Liver Disease in Pregnancy

UCSF Obstetrics & Gynecology Update
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Division of GI/Hepatology

Outline
Liver disease in pregnancy- what an OBGYN should know...
- Chronic liver disease
- Coincidental to pregnancy
- Unique to pregnancy

Case 1:
- 30 yo Asian F, G0P1 at 8 weeks gestation
- HBsAg screen is positive
- Liver tests are normal. She is not aware of having HBV.
  - WHAT ADDITIONAL TESTS TO SEND?
  - WHEN TO REFER TO HEPATOLOGY?

Disclosures
• None
Case 2:
- 30 yo G0P1 at 18 weeks gestation
- Went to ED with abdominal pain
- Liver tests elevated and told to follow-up in clinic
- Pain resolved with maalox, but liver tests unchanged on follow-up 2 weeks later

WHAT DO YOU DO?

<table>
<thead>
<tr>
<th>Tbil 0.6</th>
<th>AST 90</th>
<th>ALT 75</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alk Phos 180</td>
<td>albumin 3.5</td>
<td></td>
</tr>
</tbody>
</table>

Expected Changes With Pregnancy

<table>
<thead>
<tr>
<th>Laboratory</th>
<th>No change</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST, ALT</td>
<td>Elevations in transaminases, bilirubin, and INR are abnormal in pregnancy and should be investigated</td>
</tr>
<tr>
<td>Total Alkaline Phosphatase</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>↓</td>
</tr>
<tr>
<td>Alpha fetoprotein</td>
<td>↑</td>
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*ALT of 19IU/ml is the upper limit of normal for women

Liver diseases in pregnancy

- 3 main categories:
  - Chronic liver disease
  - Diseases coincidental to pregnancy
  - Diseases unique to pregnancy

Liver diseases in pregnancy

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Chronic liver diseases
- For OB to consider:
  - Hepatitis B
  - Hepatitis C

- For hepatologist to consider:
  - Autoimmune hepatitis
  - Primary biliary cholangitis
  - Wilson’s disease
  - Hemachromatosis

Hepatitis B in Pregnancy

Pregnancy & Hepatitis B

- 95% of adults clear acute HBV
- But 80-90% of infants with vertical transmission develop chronic HBV
- Perinatal transmission accounts for 50% of the global burden of chronic HBV
- Transmission from exposure to maternal blood/ at delivery, and less commonly via placenta

Impact of Immigration on US HBV Prevalence

Transmission from exposure to maternal blood/ at delivery, and less commonly via placenta

Ordering and Interpreting HBV and Related Labs

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<th>What It’s Assessing</th>
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<td>HBeAg/HBeAb</td>
<td>Immune state of active HBV that guides treatment thresholds</td>
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<td>HBcIgG</td>
<td>Exposure (cleared or chronic infection)</td>
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<tr>
<td>HBcIgM</td>
<td>Acute infection</td>
</tr>
<tr>
<td>HBsAb</td>
<td>Immunity (from cleared infection or vaccine)</td>
</tr>
<tr>
<td>HBV DNA</td>
<td>Level of viremia</td>
</tr>
<tr>
<td>ALT</td>
<td>HBV disease activity (liver inflammation)</td>
</tr>
<tr>
<td>HDV Ab (delta)</td>
<td>Co-existence of hepatitis D</td>
</tr>
<tr>
<td>INR, albumin, platelets, Bilirubin, ultrasound</td>
<td>Advanced fibrosis/cirrhosis</td>
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**Case 1. What to order if pre-natal HBsAg screen positive**

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*False positive HBsAg uncommon in healthy patients, unless within 1-3 weeks of HBV vaccination

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**Case 2. What to order if working up abnormal liver tests?**

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**Pregnancy & Hepatitis B**

- High HBV DNA levels and presence of HBeAg are the most important risk factor
  - Likelihood of transmission without immunoprophylaxis: >90%
  - Likelihood of transmission with immunoprophylaxis: <10%
- Insufficient data to advise on the mode of delivery
- Breastfeeding doesn’t increase perinatal transmission

*Li et al, J Clinical Gastro 2017; AASLD Guidelines 2017; EASL Guidelines 2018*

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**Refer ALL HBsAg Positive Women to Hepatologist**

**WHY?**

- To assess whether MOM’s liver needs treatment now
- To assess whether BABY needs to be protected from vertical transmission
- To discuss drug safety in pregnancy
- To counsel women on natural history of HBV and liver cancer risk, need for long-term monitoring, post delivery HBV management, and family screening
Mother to Child Transmission (MTCT) of HBV

- MTCT is reduced with passive + immunization
  - Fails in 10-30% of infants of highly viremic moms
- Third trimester antiviral therapy reduces MTCT to 0-3% (rare transmission via placenta)

![Graph showing MTCT reduction with antiviral therapy](image)

Tan et al. J Viral Hep 2016
Pan et al. NEJM 2016

HBV Treatment During Pregnancy

<table>
<thead>
<tr>
<th>Antiviral</th>
<th>Pregnancy Category</th>
<th>Resistance</th>
<th>Risk of birth defects</th>
<th>Rate of maternal-to-child transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>C</td>
<td>↑↑↑↑</td>
<td>No increased risk</td>
<td>3%</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>B</td>
<td>↑↑</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>B</td>
<td>None reported</td>
<td></td>
<td>0%</td>
</tr>
</tbody>
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Sarkar M & Terrault N, Hepatology 2014

Breastfeeding on antivirals is not contraindicated (2017 AASLD Guidelines)

Hepatitis C in Pregnancy

*TBV and TDF preferred drugs. Initiation earlier (%28) only if viral load >10^10 copies/mL, to allow time for viral load reduction to <10^5 copies/mL.
**Hepatitis C & Pregnancy**

- 364% increase in HCV infection related to injection drug use among persons aged < 30 in southeast U.S. (KY, TN, WV, VA)
- ~4% of pregnant women in U.S. are chronically infected

**Pregnancy & Hepatitis C**

- Overall, HCV has little impact during pregnancy
- Mom may be slightly increased risk of gestational diabetes and premature rupture of membranes
- Vertical transmission of HCV:
  - Transient HCV perinatal infection in 14-17% → spontaneous clearance in 25-50% → chronic infection in 3-5%
  - At least 1/3 acquire infection in early/middle stages of pregnancy
- Increased risk of vertical transmission with HIV-HCV co-infection, high viral load, prolonged rupture of membranes >6 hrs

**Factors Linked with Risk of MTCT**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Studies # women</th>
<th>Strength of Evidence</th>
<th>Summary of Findings</th>
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<td>Elective c-section vs. vaginal delivery</td>
<td>4 cohort studies, N=2080</td>
<td>Low</td>
<td>No difference, but trends in opposite directions in highest quality studies</td>
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<tr>
<td>C-section vs. vaginal delivery</td>
<td>11 cohort studies, N=2308</td>
<td>Moderate</td>
<td>No association</td>
</tr>
<tr>
<td>Invasive fetal monitoring vs none</td>
<td>3 cohort studies, N=928</td>
<td>Insufficient</td>
<td>Inconsistent but one good quality study OR=6.7 (95% CI 1.3-36)</td>
</tr>
<tr>
<td>Prolonged rupture of membranes vs. none</td>
<td>2 cohort studies, N=245</td>
<td>Low</td>
<td>Yes with &gt;6 hrs having OR=8.3 (95% CI 1.5-180)</td>
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*Breastfeeding does not increase MTCT, though avoid if nipple bleeding*
Factors Linked with Risk of MTCT

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<th>Strength of Evidence Summary of Findings</th>
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Reproductive aged women are prioritized for treatment - most insurance covers women that want to get pregnant

• High efficacy of current oral therapies
  – Cure achieved in 95-100% of patients
  – Short treatment duration (8-12 wks)
  – Tolerable side effect profile

- Most have favorable outcomes in animal studies
- Too limited data in humans to prescribe currently
- Phase I trial of 12 weeks of ledipivir and sofosbuvir during 2nd and 3rd trimester completes enrollment in September 2018...stay tuned!

Liver diseases in pregnancy

• 3 main categories:
  – Chronic liver disease
    – Diseases coincidental to pregnancy
  – Diseases unique to pregnancy

Diseases coincidental to pregnancy

• Gallstones
• Drug-induced liver injury
• Budd-Chiari syndrome
• Herpes (HSV) hepatitis
• Hepatitis A
• Hepatitis E
**Coincidental to Pregnancy Causes**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Comment</th>
<th>Appropriate test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallstones</td>
<td>Pregnancy↑ risk</td>
<td>Ultrasound</td>
</tr>
<tr>
<td>Drug-induced</td>
<td>History, especially antibiotic use</td>
<td>livertox.gov</td>
</tr>
<tr>
<td>Budd-Chiari – hepatic vein clot</td>
<td>Pregnancy↑ risk</td>
<td>Ultrasound with doppler</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>GI symptoms</td>
<td>HAV IgM</td>
</tr>
<tr>
<td>[HSV] – to consider in right clinical setting</td>
<td>Flu-like sx, rash (40%), fevers, cytopenias</td>
<td>HSV PCR</td>
</tr>
<tr>
<td>Alcohol</td>
<td>History, AST/ALT&gt; 2:1</td>
<td>Tox screen</td>
</tr>
<tr>
<td>Nonalcoholic fatty liver disease (NAFLD)</td>
<td>1/3 Americans, growing epidemic in adolescents, common in PCOS</td>
<td>Ultrasound</td>
</tr>
</tbody>
</table>

**Trimester-dependent Liver Conditions in Pregnancy**

**KEY POINTS:**
- Only pregnancy-specific cause in 1st trim.
- 60-70% have elevated liver enzymes
- AST>ALT, but values usually <500IU/ml
- Must still exclude other causes
- Liver tests normalize by week 20
- No risk of chronic liver damage or failure
Intrahepatic Cholestasis of Pregnancy

• 0.3-5% of pregnancies (more common among Latinos)

• **Clinical presentation:** Pruritus, particularly of palms and soles
  - Elevated alk phos with normal ggt
  - Elevated ALT – may be > 1,000
  - Jaundice in <¼ women, follows onset of pruritus
  - Elevated serum bile acids (BA) (>10 umol/L)
  - Elevated INR (from vitamin K deficiency)

Management:

• Ursodiol 13-15 mg/kg/day for pruritus until delivery, 75% improve liver tests and fetal outcomes

• Weekly bile acids, as > 40 increases IUFD

• Spontaneous resolution within 6 weeks of delivery

Trimester-dependent Liver Conditions in Pregnancy

1st trimester

• Hyperemesis gravidarum

2nd trimester

• Intrahepatic cholestasis of pregnancy

• Pre-eclampsia & HELLP
  - Hepatic hematoma rupture

3rd trimester

• Acute fatty liver of pregnancy

• Intrahepatic cholestasis of pregnancy

• Pre-eclampsia & HELLP
  - Hepatic hematoma rupture

Geenes et al, Hepatology 2014; Bacq et al, Hepatology 1997

Geenes et al, Hepatology 2014; Bacq et al, Gastro 2012; Glantz et al, Hepatology 2004
Trimester-dependent Liver Conditions in Pregnancy

1st trimester
- Hyperemesis gravidarum

2nd trimester
- Intrahepatic cholestasis of pregnancy
- Pre/eclampsia & HELLP

3rd trimester
- Acute fatty liver of pregnancy

• Viral hepatitis, gallstones, drug-induced hepatitis, Budd-Chiari

Acute fatty liver of pregnancy (AFLP)

- 3rd trimester-early post-partum
- RARE!
- Risk factors: multiples, low maternal BMI, male fetus
- Homozygous LCHAD deficient offspring spill unmetabolized LC fatty acids in maternal circulation
  → microvesicular steatosis

- Management: Immediate delivery, LT rarely needed

Thank you!

- Questions...