Atypical cholestasis in pregnancy

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Objectives

- Recognize atypical presentation of pruritus in pregnancy (ICP)
- Recognize diseases that mimic intrahepatic cholestasis of pregnancy (ICP)
- Use second or third line treatment for intractable pruritus in these patients
“atypical” case of ICP

- 32 year old G1, 16th weeks of gestation
  - Pruritus since week 10
  - No rash
  - ALT 88 (N 14-40)
  - Total bile acids (TBA) 15 (N<10 umol/L)
What’s new/Areas uncertainty

Question 1: Which diseases should be excluded?

Diagnostic criteria/Definition

Question 2: Which abnormal labs are necessary for diagnosis of ICP?

Question 3: What are the treatment options for her pruritus?

Treatment

Question 4: What should be the timing of delivery?
Question 1:
Which diseases should be excluded?

- Usual definition ICP: “typical”
  - Pruritus late 2\textsuperscript{nd} or 3\textsuperscript{rd} trimester
  - No rash
  - Elevated TBA and/or transaminase
  - Exclusion of other liver diseases
  - Post partum resolution
Question 1:
Which diseases should be excluded?

- Great variability between studies, guidelines, expert opinions. Include:
  - Virus: hepatitis A, B, C, EBV, CMV
  - Hereditary: hemochromatosis, a1 antitrypsin deficiency, Wilson’s disease
  - Auto-immune: hepatitis, primary biliary cirrhosis
  - Fatty liver disease
  - Extra hepatic biliary obstruction
  - Mutations bile salt transporters
Question 2:
Which diseases should be excluded?

- Shouldn't we use the concept of:
  Primary versus secondary ICP?
Association with genetic bile salts transporter defects

Mutations ATP8B1 gene

Mutations ABCB11 gene

Mutations ABCB4 gene
Genetic cause

- Large spectrum of clinical presentation of mutations including:
  - ICP
  - BRIC (Benign recurring intrahepatic cholestasis)
  - Cholesterol gallstones
  - PFIC (Progressive familial intrahepatic cholestasis)

- Bacq Y and al*:
  - Identified 4 mutations almost exclusively in 16% of Caucasians with ICP* (versus controls without ICP)

**Genetic cause**

- Bacq Y and al. Digestive and Liver disease 2016 (accepted manuscript)

<table>
<thead>
<tr>
<th></th>
<th>Onset pruritus</th>
<th>TBA concentration</th>
<th>TBA concentration &gt; 40 umol/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABCB4 mutation</td>
<td>30 1/7 weeks</td>
<td>42.9 umol/L</td>
<td>35.3%</td>
</tr>
<tr>
<td>17/98</td>
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<tr>
<td>No mutation</td>
<td>33 2/7 weeks</td>
<td>24.3 umol/L</td>
<td>13.6%</td>
</tr>
<tr>
<td>81/98</td>
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  - Auto-immune: hepatitis, primary biliary cirrhosis
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  - Extra hepatic biliary obstruction
  - Mutations of bile salt transporters
Question 2: Which abnormal labs are necessary for diagnosis of ICP?

Probable sequence of abnormalities:

- **Pruritus**: no lab abnormality: Pruritus Gestationis (23% pregnancies)
- **TBA elevation**: (versus individual bile acid measurement*) Dx ICP
- **Transaminase elevation**: (30%) Mild alkaline phosphatase elevation
- **Rare GGT and bilirubin elevation**

*Why do ALT increase before GGT. Isn’t this cholestasis????*

*Huand WM. Am J Perinatol 2009; 26: 291*
Question 2:
Which abnormal labs are necessary for diagnosis of ICP?

- Why do guidelines/experts mention elevated TBA and/or transaminase?
  - Probably because TBA levels not universally available
  - “Serum bile acids are increasingly recognized as the most definitive laboratory test for diagnosis of ICP”*

- Can we diagnose ICP if elevation of transaminase but not TBA? probably not

- Can we diagnose ICP if elevated TBA but asymptomatic? Yes

Back to our case

- TBA: 15 umol/L at diagnosis
- Treated with UDCA 500 mg 3 times a day
- Initially better with ALT decrease to normal
- Deterioration at 26 weeks: severe pruritus, ALT 120, TBA 50 umol/L
### Question 3: What are the treatment options for her pruritus?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Improved chemistry</th>
<th>Improved pruritus</th>
<th>Improved fetal outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>UDCA 450-1000 mg/day**</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>SAMe</td>
<td>+</td>
<td>+</td>
<td>- / ?</td>
</tr>
<tr>
<td>Activated charcoal</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Guar gum</td>
<td>?</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>+ (less than UDCA)</td>
<td>+( less than UDCA)</td>
<td>Less than UDCA</td>
</tr>
<tr>
<td>Dexamethasone (versus UDCA)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Rifampicin (combination with UDCA)</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
</tbody>
</table>

*Ovadia C and al. Clinics in dermatology 2016; 34: 327-334

**Kong X and al. Medicine 2016; 95(40)
Question 3:
What are the treatment options for her pruritus?

- **Other treatment options**:
  - Phenobarbital: no effect
  - Phototherapy UV-B: anecdotal
  - Plasmapheresis: case reports with success
  - Sertraline (SSRI): no data in ICP
  - Oral naltrexone (opioid antagonist): no data in ICP
Question 3: What are the treatment options for her pruritus?

- Treatment plan for our patient:
  - UDCA (maximum dose 15 mg/kg/day)
    - Up to 3.5 g per day described*: safe?
    - plus rifampicin (caution if ALT very high).
  - Consider cholestyramine 8g/day (caution with timing)
  - If very extremely severe and <34 weeks: plasmapheresis

Question 3: What are the treatment options for her pruritus?

- Teaser: Use of grapefruit juice
  - See poster by Dahl K and al. NASOM 2016
- 4 patients with “secondary ICP”
Question 4:
What should be the timing of delivery?

- Role of gestational age on fetal prognosis, what we know:
  - Series of 20 UIFDs: median 38 weeks, 2/20 before 37 weeks**

*Williamson C and al. BJOC 2004; 111:676
Question 4: What should be the timing of delivery?

- 2 recent publications using different experimental approaches suggest delivery 36 weeks = best outcome*, **

- Multiple methodological flaws, do not take into account TBA, subject of debate between experts.

** Lo JO and al. The Journal of Maternal-Fetal and Neonatal Medicine 2015; 18(18): 2254-2258
Question 4:
What should be the timing of delivery?

- Position that seems most consensual: continue delivering ICP at 37 weeks unless:
  - Past history of IUFD
  - Intolerable pruritus
  - Other indication for delivery
  - Personal preference
  - Elevated TBA
Role of TBAs

- Role of bile acids in fetal morbidity and mortality*
  - Induction of arrhythmia/fetal heart US abnormalities**
  - Affect placental vasculature
  - Could increase preterm labor (via prostaglandin pathways)
  - Stimulate gut motility: meconium-stained amniotic fluid
  - Disrupt pulmonary surfactant in neonates
  - Long term: effect on metabolic health of teenagers

**Alaalla WM and al. J Mat Fetal Neonat Med 2016; 29(): 1445-1450
Role of TBAs


- Prospective case-control

- 669 ICP singleton pregnancies with TBA > 40 umol/L
  - Stillbirth 1.5% versus 0.5%
    - 10 stillbirths in ICP group
    - 6/10 before 37 weeks
    - 7/10 another pregnancy complication (PE, gestational diabetes)
  - Median TBA 137 umol/L (104-159) versus live births 72 umol/L (52-107)
Role of TBAs

- TBA > 100 umol/L: 10-15% IUFD*, **
  - Towards a new classification of ICP depending on max TBA:
    - Mild 10-39 umol/L
    - Moderate 40-99
    - Severe > 100

- Is the fetus protected if TBA > 100 and then decrease <40
  - IUFD case D**: max TBA 114, last recorded TBA 36 within 1 week of stillbirth**?

*Brouwers L and al. AJOG 2015; 212:100
**Kawakita T and al. AJOG 2015; 213:570
Conclusions

- Mutations of bile salt transporters linked to up to 15% of cases of ICP
  - Should we test every case? Selected cases?

- Notion of primary versus secondary ICP

- TBAs is the most accepted marker for diagnosis of ICP
  - Toward a new classification of ICP based on maximal recorded TBA?
    - 10-39 umol/L: mild
    - 40-99 umol/L: moderate
    - >100 umol/L: severe
Conclusions

- Treatment options remain limited
  - Should always include UDCA
    - Consider: rifampicin, cholestyramine 8g/day, Grapefruit juice (500-1000 ml/day)
  - If very extremely severe and <34 weeks: plasmapheresis
  - Delivery
Conclusions

- The ideal timing of delivery is not yet known
  - Difficult question with medical legal implications, necessity of group consensus
  - Variable availability of TBA testing
- 37 weeks or earlier if:
  - Past history of stillbirth
  - Intolerable pruritus
  - Other indication for delivery
  - Personal preference
  - TBA $>40$ umol/L (especially if $>100$)
New diagnostic tests

- Novel diagnostic avenues?
  - Measurement of sulfated progestin metabolites*
  - Measurement of autotaxin activity**

Induction of Autotaxin
By cholestasis

Lysophosphatidylcholine \(\rightarrow\) LPA (in skin) \(\rightarrow\) potentiates action potential in itch fibers

Question: Why her? Risk factors

- Prior ICP (60-70% recurrence)
- Latin American:
  - ICP incidence 0.1-15%
  - Geographic variations
- Winter (selenium deficiency?)
- Twin pregnancies

- Exogenous progesterone
- Genetic predisposition
Exogenous progesterone

- Bacq Y and al. Hepatology 1997; 26: 358
  - 50 women with ICP, 64% oral natural progesterone

  - In ICP: Elevated sulfated progesterone metabolites:
    - Competitively inhibit bile acid uptake and efflux: contribute to cholestasis
    - Participate to pruritus
    - Future pathway for treatment and diagnosis?
Exogenous progesterone

- Clinical significance:
- Some experts recommend avoiding progesterone supplementation if:
  - Prior ICP
  - Current ICP
Question: Risk for other pregnancy related problems?

- Martineau MG and al. Diabetes Care 2015; 38: 243
  - 26 ICP versus 27 normal pregnancies:
    - ICP associated with impaired glucose intolerance
    - Dyslipidemia
    - Increased fetal growth

<table>
<thead>
<tr>
<th></th>
<th>ICP</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks at delivery</td>
<td>37,4</td>
<td>40,1</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>3,298 (69,9 centile)</td>
<td>3,381 (36,1 centile)</td>
</tr>
</tbody>
</table>
Question:
Risk for other pregnancy related problems?

Severe intrahepatic cholestasis of pregnancy is a risk factor for preeclampsia in singleton and twin pregnancies

  - Severe ICP (TBS>40 umol/L):
    - major risk factor for PE:
      - Singletons: 7.4% versus 1.5%
      - Twins: 33% versus 6.2%
    - Increase in severe PE
  - TBS normal in 33 patients with PE but no ICP
  - Closely follow ICP patients for PE
Question:
Risk for other pregnancy related problems?

  - Retrospective cohort case-control study:
  - 15,083 deliveries, 348 ICP (2,3%):
    - No difference between estimated blood loss and variation in hemoglobin
    - Moderate and severe ICP (TBS 40-99 and >100):
      - More meconium staining
      - Non significant difference in stillbirth (1,8% versus 0,6%)

- Reassuring, no vitamin K supplementation unless elevated INR
Question:
Are there any long term consequences?

- Possible increases risk:
  - liver/biliary tract cancer (HR 3.6)
  - diabetes (HR 1.5)
  - thyroid disease (HR 1.3)
  - Crohn’s disease (HR 1.6)
  - Cardiovascular disease (if associated with PE)*

- Clinical significance?
- Probably more related to underlying liver disease