Liver disease in pregnancy: diagnosis and treatment

XIII Falk Liver Week, Freiburg,
10th October, 2006

Jurate Kondrackiene, and Limas Kupcinskas

Department of Gastroenterology, Kaunas University of Medicine,
Kaunas, Lithuania
Liver during normal pregnancy

- **Physical examination**
  - Spider angioma
  - Palmar erythema

- **Hemodynamics**
  - Plasma volume ↑
  - Cardiac output ↑

- **Proteins and lipids**
  - Albumin ↓
  - Protrombin time normal
  - Ceruloplasmin ↓
  - Cholesterol/ triglyceride ↑

- **Liver tests**
  - AP ↑ 2x
  - ALT, AST, \(\gamma\)-GT, bilirubin - normal
  - Total bile acids - normal
# Causes and timing of liver disease in pregnancy

<table>
<thead>
<tr>
<th>Disease category</th>
<th>Specific disease</th>
<th>Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver disease related to pregnancy</td>
<td><strong>Hyperemesis gravidarum</strong></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td><strong>Intrahepatic cholestasis of pregnancy</strong></td>
<td>2-3</td>
</tr>
<tr>
<td></td>
<td><strong>Preeclampsia</strong></td>
<td>3, late 2</td>
</tr>
<tr>
<td></td>
<td><strong>HELLP syndrome</strong></td>
<td>3, late 2</td>
</tr>
<tr>
<td></td>
<td><strong>Acute fatty liver of pregnancy</strong></td>
<td>3</td>
</tr>
<tr>
<td>Liver disease coincidental with pregnancy</td>
<td><strong>Acute viral hepatitis</strong></td>
<td>1-3</td>
</tr>
<tr>
<td></td>
<td><strong>Budd-Chiari syndrome</strong></td>
<td>Postpartum</td>
</tr>
<tr>
<td></td>
<td><strong>Gallstones</strong></td>
<td>1-3</td>
</tr>
<tr>
<td></td>
<td><strong>Drug-induced hepatitis</strong></td>
<td>1-3</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td><strong>Chronic viral hepatitis</strong></td>
<td>1-3</td>
</tr>
<tr>
<td></td>
<td><strong>Autoimmune hepatitis</strong></td>
<td>1-3</td>
</tr>
<tr>
<td></td>
<td><strong>Cirrhosis</strong></td>
<td>1-3</td>
</tr>
<tr>
<td></td>
<td><strong>Wilson’s disease</strong></td>
<td>1-3</td>
</tr>
</tbody>
</table>
Timing of liver disease unique to pregnancy

- **First trimester**: Hyperemesis gravidarum
- **Second trimester**: Intrahepatic cholestasis of pregnancy, Preeclampsia, HELLP
- **Third trimester**: Acute fatty liver of pregnancy
Hyperemesis gravidarum

- Hyperemesis gravidarum – intractable nausea and vomiting until 16 - 18 weeks of gestation, until delivery - 5%

- Incidence – from 3: 1000 to 1: 100 pregnancies

- Prognosis – favourable
Hyperemesis gravidarum

Pathogenesis

Theories:
- psychologic factors
- gestational hormones (human chorionic gonadotropin)
- gastrointestinal dysmotility
- autonomic nervous disturbance
- nutritional deficiency
- lipid metabolism
- hyperthyroxinaemia
- Helicobacter pylori
Hyperemesis gravidarum
Clinical features

- Intractable vomiting

  **benign complications:** water and electrolyte disturbances, ketosis, nutritional deficiency, weight loss greater than 5%

  **severe complications:** Wernicke encephalopathy, esophageal rupture, retinal hemorrhage, pneumomediastinum, renal damage

- Liver abnormalities in 50%: ALT 2-4 x N, bilirubin < 4 x N

- Transient hyperthyroidism

- Liver biopsy: normal or nonspecific
Hyperemesis gravidarum

Treatment (1)

- avoidance of triggers
- diet
- replenishment of fluids and electrolytes
- supplementation of vitamins (B1)
- enteral nutrition
- acupuncture, hypnosis, psychotherapy
- ginger 1 g daily
Hyperemesis gravidarum

Treatment (2)

No medication is approved by FDA

- Pyridoxine (vit. B6) 10-25 mg, TID
- Antiemetics:
  - Promethazine 12.5- 25mg Q4h PO, IM, PR
  - Dimenhydrinate 50- 100mg Q4h PO, PR
  - Metoclopramide 5- 10 mg Q8h IM, PO
  - Prochlorperazine 5- 10 mg Q3 to 4h IM, PO or 25md BID PR
- Methylprednisolone 16 mg Q8h PO, PR 3 days after 10 weeks of gestation

Intrahepatic cholestasis of pregnancy

- Intrahepatic cholestasis of pregnancy (ICP) - reversible form of cholestasis

- The most common pregnancy-related liver disorder

- Incidence – 0.2 – 4 %
Intrahepatic cholestasis of pregnancy

Pathogenesis

- genetic predisposition (MDR3, BSEP, FIC1)
- hormonal factors
- environmental factors

Jacquemin et al. Lancet 1999;
Rosmorduc et al. Gastroenterol 2003;125:452
Lucena et al. Gastroenterology 2003;124:1037
Pauli-Magnus et al. Pharmacogenetics 2004
Wasmuth et al. Gut 2006
Intrahepatic cholestasis of pregnancy

**Clinical features**

- pruritus in 2-3 trimester of pregnancy
- ALT, AST 5-10 x N, bilirubin < 6 x N
- GGT↑ in ~ 10%
- serum bile acids > 10 mmol/l
Intrahepatic cholestasis of pregnancy

Pregnancy outcome

Fetal outcome:
☐ stillbirths 1-2 %
☐ premature deliveries 19-60%
☐ fetal distress 22-33%

Maternal prognosis: benign
Reccurence 60 %
Intrahepatic cholestasis of pregnancy

Fetal complications rates in pregnant women with ICP

Serum bile acids (mmol/l)

- < 10
- 10-40
- > 40

Preterm delivery
Meconium staining of amniotic fluid
Green staining of placenta and membranes
Asphyxial events

Glantz et al., Hepatology 2004;40:467
Intrahepatic cholestasis of pregnancy

Treatment

- Ursodeoxycholic acid (UDCA)
- Cholestyramine
- SAMe
- Dexamethason
- Phenobarbital
Efficacy and safety of UDCA vs. cholestyramine in ICP: randomised parallel group study

84 patients randomized

42 patients allocated to UDCA, 8-10 mg/kg/d

Withdrawal:
4 patients discontinued treatment
6 protocol violations

42 patients analyzed on ITT basis

42 patients allocated to cholestyramine, 8 g/d

Withdrawal:
3 adverse events
1 patient discontinued treatment

42 patients analyzed on ITT basis

Kondrackiene, Beuers, Kupcinskas. Gastroenterology 2005; 129: 894
Efficacy and safety of UDCA vs. cholestyramine in ICP: randomised parallel group study

Intensity of pruritus

Pats. with value at baseline and at least one post-baseline value, n=77

'Last observation carried forward' method used every day

Kondrackiene, Beuers, Kupcinskas. Gastroenterology 2005; 129: 894
ALT before and after therapy (UDCA vs cholestyramine)

UDCA

cholestyramine

Kondrackiene, Beuers, Kupcinskas. Gastroenterology 2005; 129: 894
Serum bile acids before and after therapy (UDCA vs cholestyramine)

Kondrackiene, Beuers, Kupcinskas. Gastroenterology 2005; 129: 894
# Outcome of pregnancy (UDCA vs cholestyramine)

<table>
<thead>
<tr>
<th>Outcome of pregnancy</th>
<th>UDCA group (n=42)</th>
<th>Cholestyramine group (n=42)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Term of delivery (weeks)</td>
<td>38.7±1.7</td>
<td>37.4±1.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Newborn body weight (g)</td>
<td>3302.3±494.7</td>
<td>3078.7±447.6</td>
<td>NS</td>
</tr>
<tr>
<td>Apgar score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at 1 min</td>
<td>8.4±0.8</td>
<td>8.1±0.8</td>
<td>NS</td>
</tr>
<tr>
<td>at 5 min</td>
<td>9.4±0.5</td>
<td>8.7±0.6</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Kondrackiene, Beuers, Kupcinskas. Gastroenterology 2005; 129: 894
Preeclampsia

- Incidence – 3 to 14%
- **Pathogenesis:** placental ischemia, dysfunction of endothelium

- **Criteria**
  - systolic blood pressure $\geq 140$ mmHg
  - or diastolic $\geq 90$ mmHg
  - and proteinuria $\geq 0.3$ g in a 24-hour urine specimen

Preeclampsia

- Liver involvement in 20 to 30%
- Clinical manifestations – right upper quadrant or epigastric pain, elevated aminotransferases, thrombocytopenia
- Complications – HELLP syndrome, subcapsular hemorrhage or hepatic rupture, hepatic infarction, fulminant failure
- Maternal mortality < 1%
HELLP syndrome

H- hemolysis, EL- elevated liver enzymes, P- low platelet

(L. Weinstein, 1982)

- Incidence – 0.1- 0.6 %

- In 10 - 20 % patients with severe preeclampsia/eclampsia
  15 - 20 % of patients do not have preeclampsia

- Time of onset:
  antepartum 70 %
  postpartum 30 %
HELLP syndrome

Clinical features

- proteinuria 87 %
- hypertension 85 %
- abdominal pain 40 – 90 %
- nausea, vomiting 29 – 84 %
- headache 33 – 60 %
- jaundice 5 %
- ascites 8 %
- DIC 20 %
HELLP syndrome

Diagnosis

- Hemolysis: microangiopathic hemolytic anemia (schistocytes), indirect bilirubin ↑, LDH >600 U/L, haptoglobin <25 mg/dL
- AST >70 U/L
- Platelet count < 100 000/mm³


- Liver biopsy: periportal hemorrhage, fibrin deposition
HELLP syndrome
Complications

- hepatic infarction (marked elevation of aminotransferases)
- liver hematoma and rupture 1%
- DIC 20%
- abruptio placenta 16%
- acute renal failure 7%
- pulmonary edema 6%
HELLP syndrome

Treatment

- **Delivery**
  Corticosteroids for acceleration of fetal lung maturity:
  Dexamethasone 10 mg IV Q12h until clinical improvement

- **Supportive therapy**
  Magnesium sulfate – 6g IV, 2g/h infusion
  Labetalol, hydralazine, nifedipine, sodium nitropruside
  Plasma exchange
  Platelet transfusion – plts <20,000/mm³

HELPP syndrome

Prognosis

- Maternal mortality 1 %
- Fetal mortality 7-20 % (35 %)
- Prematurity 70 %
- Abruptio placentae 16 %
- Recurrence 3- 27 %
Acute fatty liver of pregnancy

- Incidence 1 : 7.000 – 16.000
- Time of onset – 3 trimester (28–40 wk)
- Primigravidas 42 – 70 %
- Male gestation 60 – 76 %
- Twin gestation 13 %
Acute fatty liver of pregnancy

Pathogenesis

- 10-20% inherited defect in mitochondrial b-oxidation of fatty acids - deficiency of long-chain 3-hydroxyacyl-CoA-dehydrogenase (mother heterozygotes, fetus homozygotes)
- mutation E474Q in 65-90%

Acute fatty liver of pregnancy

Clinical features

- nausea, vomiting
- malaise
- fatigue
- anorexia
- headache
- abdominal pain
- jaundice
- preeclampsia in 50 %
Acute fatty liver of pregnancy

Laboratory tests

- AST/ALT $\uparrow$ 5-10 x N
- bilirubin $\uparrow$ 6-8 x N
- prothrombin time, APTT $\uparrow$
- fibrinogen $\downarrow$
- white blood cells $\uparrow$
- glucose $\downarrow$
- ammonia $\uparrow$
Acute fatty liver of pregnancy

Histology

Microvesicular fatty infiltration in central zone

Sudan-Hematoxylin

Sherlock & Summerfield, 1991
Acute fatty liver of pregnancy

Complications

- fulminant hepatic failure
- bleeding
- DIC
- infection
- severe hypoglycemia
- acute renal failure
- pancreatitis
- diabetes insipidus
Acute fatty liver of pregnancy

Management

- Prompt delivery!
- Supportive therapy:
  - glucose
  - packed red blood cells, platelets
  - fresh frozen plasma
  - cryoprecipitate
  - lactulose
  - antibiotics

- Liver transplantation

- Babies with LCHAD deficiency – glucose IV, foods with medium-chain fatty acids, low-fat diet
Acute fatty liver of pregnancy

Prognosis

- Maternal mortality less than 10 % (70-90 % before 1970)

- Fetal mortality 10 – 20 %
Summary

- Gestational age is the best guide to differential diagnosis of unique to pregnancy liver disease
- ICP is the most common pregnancy-related liver disorder
- UDCA is the first-line therapy for ICP
- Early diagnosis of HELLP syndrome and AFLP, and prompt delivery with supportive therapy could avoid fatal maternal and perinatal outcome
Kaunas, Lithuania