“ITCHY MOMS”: INTRAHEPATIC CHOLESTASIS OF PREGNANCY

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INTRAHEPATIC CHOLESTASIS OF PREGNANCY (IHCP): DEFINITION

- Pregnant, usually 3rd trimester
- Pruritus, usually severe
- NO RASH
- Elevated bile acids
- Elevated liver functions
IHCP: EPIDEMIOLOGY

- High incidence in certain ethnicities:
  - Scandinavian
  - Araucana (Chile)
  - Aymara (Bolivia)
  - Yup’ik/Inupiaq (Alaska/Greenland)
  - Hispanic (Mex-Am in USA)
IHCP: Pregnancy Complications

- Severe (intolerable) pruritus: 100%
- Preterm birth: 10-35%
- Stillbirth: 1-9%
- Meconium, NRFS in labor
- Cholelithiasis
- PPH
- Recurrence (next pg): 40-70%
Bile Physiology

- Bile acids (BA) are cholesterol breakdown products and are toxic
- BA are conjugated to bile salts and excreted, where they act as emulsifiers in the gut to enable fat digestion
- Basically, bile salts + phosphatidyl choline = bile
- Bile salts are transported back to the liver via the enterohepatic circulation
Cholesterol

Primary bile acids

Cholic acid (CA)

Chenodeoxycholic acid (CDCA)

Secondary bile acids

Deoxycholic acid (DCA)

Lithocholic acid (DCA)

Ursodeoxycholic acid (UDCA)

+ glycine $\rightarrow$ $R\text{-}C\text{-}N\text{-}CH_2\text{COO}^-$

+ taurine $\rightarrow$ $R\text{-}C\text{-}N\text{-}(CH_2)_2SO_2O^-$
Cholesterol

5% (0.5 g/day)

Bile acids

95%

Spillover in systemic circulation

Active resorption renal tubules

Portal venous circulation

Biliary secretion:
BS pool 2–3 g which cycles 4–6 times per day

5% (0.5 g/day)
IHCP: Genetics

- Genetically heterogeneous in different populations
- Mutations in the bile acid (BA) transporter genes (that control export of BA from hepatocyte to biliary canaliculus)
- Mutations in these transporters result in familial cholestasis syndromes
- E2 and P4 can up-regulate the genes that result in reduced BA transport in susceptible women
A link between FAO and IHCP?

- FAO = fatty acid oxidation disorders
- LCHAD and acute fatty liver of pg
- CPT-1 deficiency and IHCP?
- CPT-1 deficiency most common gene disorder in our population (allele frequency 0.70 in Eskimos)
- Evolutionary response to the traditional ketogenic high-fat diet
- Is IHCP a side effect?
IHCP: Diagnosis (Clinical)

- Intractable itching, particularly palms and soles
- NO RASH
- Patient scratching constantly during exam
- Pruritus usually precedes elevated bile acids
- May have had in a prior pregnancy
Fig. 2. Location of most severe pruritis.

Diagnosis (Laboratory)

- Total bile acids >10 (7)mmol/L
- Cholic acid >3 mmol/L
- ALT/AST > 35 U/L
- Alk ptase >200 U/L
- Occasionally (1-3%) elevated bili and clinical jaundice
Diagnosis of IHCP
Bile Acids “In’s and Out’s”

- In pregnancy, >10mmol/L is considered abnormal
- (Non-pregnant>19 mmol/L)
- If itching but nl BA, repeat in 2 wks, but treat as if IHCP!
- Cholic a. elevated first (>3mmol/L)
- CA:CDCA ratio>1.9 (most sensitive)
- BA drawn fasting or postprandial
IHCP – Maternal issues

- Increased PPH (decreased vit K?)
- Increased GBD (22% in one study)
- Generally resolves within 48 hr PP
- Not a contraindication to hormonal contraception PP
- Increased preterm birth
- Increased stillbirth
IHCP – Fetal Issues

- **IUFD**
- Mechanism unknown
  - Acute hypoxic injury at autopsy
  - Elevated BA in meconium
  - Placental vasoconstriction
  - Maternal BA > 40 umol/L predictive?
IHCP – Fetal Issues

- BA increases myometrial sensitivity to oxytocin (PTB?)
- BA increases colonic motility (meconium?)
- BA directly toxic to cardiomyocytes (sudden IUFD?)
IHCP – Fetal Issues
Data from 5 studies (n=550)

- NRFS: 8 - 14%
- Meconium: 16 - 44%
- PTB: 3 - 16%
- IUFD: 2 - 23%
- NND: 1 - 2%
Active management
No active management
<table>
<thead>
<tr>
<th>Outcome</th>
<th>IHCP (79)</th>
<th>Control (79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA (Wks)</td>
<td>38.5</td>
<td>38.8</td>
</tr>
<tr>
<td>FIL (%)</td>
<td>7.6%</td>
<td>1.3%</td>
</tr>
<tr>
<td>PTB (%)</td>
<td>14%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Mec (%)</td>
<td>44%</td>
<td>7.6%</td>
</tr>
<tr>
<td>MAS (%)</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>IUFD (%)</td>
<td>2%</td>
<td>0%</td>
</tr>
</tbody>
</table>
IHCP – Active Management

- **Fetal surveillance**
  - 2x/wk NST
  - Weekly BPP and AFI
  - FKC TID
  - Dopplers?
  - Early delivery at 37 weeks
IHCP – Active Management

- **Ursodiol**
  - Works mainly in EHC; <10% absorbed
  - Stimulates bile secretion by regulating BSEP and MRP4
  - Normalizes CA:CDCA ratio
  - Reduces BA and ALT levels
  - Rarely any side effects (diarrhea)
IHCP – Active Management

- **Ursodiol**
- Initial dose: 15 mg/kg/d ÷ BID
- If no relief: 25 mg/kg/d ÷ TID/QID
- Give enough!
IHCP - Management

- **Treatments of unproven value:**
  - Steroids
  - Vitamin K
  - SAMe
  - Anti-histamines
  - Cholestyramine
What to do for the itching?
- Anti-histamines not effective
- Steroids not effective
- Anti-histamines may allow sleep if taken in large doses at h.s.
- Eucerin cream after cool shower
- Delivery!
Clinical Characteristics (n=206)

- Maternal Age (yrs) 26.7±6.7
- Parity 2 (0-12)
  - (primigravidas (n=50) (24.4%)
- Weight (kg) 82.5±16.5
IHCP – ANMC Data (2007-2010)

- **Ethnicity (n=206)**
  - Yup’ik 43%
  - Inupiaq 31%
  - Athabaskan 7%
  - Aleut 4%
  - “Other” 15%
IHCP –ANMC Data (2007-2010)

- Clinical Characteristics (n=206)
  - GA at diagnosis (wks) 33.6±3.8
  - GA at delivery (wks) 36.9±1.5
  - Recurrence (%) 43/199 (21%)
    - (37 x1, 5 x2, 1 x4)
IHCP –ANMC Data (2007-2010)

- **Preterm Birth**: 48/198 (24%)
- **Age at PTB (wks)**: 35.1 ± 1.6
- **NICU admits**: 23 (11%)
  - no neonatal deaths
  - no MAS cases
  - 3 infants born at 37 wks (1.45%)
IHCP – ANMC Data (2007-2010)

- **Stillbirths**
- Prior IUFD: 11/195 (5.6%)
- IUFD this pg: 3/206 (1.45%)
- GA at IUFD: 36.5 wks
IHCP with IUFD – Current Group

- **Case #1**
  - 21 y/o G4P2 presented with absent FM at 38.1 wks
  - “I had itching with all my babies, and I thought it was normal, so I didn’t bother the doctor”
  - PP bile acids 79 umol/L
IHCP with IUFD – Current Group

- **Case #2**
- 20 y/o G1P0 c/o itching since 32 wks, BA not drawn
- IUFD at 36.5 wks
- “The doctors told me itching was normal in pregnancy, and that I should take Benadryl”
- PP bile acids 28 umol/L
Case #3

- 29 y/o G3P1 with pruritus at 32 wks and begun on ursodiol
- Bile acids returned normal (6.6) and itching got better, so urso stopped
- Itching resumed, BA not repeated, given Benadryl
- IUFD at 37.0 weeks
- PP bile acids 169 umol/L
Clinical Presentation
- Pruritus 99%
  - 2 pts had h/o IHCP→ asx but BA up
- Jaundice (5) 2.4%

Your guess: What was the leading identifiable dx of those pts w/ itching who didn’t have IHCP?? (_____)

IHCP-ANMC Data (2007-2010)
IHCP – ANMC Data (2007-2010)

- **Lab abnormalities (bile acids):**
  - Total bile acids (umol/L) 39±58
  - Cholic acid (umol/L) 23±45

- Normal (<10 umol/L) 39.5%
- >40 umol/L 25.4%
- >200 umol/L 4.9%
IHCP – ANMC Data (2007-2010)

- **Laboratory abnormalities**
- **ALT (U/L)** 61±94
- **AST (U/L)** 43±49
- **Alk ptase (U/L)** 221±105
- **Alk ptase >300** 22%
- **Bilirubin (mg/dL)** .58±.49
Laboratory abnormalities
- Normal ALT(<35) 61%
- Normal AST(<35) 65%
- Women w/ 1+abn lab 77%
- Women w/ no abn lab 23%

Problem:
- “pruritus gravidarum” vs. IHCP?
IHCP – ANMC Data (2007-2010)

- Neonatal outcomes
  - Weight (g) 3166±619
  - Apgar @ 5 min 9 (0-10)
  - Twins 8 sets (4%)
  - NICU admit 11% (3>37 wks)
  - Meconium 16%
  - IRDS 4%
Diagnosis of IHCP
We Need a More Sensitive Marker!

- **Candidate Lab Tests:**
  - Glutathione-S Transferase (GST)
  - Proteomic profiling
  - Gene (or gene product) testing
  - Liver ultrasound for fat?
  - Dopplers?
  - Are CPT-1 and IHCP connected??
Proteomic Biomarkers for Diagnosis

- Proteomic profiling of amniotic fluid in preterm labor. JMFNM 2008.
- Proteomic profiling of urine biomarkers of preeclampsia. AJOG 2009.
- Proteomic profiling to detect fatty liver disease. Gut 2009.
ICP and IUFD: Is the mechanism cardiac?

- IUFD is usually sudden/unexpected
- In vitro experiments with murine cardiomyocytes show an arrhythmogenic effect of bile acids
- Mechanism might be an effect on the fetal conduction system (as DM)
- Fetal PR interval prolonged in fetus with ICP
GOT QUESTIONS?