Diagnosis and Management of Cholestasis

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PREGNANCY CARE ECHO
Intrahepatic cholestasis of pregnancy (ICP)- Definition

- Itching with OUT rash
- Elevated serum bile acids ($\geq 10 \, \mu\text{mol/L}$)
Epidemiology of ICP

- Incidence varies widely (0.1 to 15.6%)
  - In the US, 0.32-5.6%

- More common in certain ethnic groups → Latina women

- More common in certain geographical areas → Chile, Bolivia, Scandinavia
Pathogenesis of ICP

- **Genetic factors** → ABCB4, ATP8B1, and ABCB11 genes found in women with ICP.

- **Hormonal factors** → Estrogens are known to be involved as evidenced by higher incidence in twin pregnancies and increasing incidence as gestation advances.

- **Hormonal factors** → Progesterone may saturate hepatic transport receptors for biliary excretion of bile acids.

- **Environmental factors** → Seasonal variability has been established in some countries with higher incidence during colder months.
Pathogenesis of ICP
Risk factors for ICP

- Previous pregnancy with ICP
- Family history of ICP
- Multiple gestation
- Underlying liver disease
- Pregnancy conceived with fertility treatments
- Latina women
# Differential diagnosis of ICP

<table>
<thead>
<tr>
<th>Differential</th>
<th>Presentation</th>
<th>Distinguishing features</th>
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<tbody>
<tr>
<td>Pruritus gravidarum</td>
<td>Pruritus in 3rd trimester</td>
<td>No abnormal laboratory values</td>
</tr>
<tr>
<td>Atopic eruption</td>
<td>Pruritus in 1st trimester</td>
<td>Dry, red rash on trunk and limbs</td>
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<tr>
<td>Pruritic urticarial papules and plaques of pregnancy (PUPPS)</td>
<td>Pruritus in 3rd trimester</td>
<td>Papules, plaques, or vesicles in striae, sparing umbilicus</td>
</tr>
<tr>
<td>Pemphigoid gestationis</td>
<td>Pruritus in 2nd or 3rd trimester</td>
<td>Large, tense blisters, auto-immune with IgG antibodies</td>
</tr>
<tr>
<td>Prurigo of pregnancy</td>
<td>Pruritus in 3rd trimester</td>
<td>Red-brown papules on abdomen or limbs</td>
</tr>
<tr>
<td>Pruritic folliculitis of pregnancy</td>
<td>Pruritus in 3rd trimester</td>
<td>Acneiform eruption of shoulders, back, limbs, may be filled with pus</td>
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<tr>
<td>Psoriasis</td>
<td>Pruritus at any time, mostly painful</td>
<td>Erythematous plaques with silver scale</td>
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Making the diagnosis of ICP

- Pruritus typically in the third trimester
  - Palms and soles classically, but can be diffuse

- No rash

- Elevated serum bile acid levels (≥ 10 µmol/L)
  - May also have elevated hepatic transaminases

- On ultrasound (not necessary) liver and bile ducts appear normal
Laboratory findings with ICP

- Elevated serum bile acids ($\geq 10 \text{ µmol/L}$)
  - May be only finding

- Elevated hepatic transaminases
  - May proceed abnormal bile acid levels
  - May exceed 1000 U/L
  - No evidence of coagulopathy

- Elevated alkaline phosphatase
  - Not specific due to elevated levels in pregnancy

- Elevated total bilirubin
Implications of bile acid levels

- Common classification for bile acids:
  - Mild 10-39 µmol/L
  - Moderate 40-99 µmol/L
  - Severe >100 µmol/L

- Most adverse pregnancy outcomes are seen at levels >40
- Stillbirth seems to be increased at levels >100

Treatment for ICP- Ursodeoxycholic acid (Ursodiol, Actigall, or UCDA)

- Increases bile flow and thus may increase excretion of bile acids
- Shown in a Cochrane review to be the most useful drug for decreasing maternal pruritus
- May decrease hepatic enzymes, bile acids, and bilirubin levels
- Dose:
  - Starting- 500mg PO twice daily
  - Max- 2g per day
- Fetal concentration remains low even with high doses
Treatment for ICP - other drugs

- All current therapies primarily aimed at decreasing maternal itching:
  - Hydroxyzine: Anti-histamine; 25-50mg/day
  - Cholestyramine: Bile acid eliminator; 8-16g/day
  - Rifampicin: Antibiotic with choleretic properties; reduces severe bile acid elevation; needs further study
    - May work better when combined with UCDA
  - Steroids (dexamethasone): Decreases itching, but may not improve bile acids; dosing variable

- **UCDA is current recommended first-line therapy**
Maternal complications of ICP

- Spontaneous preterm labor
- Increased risk for gestational diabetes
- Increased risk for preeclampsia
- Pruritis
  - Increased risk for underlying liver disease including gallbladder disease, hepatitis, and carcinoma (small)
  - Increased risk for acute fatty liver of pregnancy (rare)
Fetal complications of ICP

- Meconium stained amniotic fluid
- Intrauterine demise
  - **Highest risk with bile acids >100**
  - Acute process with 2 theories for etiology:
    - Sudden cardiac death due to arrhythmia
    - Vasoconstriction of placental chorionic vessels

Neonatal complications with ICP

- Morbidity associated with prematurity
- Increased risk for respiratory distress syndrome
  - After controlling for gestational age
Antenatal testing for ICP

- May not be beneficial
- Testing designed to predict fetal asphyxia from chronic conditions (i.e. placental insufficiency)
- Fetal demise (stillbirth) from ICP thought to be acute and unpredictable
- Prescriptions for testing vary widely
  - When to start?
  - How frequent?
Antenatal testing for ICP

<table>
<thead>
<tr>
<th></th>
<th>Twice Weekly N=118</th>
<th>Weekly N=35</th>
<th>Less than Weekly N=46</th>
<th>None/Unknown N=226</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery gestational age (weeks)</td>
<td>36.8 (1.2)</td>
<td>37.4 (1.1)</td>
<td>37.2 (1.0)</td>
<td>37.5 (1.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Composite neonatal morbidity</td>
<td>3 (2.5)</td>
<td>0 (0)</td>
<td>1 (2.2)</td>
<td>4 (1.8)</td>
<td>0.942</td>
</tr>
<tr>
<td>Abnormal NST prompting delivery</td>
<td>2 (1.5)</td>
<td>2 (4.7)</td>
<td>0 (0)</td>
<td>NA</td>
<td>0.541</td>
</tr>
<tr>
<td>At least one BPP ordered</td>
<td>20 (16.9)</td>
<td>3 (8.6)</td>
<td>3 (6.5)</td>
<td>3 (1.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>NICU admission</td>
<td>25 (21.2)</td>
<td>2 (5.7)</td>
<td>8 (17.4)</td>
<td>42 (18.6)</td>
<td>0.220</td>
</tr>
<tr>
<td>RDS</td>
<td>12 (10.2)</td>
<td>1 (2.9)</td>
<td>2 (4.3)</td>
<td>12 (5.3)</td>
<td>0.312</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (0.9)</td>
<td>0.706</td>
</tr>
</tbody>
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Timing of delivery?

- Some experts advocate for early delivery (36-37 weeks)
- Others recommend delaying delivery until closer to term (39 weeks)
- Perhaps a case-by-case approach?
  - Women with mild disease (bile acids <40) could be expectantly managed until 38-39 weeks
  - Women with moderate disease (bile acids 40-99) could be delivered at 37-38 weeks
  - Women with severe disease (bile acids >100) could be delivered at 36-37 weeks
  - All of the above +/- antenatal testing
Follow-up after ICP

- Discuss recurrence risk (60-90%)
- Repeat bile acids, liver function tests to ensure normalization
  - Consider right upper quadrant ultrasound or referral to GI if abnormal
- Avoid high estrogen-containing contraceptives
  - Most OCPs are acceptable
  - Warn women that symptoms may recur with hormonal birth control
Questions?