Cholestasis of Pregnancy and Perinatal Death---Can We Predict It?

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I have no financial disclosures---would welcome offers
DON'T IGNORE THEITCH

Intense itching is not normal.
It could be ICP and it could put your baby's life at risk.

Intervention, treatment and early delivery can make all the difference.

SPREAD THE WORD AND HELP SAVE A BABY'S LIFE
Intrahepatic Cholestasis of Pregnancy

- ICP (intrahepatic cholestasis of pregnancy)
- OC (obstetric cholestasis)

- “ICP is the combination of pruritis, especially of the palms and soles, dermatographia artefacta, and elevated bile salts occurring during the second and third trimesters of pregnancy”

- “Delayed diagnosis is associated with an increased risk of adverse perinatal outcome including fetal death”
Patient LI

- 17 yo G2P1 who presented for prenatal care with history of prior delivery at 37 2/7 wk GA due to ICP. Patient had pruritis, elevated LFTs. SVD resulted in 1984 gm infant without complications.

- Current pregnancy had recurrence of pruritis and elevated LFTs in the third trimester with induction and delivery at 37 4/7 wk GA due to ICP. SVD resulted in 1928 gm infant without complications.
Patient JI

- 40 yo G6 P3 presented for care with history of ICP with prior term pregnancies. Patient had been delivered previously by C/S. Patient had pruritis and elevated LFTs including elevated bilirubin during third trimester. Patient was scheduled for repeat cesarean section at 37 3/7 week GA, but called in morning of section c/o absent fetal movement. Upon arrival, IUFD diagnosed; patient had repeat C/S of 3150 gm infant with thick meconium. BTL performed.
Patient JI is mother of patient LI, and both were pregnant at the same time---2008. Very stressful event for family and staff.

Patient LI subsequent had third infant, born after onset of ICP in third trimester with pruritis, elevated LFTs and bile salts. Induction at 37 0/7 wk GA of 1531 gm infant. 3 day NICU stay for TTN.
Current Case---LI

- 26 yo G4P3 presented at 9 weeks GA for prenatal care. Other than ICP, medical history unremarkable. Labs all WNL between pregnancies, and at initial prenatal visit.

- At 20 2/7 week GA presented with intense pruritis of palms and soles and unable to sleep. LFTs mildly elevated and Bile Acids 22.1 µmo/L. Began ursodiol 300 mg BID and benadryl hs. Ultrasound demonstrated normal fetal growth.
## Patient LI  ICP Labs

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>Bile Acids</th>
<th>Bilirubin (total)</th>
<th>AST/ALT</th>
<th>Alk Phos</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 3/7 wks</td>
<td>22.1*</td>
<td>0.7 ↑</td>
<td>29/36 ↑</td>
<td>261 ↑↑</td>
</tr>
<tr>
<td>26 2/7 wks</td>
<td>169.6**</td>
<td>1.3 ↑</td>
<td>55/76 ↑</td>
<td>479 ↑↑</td>
</tr>
<tr>
<td>27 2/7 wks</td>
<td>75.8 ↑↑</td>
<td>1.6 ↑</td>
<td>122/124 ↑</td>
<td>461 ↑↑</td>
</tr>
<tr>
<td>29 4/7 wks</td>
<td>59.8 ↑↑</td>
<td>1.1 ↑</td>
<td>71/98 ↑</td>
<td>452 ↑↑</td>
</tr>
<tr>
<td>33 2/7 wks</td>
<td>31.7 ↑</td>
<td>1.0</td>
<td>47/92 ↑</td>
<td>542 ↑↑</td>
</tr>
</tbody>
</table>

*Start ursodiol 300 mg TID
** ↑ursodiol 600 mg BID, add cholestyramine 4 mg BID
Pt LI—clinical course

- Admitted at 27 1/7 wk GA due to high bile acids, increasing pruritis, darker urine. No abdominal pain.
- GI consult increased ursodiol dose and added cholestyramine.
- Patient given steroids for FLM. Began twice weekly BPP.
- Significant improvement in symptoms over next 3 weeks.
Pt LI—clinical course

- At 31 3/7 wk GA complained of decreased fetal movement. BPP 4/10 (2 pts for reactive NST, 2 pts for fluid). AFI 7.1 Patients reports nausea and vomiting x 48 hours. Notes some contractions.

- Patient admitted and hydrated. EFM showed reactive tracing without decels. Fetal movement resumed and contractions decreased.
Pt LI—clinical course

- Upon discharge, patient placed on daily NST and weekly BPP. Fetus remained reactive.

- At 34 weeks GA patient induced per clinical plan and after consultation with NN staff. Successful induction with delivery of 2230 gm infant. NICU hospitalization for > 10 days

- Patient cancelled plan PPTL as may wish another child.
Presentation and Incidence of ICP

- Incidence in US varies by ethnicity---0.3% in Delaware and Connecticut, 5.6% in east LA residents.
- Chile and Bolivia reports incidence 15-17%
- Incidence in SE Asia and China reported as 2-5%
- Incidence somewhat higher in winter months

- Usually presents in third trimester with unique pruritis (23% of all pregnant women report pruritis)
- Bile salts elevated without known biliary disease
Presentation and Incidence of ICP

- Recent study did SNP genotyping of 198 women with ICP in US and Chile
- 174 pregnant control patients were matched from each country
- Identified one locus for which Native American ancestry was associated with odds ratio of 4.48 (CI 2.21-9.06) for ICP versus controls

Theories of Etiology of ICP

- Probably some genetic favorability to developing disease
- Series of single gene/gene groups have been found in familial incidence setting for both ICP and non-gestational IC
- Modifications in progesterone metabolism may also impact biliary excretion in susceptible women

Gastroenterology 2001;12:448
Lancet 1999;353:210
Proc Natl Acad Sci USA 1998;95:282
J Hepatol 1997;27:1029
Theories of Etiology of ICP

Recent study shows that certain progesterone metabolites are increased in patients destined to have ICP

Sulfated progesterone metabolites PM2DiS, PM3S, and PM3DiS are elevated prior to development of pruritis or increase in bile salts

Ursodiol reduces level of all 3 metabolites

Summary of ICP Etiology Theories*

- Elevated levels of **reproductive hormones** unmask **genetic susceptibility** in some women leading to **cholestasis** and rising bile acids.

- **Microbiome** is now known to signal gut-liver function. Pregnancy influences microbiome. This may trigger ICP in some way.

- **Epigenetic** and **genomic-driven alterations** likely play a role but are as yet not understood.

ICP and the Placenta

- Reduced lipoprotein lipase (LPL) expression and mRNA expression of LPL significantly lower in ICP patients than controls. Impact of lipid levels of fetus uncertain.

- Certain mitochondrial DNA levels are increased in placentas of women with ICP versus controls.

Mella et al. Placenta. 2016;45:16-23
ICP and Fetal Outcome

- Multiple reports suggest high rates of prematurity, meconium-stained fluid, RDS, fetal demise
- Prematurity
  - 6-60% reported in last 20 years (spont vs iatrogenic)
  - 100% in one series
- RDS
  - Increased incidence controlled for GA
- Fetal Demise
  - 1.5-15.0% in various studies, 1.2% > 37 weeks GA
ICP and Fetal Outcome

- No studies have found a strong correlation between risk of stillbirth and bile salts, LFTs, bilirubin, pruritis

- Anecdotal reports of fetal demise have seemed to occur with high bile salt levels, however <135 micromol/L

- No studies have offered any antenatal fetal surveillance that reduces risk of stillborn
The risk of infant and fetal death by each additional week of expectant management in intrahepatic cholestasis of pregnancy by gestational age

Anela Puljic, MD, Elissa Kim, MD, Jessica Page, MD, Tania Esakoff, MD, Brian Shaffer, MD, Daphne Y. LaCoursiere, MD, Aaron B. Caughey, MD, PhD

American Journal of Obstetrics & Gynecology
DOI: 10.1016/j.ajog.2015.02.012
Puljic et al. AJOG 2015;212:667.e1-5

- Retrospective cohort study of 1.6 + million deliveries, singletons, 34-40 weeks GA 205-2008
- Utilized California Vital Statistics, Patient Discharge Data, Death Certificate Data, Fetal Death File
- Control group gravid women w/o ICP at same gestational week
- Composite mortality calculated by gestational week for each group
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ICP n=5545</th>
<th>Control n=1,598,841</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1261</td>
<td>499,457</td>
<td>27</td>
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<tr>
<td>African American</td>
<td>120</td>
<td>90,495</td>
<td>4.9</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3448</td>
<td>1,005,661</td>
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</tr>
<tr>
<td>Asian</td>
<td>1027</td>
<td>218,416</td>
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<tr>
<td>Other</td>
<td>80</td>
<td>34,890</td>
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<tr>
<td>Nulliparous</td>
<td>2376</td>
<td>734,283</td>
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<tr>
<td>Chronic hypertension</td>
<td>86</td>
<td>18,824</td>
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<tr>
<td>Diabetes</td>
<td>97</td>
<td>12,980</td>
<td>0.7</td>
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<tr>
<td>Gestational diabetes</td>
<td>652</td>
<td>116,583</td>
<td>6.3</td>
</tr>
<tr>
<td>Maternal age &gt;35 y</td>
<td>1256</td>
<td>315,916</td>
<td>17.1</td>
</tr>
<tr>
<td>Maternal age &lt;20 y</td>
<td>327</td>
<td>173,480</td>
<td>9.4</td>
</tr>
<tr>
<td>Public insurance</td>
<td>2900</td>
<td>890,568</td>
<td>48.1</td>
</tr>
<tr>
<td>Education &gt;12 y</td>
<td>2891</td>
<td>808,940</td>
<td>45</td>
</tr>
<tr>
<td>Limited prenatal care (&lt;5 prenatal visits)</td>
<td>221</td>
<td>63,558</td>
<td>3.5</td>
</tr>
</tbody>
</table>
Risk of stillbirth and infant death in women with and without ICP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stillbirth per 10,000 ongoing pregnancies (95% CI)</th>
<th>Infant death per 10,000 live births (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA, wks</td>
<td>ICP</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>ICP</td>
<td>Control</td>
</tr>
<tr>
<td>34</td>
<td>2.3 (0.0-6.2)</td>
<td>1.7 (1.5-1.9)</td>
</tr>
<tr>
<td>35</td>
<td>4.4 (0.0-9.9)</td>
<td>1.9 (1.7-2.1)</td>
</tr>
<tr>
<td>36</td>
<td>6.8 (0.0-13.8)</td>
<td>2.1 (1.9-2.3)</td>
</tr>
<tr>
<td>37</td>
<td>8.0 (0.0-16.0)</td>
<td>2.3 (2.1-2.5)</td>
</tr>
<tr>
<td>38</td>
<td>4.7 (0.0-11.9)</td>
<td>3.2 (2.9-3.5)</td>
</tr>
<tr>
<td>39</td>
<td>11.1 (0.0-25.1)</td>
<td>4.2 (3.8-4.5)</td>
</tr>
<tr>
<td>40</td>
<td>26.5 (0.0-56.5)</td>
<td>5.8 (5.2-6.4)</td>
</tr>
</tbody>
</table>
Risk of Expectant Management by Gestational Age

Deaths (per 10,000)

Gestational Age (week)

- Delivery (Infant Deaths per 10,000 Live Births)
- Expectant management (per 10,000)
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<thead>
<tr>
<th>Variable</th>
<th>ICP (n=5545)</th>
<th>Control (n=1,598,841)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GA, wks</td>
<td>Infant death per 10,000 live births (95% CI)</td>
<td>Risk of expectant management per 10,000 (95% CI)*</td>
</tr>
<tr>
<td>34</td>
<td>22.2 (10.2-34.2)</td>
<td>29.2 (15.5-43.0)</td>
</tr>
<tr>
<td>35</td>
<td>26.9 (13.5-40.3)</td>
<td>9.1 (1.4-16.9)</td>
</tr>
<tr>
<td>36</td>
<td>4.7 (0.0-10.5)</td>
<td>19.2 (7.6-30.8)</td>
</tr>
<tr>
<td>37</td>
<td>12.3 (2.4-22.3)</td>
<td>21.7 (8.5-35.0)</td>
</tr>
<tr>
<td>38</td>
<td>13.7 (1.5-26.0)</td>
<td>23.1 (7.2-38.9)</td>
</tr>
<tr>
<td>39</td>
<td>18.3 (0.5-36.2)</td>
<td>33.6 (9.5-57.8)</td>
</tr>
<tr>
<td>40</td>
<td>22.5 (0.0-50.2)</td>
<td>25.18 (0.0-54.51)</td>
</tr>
</tbody>
</table>

*Risk of SB at this GA plus risk of infant death in next week
To solely prevent mortality in ICP, delivery at 36 weeks has the lowest mortality risk; however----

Risk of RDS is 1% higher at 36 v 37 weeks GA, risk of NICU admission is 8% higher, and risk of mortality is higher at 36 v 37 weeks, thus neonatal ‘cost’ would be 10 neonates requiring respiratory support, and 80 NICU admissions to prevent one fetal death

That ‘cost’ seems reasonable until etiology and better understood and methods of fetal reassurance are developed.
Questions in regards to data???

- Is the control group the correct comparison?

- Does the composite risk underestimate fetal risk---expectant management is “2 week risk” versus “1 week risk” for intervention group

- Do bile acids levels correlate with adverse outcome risk?
Management of ICP

- Pay attention to sx of pruritis—18% of gravid patients report pruritis, but ICP unique with pruritis of palms and soles
- Incidence appears higher in patients with metabolic disorders—DM, hypertension—may also precede preeclampsia
- Presence of pruritis and elevated LFTs and bile salts confirms diagnosis
- Repeat LFTs at least every 4 weeks—also bile salts every 4 weeks*
Management of ICP

- Medical management for pruritis (and possibly stabilization of bile salts)
  - Ursodiol 200 mg TID → 600 mg BID
  - Cholestyramine 4 mg BID can further improve symptoms
  - Metformin may have benefit based upon recent case report OBG 2016;128:1320.
  - Rifampicin reduced bile salts in 2/3s of small series.
  - Hydroxyzine 25-50 mg/day may improve ability to rest
Levels of bile acids...

Managing Recurring Obstetric Cholestasis With Metformin

Elfituri, Abdullatif; Ali, Amanda; Shehata, Hassan
doi: 10.1097/AOG.0000000000001748

Levels of bile acids (A), aspartate aminotransferase (AST) (B), gamma-glutamyl transferase (GT) (C), alanine transaminase (ALT) (D), and bilirubin throughout the fifth pregnancy (E). The red line indicates the start of metformin treatment at 31 5/7 weeks of gestation. The green line indicates the time of delivery at 38 2/7 weeks of gestation. A drop in bile acids, ALT, and AST was noted after metformin treatment. However, no effect of treatment was seen on gamma GT or bilirubin. Fig. 1. Elfituri. Metformin in Obstetric Cholestasis. Obstet Gynecol 2016.
Management of ICP

- Progesterone supplementation should not be used with ICP or history of ICP
- Patients are at risk for preeclampsia and preterm labor
- Patients may have up to 60% risk of recurrence in subsequent pregnancies---
- Also increased risk (small) of chronic liver disorders later in life
Fetal Surveillance

- No method has shown benefit (small study issues)
- One author advocates admission at 34 weeks GA and continuous EFM until delivery at 35-36 weeks GA
- It is reasonable to do serial growth scans and (bi)weekly testing——MBPP. In addition to kick counts
- Based upon current data, delivery should be strongly considered at/during 36th week of gestation