Liver Diseases Unique to Pregnancy

Giada Sebastiani
Hepatology & Gastroenterology
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McGill
DISCLOSURES

- Speaker for Merck, Vertex, Gilead, ViiV
- Advisory board member for Boheringer Ingelheim, Novartis
- I received research funding from Vertex and ViiV
**Medical Expert** (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional attitudes in their provision of patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS framework.)

**Communicator** (as Communicators, physicians effectively facilitate the doctor-patient relationship and the dynamic exchanges that occur before, during, and after the medical encounter.)

**Collaborator** (as *Collaborators*, physicians effectively work within a healthcare team to achieve optimal patient care.)

**Manager** (as *Managers*, physicians are integral participants in healthcare organizations, organizing sustainable practices, making decisions about allocating resources, and contributing to the effectiveness of the healthcare system.)

**Health Advocate** (as *Health Advocates*, physicians responsibly use their expertise and influence to advance the health and well-being of individual patients, communities, and populations.)

**Scholar** (as *Scholars*, physicians demonstrate a lifelong commitment to reflective learning, as well as the creation, dissemination, application and translation of medical knowledge.)

**Professional** (as *Professionals*, physicians are committed to the health and well-being of individuals and society through ethical practice, profession-led regulation, and high personal standards of behaviour.)
Liver disease is uncommon in pregnancy

A palpable liver or spleen is not usually normal

Unchanged: AST, ALT, GGT, bilirubin, LDH, PT, PTT

Increased: ALP, chol/TG, WBC, fibrinogen, ceruloplasmin, a & B-globulins, AFP

Decreased: HgB, albumin, G-globulins, uric acid, BUN, total protein, and antithrombin III concentrations, Gallbladder contractility*
### Pre-existing underlying liver disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Typical time of presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hepatitis B and C</td>
<td>Present throughout the pregnancy, can have a variable course from patient to patient</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td></td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td></td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis from any cause</td>
<td></td>
</tr>
</tbody>
</table>

### Liver disease coincidental to pregnancy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Typical time of presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute viral hepatitis (HSV, CMV, HEV)</td>
<td>First/second/third</td>
</tr>
<tr>
<td>Gallstones</td>
<td>Second/third</td>
</tr>
<tr>
<td>Budd-Chiari syndrome</td>
<td>First/second/third or during post-partum</td>
</tr>
<tr>
<td>Drug induced hepatotoxicity</td>
<td>First/second/third</td>
</tr>
</tbody>
</table>

### Liver disease unique to pregnancy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Typical time of presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperemesis gravidarum</td>
<td>First, but can present during second/third</td>
</tr>
<tr>
<td>Intrahepatic cholestasis of pregnancy</td>
<td>Second/third</td>
</tr>
<tr>
<td>Acute fatty liver of pregnancy</td>
<td>Third</td>
</tr>
<tr>
<td>Pre-eclampsia and eclampsia</td>
<td>Second/third or shortly after delivery</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>Third, during or shortly after delivery</td>
</tr>
</tbody>
</table>
3 Questions to Remember:

- How many weeks pregnant is she?
- Is this a new liver disease in someone who is pregnant, or is someone with liver disease now pregnant?
- Is this one of the liver diseases unique to pregnancy?
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- How many weeks pregnant is she?
- Is this a new liver disease in someone who is pregnant, or is someone with liver disease now pregnant?
- Is this one of the liver diseases unique to pregnancy?
How Many Weeks Pregnant is She?

HG = hyperemesis gravidarum
ICP = intrahepatic cholestasis of pregnancy
BCS = Budd Chiari Syndrome
HELLP = Hemolysis, elevated liver enz, low plt
AFLP = Acute Fatty Liver of Pregnancy

Viral Hepatitis, drug toxicity, gallstones, malignancy, transplant, BCS

Preeclampsia, HELLP, AFLP

Portal HT & Bleeding

20 wk

13

TM1

HG

13

TM2

ICP

27

TM3

ICP

40

POST PARTUM

Budd Chiari

(ANY TRIMESTER)
3 Questions to Remember:

- How many weeks pregnant is she?
- Is this a new liver disease in someone who is pregnant, or is someone with liver disease now pregnant?
- Is this one of the liver diseases unique to pregnancy?
Abnormal liver tests occur in 3-5% of pregnancies

Viral hepatitis: A, B, C, D, E, HSV, CMV, EBV =40% of all jaundice in pregnancies in the USA
- HAV: 1/1000 pregnancies
- HBV: 2/1000 pregnancies

ICP commonly causes jaundice

Uncomplicated gallstones are found in up to 11% of pregnancies (pregnancy = more gallstones!!)
- 5% of all jaundice
3 Questions to Remember:

- How many weeks pregnant is she?
- Is this a new liver disease in someone who is pregnant, or is someone with liver disease now pregnant?
- Is this one of the liver diseases unique to pregnancy?
### Main features of liver diseases unique to pregnancy

<table>
<thead>
<tr>
<th>Liver disease</th>
<th>Onset</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperemesis gravidarum</td>
<td>First trimester</td>
<td>Supportive, rehydration</td>
</tr>
<tr>
<td>Intrahepatic cholestasis of pregnancy</td>
<td>Third trimester</td>
<td>Ursodeoxycholic acid or cholestiramine; preterm delivery at fetal maturity</td>
</tr>
<tr>
<td>Pre-eclampsia and eclampsia</td>
<td>Second to third trimester</td>
<td>Anti hypertensive drugs, magnesium sulfate</td>
</tr>
<tr>
<td>HELLP syndrome</td>
<td>Second to third trimester, or within a few days of delivery</td>
<td>Induction of delivery</td>
</tr>
<tr>
<td>Acute fatty liver of pregnancy</td>
<td>Third trimester</td>
<td>Induction of delivery</td>
</tr>
</tbody>
</table>
Diseases Unique to Pregnancy are either with or without preeclampsia

- Not Associated With Preeclampsia
  - ✔ Hyperemesis Gravidarum
  - ✔ Cholestasis of Pregnancy
- Associated With Preeclampsia
  - ✔ HELLP syndrome
  - ✔ Acute Fatty Liver of Pregnancy
  - ✔ Hepatic rupture
  - ✔ Hepatic infarct
Diseases Unique to Pregnancy without preeclampsia

- Not Associated With Preeclampsia
  - ✓ Hyperemesis Gravidarum
  - ✓ Cholestasis of Pregnancy
Hyperemesis Gravidarum

- N&V: up to 90% of all pregnancies
- Hyperemesis gravidarum: 1-1.5%
  - Intractable N&V with dehydration, loss of >5% pre-pregnant BW and ketosis
- usually TM₁ (4-18 wks)
- 50% of HG patients have abnormal enzymes
  - AST/ALT < 20x ULN
  - Jaundice rare
Causes of hyperemesis gravidarum

- Abnormal Gastric Emptying?
  - no delay in gastric emptying, actually accelerated
    Maes BD et al. Aliment Pharmacol Ther 1999

- Increased β-HcG (stimulates thyroid)
  - More common in molar pregnancy

- ? Thyrotoxicosis (seen in 60%)

- Risk Factors:
  - Elevated BMI, psychiatric illness, preexisting DM, multiple pregnancies

Maternal and Fetal Outcomes

• HG usually resolves by the 20th week of pregnancy

• Conflicting fetal outcomes:


  ▪ increased rates of fetal abnormalities including undescended testicles, hip dysplasia, and Down Syndrome, lower birth weights and higher rates of being small for gestational age, but no effect on perinatal survival (Kallen B. Eur J Obstet Gynecol Reprod Biol 1987; Bailit JL. Am J Obstet Gynecol 2005)

• A meta-analysis showed more low birthweight < 2500 kg, small for gestational age, and premature delivery.

  • No correlations with Apgar scores, congenital anomalies or perinatal death.
  • Some of those poor outcomes were more likely in pregnant women with low gestational weight gain (Veenendaal et al)
Supportive Treatments usually efficient

- IVF, high CHO diet with low fat, thiamine*, antiemetics

- Diclectin® is approved in pregnancy (doxylamine/pyridoxine)
  - Droperidol & Diphenhydramine may be effective
  - Methylprednisolone
  - Diazepam
    - Ditto A et al. Gynecol Obstet Invest 1999

SOGC Practice Guidelines 1995
Intrahepatic Cholestasis of Pregnancy

- Common in 3rd Trimester (2nd also reported)
- Incidence ranges from 0.7% (US) to 6.5% (Chile)
  - Intense pruritus onset 25-32 weeks
  - Varying severity constitutional symptoms
  - Diarrhea, rarely steatorrhea and Vit. K deficiency
- 2nd only to viral hepatitis as cause of jaundice in pregnancy (10-25% of jaundice)
ICP – blood tests

- Elevated fasting serum bile acids level (> 10 μmol/L) confirms the diagnosis
- Aminotransferases can be elevated up to 2-10 folds
- ALP not helpful due to higher physiological levels in late pregnancy
- Clinical jaundice is detected in 10%-15% of the cases only and bilirubin levels rarely exceed 100 μmol/L
Pathogenesis: Genetic predisposition and hormonal factors

- Accumulation of bile acids results from abnormal biliary transport across the hepatic canalicular membrane
  - Mutations to the ATP-cassette transporter B4 (ABCB4) or multidrug resistant protein-3 (MDR3)
    - May cause up to 15% of all cases of ICP
  - Increased sensitivity to estrogen, impairing sulfation and bile acid transport
    - Hormonal: Increased levels in TM3, twin pregnancies and precipitated by the progesterone in TM3. All inhibit the bile salt export pump

- Genetics: clustering in families and certain ethnic groups show predisposition
Hepatobiliary Transporters
Exogenous Risk Factors

- Hepatitis C Infection
  - N=145/16 271 ICP   N=63/16 271 HCV
  - rate of ICP in HCV vs. no HCV: 15.9% vs. 0.8% (p<0.001)

- Seasonal trends and dietary (selenium) deficiencies
  - Reyes H et al. J Hepatol 2000
  - increased ICP during autumn/winter - correlation with seasonal low selenium levels (less during summer)
ICP Maternal Outcomes

- Risks to develop ICP
  - advanced maternal age, multiparous women, and in women with a personal history of cholestasis with oral contraceptive use
  - Twin pregnancies
- Long-term risk of gallstones and cholecystitis
- Increased risk of pancreatitis, diarrhea, steatorrhea
- Recurs in subsequent pregnancies 45-70%
ICP Fetal Outcomes

- More prematurity (up to 60%) and sudden fetal death (1%) from placental insufficiency and fetal distress (20-40%)

- Risk of aspiration, meconium staining

- Consult high risk obstetrics and monitor for chronic placental insufficiency

Bacq Y et al. Hepatology 1997
URSO is safe
Control of itching is main concern

Symptomatic treatment for mother and monitor baby for early delivery

Antipruritics, URSO®, Questran®, fat soluble vitamins for malabsorption

Ursodeoxycholic Acid (15 mg/kg/d) ➔ first line therapy may decrease plasma bile acids and sulphated progesterone metabolites
  - UDCA increases expression of placental bile acid transporters, which may allow for improved bile acid transfer
  - Less prematurity
Liver diseases associated with preeclampsia

Table 3 Preeclampsia associated liver diseases

<table>
<thead>
<tr>
<th>Severe preeclampsia and eclampsia</th>
<th>HELLP syndrome</th>
<th>Acute fatty liver of pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time</td>
<td>Late second trimester to early postpartum</td>
<td>Third trimester</td>
</tr>
<tr>
<td>Prevalence</td>
<td>Increases in multiple gestation (5%-7%)</td>
<td>0.10%</td>
</tr>
<tr>
<td>Findings</td>
<td>Abdominal pain, nausea/vomiting, overlap with findings in preeclampsia</td>
<td>Abdominal pain, nausea/vomiting, jaundice, hypoglycemia and hepatic failure</td>
</tr>
<tr>
<td>Tests</td>
<td>Low platelets; hemolysis; elevated liver enzymes; prothrombin time may remain normal; normal fibrinogen</td>
<td>Platelets &lt; 100000; AST and ALT 300-1000 U/L; low antithrombin II; high prothrombin time; low fibrinogen; high bilirubin; DIC</td>
</tr>
<tr>
<td>Management</td>
<td>Prompt delivery</td>
<td>Prompt delivery; liver transplant</td>
</tr>
<tr>
<td>Outcome</td>
<td>5% maternal death 1% hepatic rupture</td>
<td>10% maternal death</td>
</tr>
<tr>
<td></td>
<td>1% maternal death</td>
<td>Up to 45% fetal death</td>
</tr>
<tr>
<td></td>
<td>1%-30% fetal death</td>
<td></td>
</tr>
</tbody>
</table>


Preeclampsia

- Triad of hypertension, proteinuria and +/- edema in the third trimester (5%-10% of pregnancies)
- Liver involvement infrequent but always indicates severe preeclampsia (significant perinatal morbidity/mortality)
- Commonest cause of hepatic tenderness and liver dysfunction in pregnancy
- AST/ALT: 10-20x elevations
- Bilirubin: < 5 mg/dL
- No specific therapy for the hepatic involvement
  - an indicator of severe disease with need for immediate delivery to avoid eclampsia, hepatic rupture, or necrosis
HELLP syndrome:

- Hemolysis, Elevated Liver enzymes*, Low Platelets
- Severe pre-eclampsia: 0.2-0.6%
- 27-36 weeks most cases, occasionally postpartum
- HELLP occurs in 20% of patients with severe pre-eclampsia

Sibai, Am J Obstet Gyne 1993
Microangiopathic hemolytic anemia with vascular endothelial injury, fibrin deposition in vessels and platelet activation and consumption leading to necrosis in Zone 1 to whole lobule, eventually creating large hematomas, capsular tears, infarct/rupture or intraperitoneal bleeding.
Panel 2: Classification systems used in HELLP syndrome

Tennessee system
- AST > 70 IU/L
- LDH > 600 IU/L
- Platelets < 100×10^9/L

Mississippi system
AST > 40 IU/L and LDH > 600 IU/L and:
- Class I: platelets < 50×10^9/L
- Class II: platelets 50–100×10^9/L
- Class III: platelets 100–150×10^9/L

HELLP = haemolysis, elevated liver enzymes, and low platelets. AST = aspartate aminotransferase. LDH = lactate dehydrogenase.
Liver Disease and Pregnancy
HELLP: Risk for Future Pregnancies

- HELLP recurs in 5-25%
  - more common among older multiparous women.
- Preeclampsia 20-40%

Sibai Am J Obstet Gyne 1995
Fetal Prognosis

- Fetal complications
  - Prematurity 70%
  - Intrauterine growth retardation
  - Abruptio placenta

- Overall perinatal mortality 7-20%
Supportive care and deliver baby if end organ damage

- Supportive therapy for BP, DIC, seizures, fetal monitoring
- Deliver the baby if > 34 weeks (steroids if < 34 wks) or if evidence of organ damage (DIC, ARF, placental)
- Most resolve x 5 days
- Correct coagulopathy, prophylactic antibiotics
- Evidence is lacking for:
  - Steroids, plasma exchange, plasmapharesis, volume expansion, antithrombotic drugs, dialysis
Hepatic Infarct and Hematomas

- Usually in 3rd TM or post partum
- Occurs with HELLP, AFLP, TTP, HUS or Preeclampsia

- Patients generally do well
- fever, anemia, jaundice, right upper quadrant pain
- coagulopathy and AST/ALT > 1000
- CT: infarction often in the left lobe.
- Treatment: prompt delivery and ICU care
Hepatic Rupture

- Often associated with HELLP syndrome
- Multiparous women in the latter half of pregnancy
- Hepatic vascular thrombosis and necrosis
- Sudden RUQ or epigastric pain with shock with 50% maternal mortality
- Elevated transaminases

- CT scan or MRI are superior to U/S
- Partial resection or lobectomy, embolization and hepatic artery ligation

Sibai. Semin Perinatol 2003
Acute Fatty Liver of Pregnancy

- Mitochondrial cytopathy, like Reye’s syndrome
- Occurs in 1/13-16000 deliveries, most in 2nd or 3rd trimester, between 32-38 weeks or postpartum
- 40-50% nulliparous
- Increased with twin/triplet pregnancies
- 50% have pre-eclampsia
- Some overlap with HELLP
Acute Fatty Liver of Pregnancy

- Asymptomatic to fulminant liver failure
- Nausea and vomiting, fatigue, right upper quadrant and epigastric pain
- AST/ALT <=1000
- BILI < 5 mg/dL
- Manifestations of portal HT
  - Ascites, bleeding
- Polydipsia and polyuria (no DM)
AFLP is true liver dysfunction

- Microvesicular fatty infiltration (FFA) caused by liver failure, DIC or both
- Hepatic failure
- Encephalopathy -- high ammonia
- Hypoglycemia*
- Abnormal PT, APTT, low fibrinogen
- Pancreatitis
- Oliguric renal failure
Table 1  Proposed (Swansea) diagnostic criteria for acute fatty liver of pregnancy

<table>
<thead>
<tr>
<th>Vomiting</th>
<th>Abdominal pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polydipsia/polyuria</td>
<td>Encephalopathy</td>
</tr>
<tr>
<td>Elevated bilirubin</td>
<td>Hypoglycaemia</td>
</tr>
<tr>
<td>Elevated uric acid</td>
<td>Leucocytosis</td>
</tr>
<tr>
<td>Ascites or bright liver on US</td>
<td>Elevated transaminases</td>
</tr>
<tr>
<td>Elevated ammonia</td>
<td>Renal impairment</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Microvesicular steatosis on liver biopsy</td>
</tr>
</tbody>
</table>

To meet the criteria the patient should have 6 or more of these clinical findings. Source: Ref. [80], with permission; US: Ultrasound scan.
Pathophysiology of AFLP – abnormal fatty oxidation

- Maternal heterozygosity for LCHAD (longchain 3-hydroxyacyl-CoA dehydrogenase) deficiency reduces the maternal capacity to oxidize long-chain fatty acids both in liver and placenta, and this, together with the metabolic stress of pregnancy and fetal homozygosity for LCHAD deficiency, causes accumulation in the maternal circulation of potentially hepatotoxic LCHAD metabolites.

- Perhaps external factors, such as carnitine deficiency or other dietary factors, exacerbate this situation.
Normal Energy Production:

- Fatty Acids → \( \beta \)-oxidation → 2 Acetyl CoA → Citric Acid Cycle → Oxidative Phosphorylation → ATP + H\(_2\)O

Normal Process Within Mitochondria

- Energy for skeletal and cardiac tissue
Normal Energy Production:

LCHAD Deficiency
- Stops Energy Production
- High Levels of Fatty Acids Accumulate
- Microvesicular pattern
- Liver failure and encephalopathy
(A) Sudan stain (low power) shows diffuse fatty infiltration (red staining) involving predominantly zone 3, with relative sparing of periportal areas. 
(B) Hematoxylin-eosin stain (high power) shows hepatocytes stuffed with microvesicular fat (free fatty acids) in zone 2 and 3 and centrally located nuclei.
Maternal mortality rates:
- <1970 = 90%
- <1985 = 50%
- Currently <10%

Mjahed. Arch Gynecol Obst 2006

Improved outcomes from early delivery, ICU care

Fetal mortality rates of ~ 25 – 65%
- may be lower 9-23%
Future pregnancies

- Most do not become pregnant again
  - Traumatic, many get TAH to control bleeding
  - Can recur in future pregnancies even if the LCHAD mutant is negative

- LCHAD carrier: increased risk of recurrence in 20-70%

- All children need to be tested for metabolic defects
<table>
<thead>
<tr>
<th></th>
<th>ICP</th>
<th>HELLP</th>
<th>AFLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Pregnancies</td>
<td>0.1% (USA)</td>
<td>0.2%–0.6%</td>
<td>0.005%–0.01%</td>
</tr>
<tr>
<td>Onset/trimester</td>
<td>25–32 weeks</td>
<td>3 or postpartum</td>
<td>3 or postpartum</td>
</tr>
<tr>
<td>Family history</td>
<td>Often</td>
<td>No</td>
<td>Occasionally</td>
</tr>
<tr>
<td>Presence of preeclampsia</td>
<td>No</td>
<td>Yes</td>
<td>50%</td>
</tr>
<tr>
<td>Typical clinical features</td>
<td>Pruritus</td>
<td>Hemolysis</td>
<td>Liver failure with coagulopathy, encephalopathy hypoglycemia, DIC</td>
</tr>
<tr>
<td></td>
<td>Mild jaundice</td>
<td>Thrombocytopenia(&lt;50,000 often)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Elevated bile acids</td>
<td>Vitamin K ↓</td>
<td></td>
</tr>
<tr>
<td>Aminotransferases</td>
<td>Mild to 10-20-fold elevation</td>
<td>Mild to 10-20-fold elevation</td>
<td>300-500 typical but variable ++</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>&lt;5 mg/dL</td>
<td>&lt;5 mg/dL unless massive necrosis</td>
<td>often &lt;5 mg/dL, higher if severe</td>
</tr>
<tr>
<td>Hepatic imaging</td>
<td>Normal</td>
<td>Hepatic infarcts</td>
<td>Fatty infiltration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hematomas, rupture</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>Normal–mild cholestasis, no necrosis</td>
<td>Patchy/extensive necrosis and hemorrhage</td>
<td>Microvesicular fat in zone 3</td>
</tr>
<tr>
<td>Maternal mortality</td>
<td>0%</td>
<td>1%–25%</td>
<td>7%–18%</td>
</tr>
<tr>
<td>Fetal/perinatal mortality</td>
<td>0.4%–1.4%</td>
<td>11%</td>
<td>9%–23%</td>
</tr>
<tr>
<td>Recurrence in subsequent pregnancies</td>
<td>45%–70%</td>
<td>4%–19%</td>
<td>α-subunit, long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) defect—yes No fatty acid oxidation defect—rare</td>
</tr>
</tbody>
</table>
Dr Philip Wong for contribution with scientific inputs and slides.