress
  – Immediate delivery especially after wk 34
  – Use of steroids to improve lung maturity if < 34 weeks

• Maternal:
  – Urgent delivery
  – Liver transplant

Intrahepatic Cholestasis of Pregnancy (ICP)

• 3rd and late 2nd trimester
• Pruritus and cholestasis
• Severe cases; steatorrhea
• Labs
  ↗ ALT/AST range mild → severe
  – Bilirubin <5
  – Elevated bile acids (>10 μmol/L)
    • >40 μmol/L ** higher fetal morbidity
ICP Risk Factors and Geography

• Geographic variability: Chile (14%) Netherlands (1-2%)
• Risk factors:
  – multi-parity
  – advancing maternal age
  – twin pregnancies
  – history of cholestasis 2/2 to OCPs
• Recurs in approximately 60-70%

Etiology of ICP

• Genetic:
  – Familial clustering
  – Ethnic predisposition
  – Increase in twin pregnancies
  – Higher incidence in sisters of affected patients
  – ABCB4, ABCB11
  – 1B3 in placenta

From Jungst et al., Eur JCI 2013

Multiple sources
Etiology of ICP - Hormonal

- **Hormonal**
  - Symptom severity highest late pregnancy
  - Pruritis in patients on OCPs prior or following ICP
  - Both estrogens (mainly estradiol-17β-D-glucuronide) and progesterone metabolites can promote cholestasis

ICP: Fetal Outcomes

- **Increased fetal morbidity**
  - Pre-term delivery: 25% (adj. OR 5.39)
  - NICU admission: 12% (adj. OR 2.68)
  - Stillbirth: 1.5% (adj. OR 2.58)
    - Chronic placental ischemia
    - Acute anoxia

- Morbidity and mortality for the fetus is increased, particularly in women with serum bile acid levels ≥ 40μm

ICP: Outcomes

- Low maternal morbidity usually limited to pruritus resolving after delivery
- Association with gallstone disease (ABCB4)\(^1,2\)
- Increased risk of gestational diabetes\(^3\)


Association between ICP and Hepatobiliary disease, HCV

- 1%/yr increased risk of liver disease in women with h/o ICP
- Later HCV: HR 4.16
- HCV+ OR 5.76 for future ICP

1. Marschall et al. ICP: A Population Based Cohort Study. Hepatology 2013

Fig. 1. Time after ICP to first hepatobiliary disease. For this analysis all women with a prior liver disease were excluded as well as all matched controls for each women with a prior liver disease.
ICP Management

• Optimal delivery ≈ 37-38 weeks
• Consider peri-partum vitamin K
• Patients with serum bile acids >40 should be treated with UDCA (10-15mg/kg/d)
  – UDCA Improves pruritus, ALT, bile acid levels \(^1\)
  – May improve fetal outcome \(^2\)


Summary

• Pregnancy associated liver disease is very trimester specific
• Pre-ecclamptic syndromes are usually cured by prompt delivery
  – Recurrence approx. 25%
  – AFLOP recurrence: varies according to LCHAD status of fetus
Summary

• ICP:
  – Association with gallstone disease
  – May increase risk of later chronic liver disease (HCV), cirrhosis
  – Fetal outcomes worsen with high maternal serum bile acids (>40)
  – UDCA improves liver enzymes and fetal outcome
  – Delivery at 37-38 weeks is preferred