Liver disease in pregnancy

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22.03.2017
Physiological changes during pregnancy:

- Rise in maternal heart rate
- Cardiac output increases by 40%
- Circulating plasma volume increases by 30%
- Reduction in peripheral vascular resistance

Hyperdynamic circulation
Physiological changes in laboratory tests during pregnancy:

<table>
<thead>
<tr>
<th>Test</th>
<th>Change in pregnancy</th>
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<tbody>
<tr>
<td>AST/ALT</td>
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<tr>
<td>Bilirubin</td>
<td></td>
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<tr>
<td>Prothrombin/INR</td>
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<tr>
<td>Albumin</td>
<td>↓</td>
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<tr>
<td>Alkaline phosphatase</td>
<td>↑</td>
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<tr>
<td>Hemoglobin</td>
<td>↓</td>
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<tr>
<td>Alpha fetoprotein</td>
<td>↑</td>
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<tr>
<td>5’ nucleotidase</td>
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<tr>
<td>Gamma glutamyl transpeptidase</td>
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</table>
Liver disease in pregnancy

Introduction

Workup of abnormal liver test in a pregnant woman:

Pregnant woman: initial workup of abnormal liver tests

Hepatocellular profile? AST/ALT

Rule out: Viral hepatitis
Herpes
Medications
Other**

Anti-HAV IgM
HBsAg
Hepatitis E IgM
HSV PCR

Biliary profile? elevated bil/alk phos

Bilirubin +/- alk phos

Alk phos only

Biliary imaging

No evidence of obstruction

See Pregnancy-related workup
Liver disease in pregnancy

Introduction

**Specific liver diseases of pregnancy:**
- Hyperemesis gravidarum
- Intrahepatic cholestasis of pregnancy
- Eclampsia and preeclampsia
- HELLP syndrome
- Acute fatty liver of pregnancy

**Liver disease occurring during pregnancy:**
Acute viral hepatitis, gallstone disease, vascular liver disease

**Pregnancy in patients with pre-existing chronic liver disease:**
Chronic hepatitis B, chronic hepatitis C, AIH, PBC, PSC, genetic disorders, metabolic disorders, vascular liver disease, liver cirrhosis and portal hypertension
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Introduction

- Pregnancy–related disorders in previously healthy pregnant woman
- Up to 3% of pregnant woman → most frequent cause of liver dysfunction in pregnancy
- Severe liver disease in pregnancy is rare
- When severe, they are associated with significant morbidity and mortality for both mother and infant
- Significant medical management issue
Liver disease in pregnancy

Introduction

PREGNANCY RELATED DISORDERS

EARLY PREGNANCY
Hyperemesis gravidarum (HG)

LATE PREGNANCY
- Intrahepatic cholestasis of pregnancy (ICP)
- Eclampsia and pre-eclampsia
- Haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome
- Acute fatty liver of pregnancy (AFLP)
Intractable vomiting resulting in dehydration, ketosis and weight loss ≥ 5%

0.1-2.0% pregnancies (very rarely lethal)
Start at week 4; resolution typically by week 18

Unclear aetiology → Human chorionic gonadotropin (HCG) hormone, which peaks in the first trimester has been correlate with the severity of HG

Laboratory findings: ↑ serum urea and creatinine, electrolyte abnormalities (hypophosphatemia, hypomagnesaemia, hypokalaemia), abnormal liver function tests (50% of patients, usually mild aminotransferase elevation)

Severity of nausea and vomiting in patients with liver involvement correlates with the degree of liver enzyme elevation
Liver disease in pregnancy
Hyperemesis gravidarum (HG)

**Treatment** (mainly supportive)

- Intravenous rehydration and correction of electrolyte abnormalities

- Antiemetics:
  - first-line vitamin B6 ± doxylamine
  - second-line: metoclopramide, pnenothiazines, anticholinergics
  - refractory cases: ondanserton or glucocorticoids

- Gradual reintroduction of oral intake and vitamins supplementation
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**Intrahepatic cholestasis of pregnancy (ICP)**

- **Reversible form of cholestasis characterized by pruritus** (worse on the palms and soles) and **elevated fasting or post-prandial serum bile acids** (spontaneously reversible within 4-6 weeks after delivery).

- **Commonest pregnancy specific liver disease (0.7-5%);** high recurrence rate in subsequent pregnancies; associated to an increased risk of hepatobiliary disease later in life.

- **Usually during the third trimester;** more common in multiple pregnancies and after fertility treatment.

- **Complex etiology:** genetic (15% mutations in genes coding for hepatocanalicular transport proteins), hormonal and environmental factors.

- **Laboratory:** bilirubin usually normal; **typically ↑ maternal serum bile acid** (concentration is related to risk of adverse pregnancy outcome, rarely reported when level is below 40 mcmol/l); elevated liver transaminases in most of cases.
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*Intrahepatic cholestasis of pregnancy (ICP)*

**Treatment**

- **First-line:** ursodeoxycholic acid (UDCA) (improvement of maternal symptoms and biochemistry in about 75% cases)

- Resistant cases: Rifampicin + UDCA

- **Vitamin K supplementation:** to reduce the risk of postpartum haemorrhage and neonatal haemorrhage

- Dexamethasone: no impact on symptoms or biochemical markers (useful only to promote fetal lung maturity)
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**Eclampsia and pre-eclampsia**

- Multisystemic disorder defined as «de novo hypertension after 20th week of pregnancy (140/90) and proteinuria (≥ 300 mg/day), other maternal organ dysfunction (liver, kidney, neurological or hematological complications)

- Presence of seizures differentiates eclampsia from pre-eclampsia

- **Pre-eclampsia**: 5-10% all pregnancies

- **Risk factors**: extreme maternal age (< 16 years and >45 years), primiparity, pre-existing hypertensions, family history, previous pre-eclampsia
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**Eclampsia and pre-eclampsia**

As cause of defective placental perfusion

Nitric oxide, prostaglandins, endothelin

Sinusoidal obstruction and ischemia: subcapsular hematoma, parenchymal hemorrhage, rupture

Westbrook RH Journal of Hepatology 2016
AISF position paper on liver disease and pregnancy, Digestive liver disease 2016
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Eclampsia and pre-eclampsia

- **Clinical manifestations**: right upper quadrant pain, headache, nausea, vomiting
- **Laboratory findings**: 30% of cases elevation in aminotransferases (10-to-20-fold)
- Maternal mortality is 15-20% while fetal mortality is 1-2%
- **3-to-25-fold increased risk of**: pulmonary oedema, abruption, aspiration pneumonia, renal failure, hepatic failure, disseminated intravascular coagulation (DIC) and stroke (haemorrhagic stroke is the most common cause of death)
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**Eclampsia and pre-eclampsia**

- **Most of cases resolve within 12 weeks postpartum** (early delivery should be considered when gestational age is over 37 weeks)

- First line arterial hypertension treatment: labetol, methyldopa, nifedipine

- Seizures prophylaxis in severe pre-eclampsia and for controlling seizures in eclampsia: Magnesium sulphate

- Breast-feeding is not contraindicated
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**Haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome**

- The **Hemolisis, Elevated Liver enzymes and Low Platelet (HELLP)** syndrom
- 4-20% of pre-eclampsia (considered as a severe pre-eclampsia by some authors)
- 70% cases between 27 and 30 weeks or postpartum
- Maternal mortality is 1% while fetal mortality is 6-70%
- Pathophysiology remains unknown: endothelial damage (pre-eclampsia) and intravascular platelet activation
Liver disease in pregnancy

Haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome

- **Clinical presentation:** right upper quadrant pain, headache, nausea, vomiting and malaise

- **Diagnostic Criteria**
  
  **Hemolysis:**
  - Lactate dehydrogenase > 600 U/L
  - Total bilirubin > 1.2 mg/dl
  - Peripheral blood smear with abnormal RBC forms

  **Thrombocytopenia**
  - < 100,000/mm3

  **Elevated Liver enzymes**
  - AST < 70 U/L or 2 times above the normal lab SD

- Once HELLP develops the only treatment is delivery of foetus

- If the gestational age is between 24 and 34 weeks corticosteroids are usually given to promote foetal lung maturity. Delivery should be considered 24 hours after administration

Westbrook RH Journal of Hepatology 2016
Tran TT ACG Clinical Guidelines The American Journal of Gastroenterology 2016
Liver disease in pregnancy

*Haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome*

- First-line of treatment: delivery of the foetus
- Management of hypertension as for pre-eclampsia
- If the gestational age is between 24 and 34 weeks: corticosteroids to promote foetal lung maturity, delivery should be considered 24 hours after administration
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**Acute fatty liver of pregnancy (AFLP)**

- Rare, life-threatening condition characterized by microvesicular fatty infiltration of the liver leading to hepatic failure.
- 1:16,000 pregnancies
- Median gestation age 36 weeks
  (Most 28 - 40 weeks or postpartum)
- Maternal mortality 7-18%
- Foetal mortality 9-23%

- Risk factors: twin pregnancies, low BMI
- Unknow aetiology: final manifestation of some insult that leads to microvascular endothelial damage and intravascular platelet activation
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**Acute fatty liver of pregnancy**

- Clinical presentation: right upper quadrant pain, headache, nausea, vomiting and malaise
- Concomitant preeclampsia in one half of cases
- Renal dysfunction and pancreatitis are common
- **Swansea Diagnostic Criteria** could obviate the need for Liver biopsy

<table>
<thead>
<tr>
<th>Six or more of features below in the absence of other aetiology</th>
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</thead>
<tbody>
<tr>
<td>Vomiting</td>
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<tr>
<td>Abdominal pain</td>
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<tr>
<td>Polydipsia/polyuria</td>
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<tr>
<td>Encephalopathy</td>
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<tr>
<td>Bilirubin (&gt;14 µmol/L)</td>
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<tr>
<td>Hypoglycaemia (&lt;4 mmol/L)</td>
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<tr>
<td>Leucocytosis (&gt;11 x 10⁹/L)</td>
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<tr>
<td>Elevated uric acid (&gt;340 µmol/L)</td>
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<tr>
<td>Elevated ammonia (&gt;42 IU/L)</td>
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<tr>
<td>Ascites or bright liver on USS</td>
</tr>
<tr>
<td>Elevated transaminases (&gt;42 IU/L)</td>
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<tr>
<td>Renal impairment (creatinine &gt;150 µmol/L)</td>
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<tr>
<td>Coagulopathy (PT &gt;14 s or APTT &gt;34 s)</td>
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<td>Microvesicular steatosis on biopsy</td>
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Tran TT  ACG Clinical Guidelines  The American Journal of Gastroenterology 2016
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Acute fatty liver of pregnancy

Management

1) early recognition and diagnosis (best maternal survival rate when the interval from occurrence of AFLP to delivery is one week)
2) aggressive maternal stabilization in intensive care setting
3) rapid delivery: if vaginal delivery cannot be achieved quickly, caesarean section is the preferred method

Evaluation for Liver transplantation if hepatic function does not rapidly improve
Liver disease in pregnancy

<table>
<thead>
<tr>
<th>Differential diagnosis between haemolysis, elevated liver enzymes, and low platelets syndrome and acute fatty liver of pregnancy.</th>
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<tbody>
<tr>
<td>HELLP</td>
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<tr>
<td>Prevalence (%)</td>
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<tr>
<td>Onset</td>
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<tr>
<td>Family history</td>
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<tr>
<td>Onset of preeclampsia (%)</td>
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<tr>
<td>Clinical features</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Aminotransferases</td>
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<tr>
<td>Bilirubin</td>
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<tr>
<td>Liver imaging</td>
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<tr>
<td>Histology</td>
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<tr>
<td>Maternal mortality (%)</td>
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<tr>
<td>Foetal/perinatal mortality (%)</td>
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<tr>
<td>Recurrence in subsequent pregnancy (%)</td>
</tr>
</tbody>
</table>

HELLP, haemolysis, elevated liver enzymes, and low platelets; AFLP, acute fatty liver of pregnancy; DIC, disseminated intravascular coagulation.
### Liver disease in pregnancy

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Trimester</th>
<th>Management</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HG</td>
<td>First/through 20w</td>
<td>Supportive management</td>
<td></td>
</tr>
<tr>
<td>IHCP</td>
<td>Second/third</td>
<td>Ursodeoxycholic acid 10–15mg/kg Early delivery at 37 weeks</td>
<td></td>
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<tr>
<td>AFLP</td>
<td>Third</td>
<td>Women with AFLP should be delivered promptly Infant should be monitored</td>
<td>A dehydrogenase including hypoketotic hypoglycemia and fatty liver</td>
</tr>
<tr>
<td></td>
<td></td>
<td>for manifestations of deficiency of long-chain 3-hydroxyacyl-coenzyme A</td>
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<tr>
<td>Eclampsia, preeclampsia</td>
<td>After 20w</td>
<td>After 36 weeks, women with severe preeclampsia should be delivered promptly</td>
<td></td>
</tr>
<tr>
<td>HELLP</td>
<td>After 22 weeks</td>
<td>Delivery after 34 weeks Platelet transfusion to 40,000–50,000 cells/µl</td>
<td>shoule be considered before delivery, especially if cesarean section is likely</td>
</tr>
</tbody>
</table>

AFLP, acute fatty liver disease of pregnancy; HELLP, hemolysis, elevated liver enzymes, low platelets; HG, hyperemesis gravidarum; IHCP, intrahepatic cholestasis of pregnancy.
Vielen Dank