Pregnancy and Liver Disease

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Disclosures

- I have no disclosures.

Normal pregnancy

Liver enzyme	1st trimester	2nd trimester	3rd trimester
ALT, AST, GGT, bilirubin	Normal	Normal	Normal
ALP	Normal	Increased	Increased
Bile acids	Normal	Normal	Normal
Albumin	Normal/decreased	Normal/decreased	Normal/decreased
AFP	Normal/increased	Increased	Increased

PE: spider angiomas/palmar erythema

Hyperdynamic state: similar to systemic changes in decompensated cirrhosis

Liver biopsy RARELY indicated

Key Concepts

- Elevations in aminotransferases, bile acids and bilirubin are **ABNORMAL**.
- Cholestasis can occur with normal alkaline phosphatase, GGTP and bilirubin levels

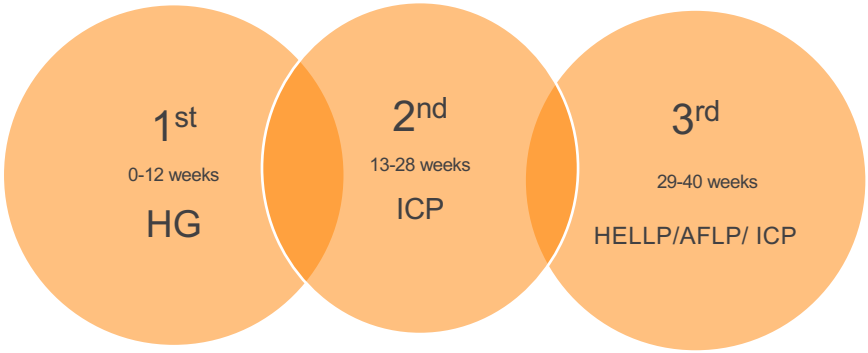
Key Concepts – 3 categories

- Diseases UNIQUE to pregnancy
- Diseases COINCIDENTAL to pregnancy
- Diseases EXACERBATED by pregnancy

Unique to pregnancy

- Occurs ONLY during pregnancy and RESOLVES post partum
  - Hyperemesis gravidarum (HG)
  - Intrahepatic cholestasis of pregnancy (ICP)
  - Acute Fatty Liver of pregnancy (AFLP)
  - Pre eclampsia/ syndrome of hemolysis, elevated liver chemistries, low platelets (HELLP)
  - Hepatic rupture

Unique to pregnancy



Gestational age aids in differential diagnosis

Abdominal imaging in pregnancy

- Abdominal ultrasound without Doppler preferred all trimesters
  - Limited Doppler can be used with caution in 2nd and 3rd trimesters
- MRI/MRCP without gadolinium is preferred over CT imaging.
  - Gadolinium contraindicated in pregnancy
- Abdominal CT without contrast generally safe but radiation exposure should be as low as possible and < 50 mGy.
  - Iodinated contrast should be used only if essential
- Breast feeding safe after iodinated or gadolinium contrast

Hyperemesis gravidarum (HG)

- Severe nausea/vomiting with dehydration/ ketosis/weight loss > 5%
- Week 4-20
- 0.35-2.0% of pregnancies –no differences in fetal outcome
- Increased transaminases- 50% of cases: ALT > AST
  - Low 100's but up to 20 X normal
  - Severity correlates with vomiting
  - Resolves with rehydration/gut rest
- Rare increased bilirubin
- Treat with thiamine, fluids and anti-emetics
- Liver biopsy – little or no abnormalities

Intrahepatic cholestasis (ICP)

- Cholestasis: a reduction of canalicular bile flow with an associated rise in serum bile acid level
- ICP of pregnancy: pruritus and elevated serum bile acids occurring in 2nd half of pregnancy that resolves after birth (6 weeks)

ICP

- Elevated fasting serum total bile acids (10-100x)
  - bile acid level > 10 μmol/L; 2^{nd}-3^{rd} trimesters
- Pruritus – severe at night; palms and soles (no rash)
- 15% develop jaundice (< 6 mg/dl); alk phos (1-4x), aminotransferases(2-10x); GGT-nl or mild increase
- Vit K deficiency due to malabsorption

- Liver biopsy – cholestasis without inflammation
- **MAY RECUR** – pregnancy, OCP use
- ↑ risk of hepatobiliary disease later in life (? cancer, autoimmune disease, cardiovascular disease)

ICP – RISK FACTORS

- HCV infection (all mothers with ICP should be screened)
- Seasonal onset (winter)
- Low selenium levels
- Low Vitamin D/ metabolic syndrome
- Multiple gestations
- Advanced age

Floreani, A and Gervasi, M. New Insights on Intrahepatic Cholestasis of Pregnancy, Clin Liver Dis 20 (2016), 177-189.

ICP – Etiologic factors

- Genetic predisposition
  - Strong regional clustering (Sweden, Chile)
  - Higher prevalence in family members
  - Variable genotypes, penetrance, environmental factors
  - Multiple gene mutations-most common: ABCB4/MDR3

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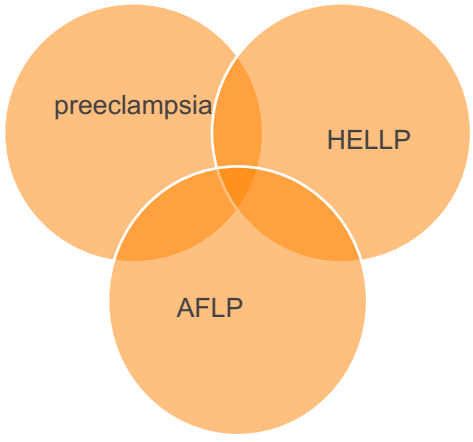
Mother – outcome/treatment

- Maternal outcome – good, may recur 66%
- Evaluate if persistent cholestasis postpartum
- Pruritus – can be severe
  - Ursodeoxycholic acid (10-15 mg/kg/day)
  - Antihistamine therapy
  - Rifampin
  - Cholestyramine (may prevent Vit K absorption)
  - S-Adenosyl-L-methionine

Fetus – outcome/treatment

- Fetal outcome- increased risk preterm birth, meconium staining, respiratory depression, intrauterine fetal demise (IUFD)
- Highest risk – bile acid level > 100 µmol/L; best outcome < 40 µmol/L
- Monitoring – no specific recommendations for antenatal monitoring
- Treatment
  - Ursodeoxycholic acid – safe and reduces maternal/fetal bile acid levels
  - Early Delivery – many guidelines recommend early delivery with induction around 37 weeks to reduce risk of stillbirth

Overlap syndromes



Preeclampsia/eclampsia

- Systolic BP >140 or diastolic > 90; Proteinuria (> 300 mg/24h); >20 weeks gestation in prev. normotensive pt
- Eclampsia if seizures or altered mental status
- 5-10% of pregnancies but liver involvement not common
- RUQ pain, aminotransferases (10-20 X nl), bilirubin < 5
- Liver biopsy - not needed for diagnosis but shows fibrin deposition, ischemic lesions, microvesicular fat, periportal hemorrhage

HELLP syndrome: hemolysis, elevated liver chemistries and low platelets

- Endotheial/microvascular injury from activation of complement, increased vascular tone, plt aggregation
  - Low haptoglobin, + schistocytes
  - Normal PT/PTT, LDH > 600 IU/L
  - Aminotransferases – mean 150 U/L (2-20X);
  - Total bilirubin > 1.2 mg/dl
  - Platelets < 50,000-100,000/mm3
- Complication of severe pre-eclampsia

  -2/3 occur in 3rd trimester, 1/3 **after** delivery
  - Treatment- expeditious delivery

HELLP SYNDROME

- Symptoms/signs
  - Epigastric/abdominal pain
  - Liver normal or increased in size
  - Jaundice – 5%
  - Generalized edema – 90%; HTN
- Maternal lab abnormalities peak in first 2 days post partum
- Maternal mortality: 1-2%; 1% - hematoma
  - Mortality – 30% with rupture
- Fetal mortality: 10-35%(depends upon gest.age)
- Mississippi and Tennessee classification systems

Martin, JN, Rose CH, Briery CM. Understanding and managing HELLP syndrome: the integral role of aggressive glucocorticoids for mother and child. Am J Obstet Gynecol 2006;195 (4): 914-34.

Acute fatty liver of pregnancy

- Hepatic microvesicular steatosis and mitochondrial dysfunction
- 1:10,000 pregnancies
- Inherited mutations with deficiency of long-chain 3-hydroxyacyl coenzyme A dehydrogenase (LCHAD) – a fatty acid beta-oxidation enzyme
- Mother is heterozygote; fetus is homozygote

Acute fatty liver of pregnancy (AFLP)

- Overlap with HELLP
- Nulliparous, ↑ maternal age, multiparity
- Nausea/vomiting, epigastric pain, jaundice
- Symptoms/signs of liver failure
- Liver frequently small
- Elevated PT/PTT, creatinine, NH3
- Transaminases – variable elevation

Swansea criteria – 6 or more with absence of another cause

- Vomiting
- Abdominal pain
- Polydipsia/polyuria
- Encephalopathy
- Elevated bilirubin
- Hypoglycemia
- Elevated urea
- Leukocytosis
- Ascites or bright liver on ultrasound
- Elevated transaminases
- Elevated ammonia
- Renal impairment
- Coagulopathy
- Microvesicular steatosis on liver biopsy

Ch'ng CL, Morgan M, Hainsworth I et al. Prospective study of liver dysfunction in pregnancy in Southwest Wales. Gut 2002;51: 876-80.

LCHAD abnormalities

- LCHAD deficiency caused by genetic defect of mitochondrial trifunctional protein (MTP)
- Mothers – obligate heterozygotes with reduced capacity to oxidize LC fatty acids
- Fetus – homozygote; unable to oxidize LC fatty acids
- Fatty acids spill into maternal circulation via placenta
- Accumulation of hepatoxic long chain fatty acid metabolites in mothers - ? 3-hydroxy-fatty acids

LCHAD deficiency in infants

- AFLP and possibly severe HELLP may indicate fatty oxidation disorder in fetus
- Fetus – if homozygous LCHAD deficiency– at risk for hypoketotic hypoglycemia
- Acylcarnitine profile and molecular screening should be done
- Early detection and treatment of LCHAD deficiency improves prognosis of newborn

Treatment of AFLP

- Early recognition and delivery!
- Disease systemic – acute pancreatitis, renal failure/oliguria, GI bleeding, DIC
- Case reports of successful liver transplantation and plasma exchange but decreasing mortality with supportive care

COINCIDENTAL to pregnancy

- Drug induced liver injury
- Viral infections – hepatitis A-E, Herpes Simplex
  - Not unique but can be more severe in pregnancy

Herpes Simplex Hepatitis

- 3rd trimester - History! - √ HSV PCR
- Prodrome of fever, malaise, URI for 4-14 days
- PE: RUQ pain, <50% cutaneous lesions
- Labs: ↑ bilirubin but very high aminotransferases, often > 1000 U/L
- CT scan – multiple low density, nonenhancing areas: hemorrhagic necrosis/microabscess
- Maternal mortality – 43%. **Start acyclovir early!**
- Transmission to infants – 33-50%

Hepatitis A and E

- Hepatitis A - increased risk of transmission during delivery if mother viremic. HAV immunoglobulin can be given
- Hepatitis E - worse outcome if infected in 2nd or 3rd trimesters
  - Mother-to-child transmission can occur
  - Ribavirin and alpha interferon contraindicated in pregnancy

Hepatitis B

- All women should be screened given risk for mother-to-child transmission (MTCT)
- Tenofovir disoproxil fumarate (TDF) is preferred antiviral therapy in pregnancy, if indicated

- Measures to prevent MTCT
  - **Infants of HBsAg-positive mothers should receive HBIG (0.5 ml) within 12 hours and 1st dose of hep B vaccine** (prevents transmission in ~90%)
  - TDF if HBV DNA > 200,000 IU/ml in 2nd trimester. Begin between weeks 28-32 or earlier if very high viral load. Stop at delivery or up to 3 months post partum
  - Avoid invasive fetal monitoring but c-section not indicated
  - Breast feeding is not contraindicated, even on antiviral therapy

Hepatitis C

- MTCT can occur intrapartum, peri or post partum (risk- 5.8%)
  - Test infants with HCV RNA 2 occasions between 2 and 6 months
  - Treatment with current direct-acting antivirals is not recommended
  - Ribavirin is contraindicated during pregnancy
- Risk factors for MTCT:
  - High levels of hepatitis C RNA/ HIV coinfection (10%)
  - Long duration between membrane rupture and delivery (>6 hours)
  - Avoid invasive fetal monitoring
  - Vaginal delivery without increased risk
  - Breast feeding acceptable unless nipple trauma

EXACERBATED by pregnancy

- Biliary disease – gallstones may occur in 10% of pregnancies
- Vascular – Budd-Chiari syndrome
  - Low molecular weight heparin is anticoagulant of choice during pregnancy
- Pre-existing liver disease
  - Cirrhosis and portal hypertension
  - Autoimmune hepatitis
    - Mycophenolic acid products contraindicated
    - Monitor liver tests each trimester with monitoring every 2-4 weeks in first 6 months post partum

Cholelithiasis and cholecystitis

- Pregnancy promotes bile lithogenicity and sludge
  - Estogen increases cholesterol synthesis
  - Progesterone impairs gallbladder motility
- Pregnancy does not increase frequency or severity of complications
- Cholecystectomy and ERCP-best performed in 2nd trimester
  - 3rd trimester – non operative management preferred
- Laparoscopic cholecystectomy - safe

Portal Hypertension in Pregnancy

- Portal pressure ↑ - increased plasma volume / cardiac output / external compression of IVC
- Risk of variceal hemorrhage - ↑ 2nd trimester and during labor
- Screening with EGD recommended for all women
  - Within 12 months of conception or in 2nd trimester if not performed pre conception
- Primary prophylaxis: non selective beta blocker (propranolol preferred) or esophageal variceal ligation (EVL)
- Bleeding management: Octreotide acceptable but avoid terlipressin or vasopressin; Emergent endoscopy for EVL
  - Limited data on TIPS

Splenic artery aneurysm

- Splenic artery rupture occurs in ~ 2.5 % of cirrhotic women during pregnancy/screen with Doppler ultrasound
- Consider surgical or IR therapy if > 2 cm
- Clinical findings: abdominal pain, pulsatile left upper quadrant mass, abdominal bruit

Hepatic adenomas

- Accelerated growth from high estrogen levels
- Complications:
  - Hemorrhage and intraperitoneal rupture
- Adenomas > 5 cm – consider bland embolization or resection before conception
- Monitor with US if adenoma < 5 cm

Contraception and pregnancy post liver transplantation

- Delay pregnancy 1 year (with 6 months stable graft function)
- Increased risk of HTN and pre-eclampsia in mother and IUGR in fetus
- Graft rejection 4-17%; fetal malformation 3%
- Mycophenolic acid products contraindicated in pregnancy/lactation
- Mammalian target of rapamycin inhibitors not recommended due to lack of safety data
- Calcineurin inhibitors, azathioprine/mercaptopurine and corticosteroids acceptable in pregnancy/lactation