Intrahepatic Cholestasis of Pregnancy

Richard H. Lee MD
Director, Maternal-Fetal Medicine Fellowship
Associate Professor of Clinical Obstetrics and Gynecology
Keck School of Medicine of USC
University of Southern California
Case

A 32 year old primigravida at 31 weeks’ gestation complains of itching all over her body for one week.

She used Calamine lotion, an OTC antihistamine, and hydrocortisone cream with no relief.
Case continued

On exam she has no rash. She has excoriations on her arms, legs, and back. She does not have jaundice and her abdominal exam is unremarkable.

She asks you for help.
Clinical features of ICP

1) Pruritus without a rash
2) 2\textsuperscript{nd} or 3\textsuperscript{rd} trimester presentation
3) Elevation in serum bile acid concentration or serum transaminases
Question:

What is the most common chief complaint with ICP?
Clinical Pearl:

Majority with ICP will state their pruritus is “all over.”

Pruritus is most severe on the soles of the feet and the palms of the hands.

Adapted from: Kenyon AP et al. Obstetric cholestasis, outcome with active management: a series of 70 cases. BJOG March 2002.
Skin changes of intrahepatic cholestasis of pregnancy vary from subtle linear scratch marks (A) to pronounced excoriations and prurigo nodules, most commonly on the shins (B); severe manifestation of intrahepatic cholestasis of pregnancy with extensive, partly superinfected prurigo nodules in a primigravida woman 5 weeks after the onset of pruritus, before ursodeoxycholic acid treatment (C), and the same patient 4 weeks after initiation of ursodeoxycholic acid treatment (15 mg/kg per day) with only postinflammatory hyperpigmentation (D).
You suspect ICP and order serum liver function tests and total serum bile acid concentration.
### Case: lab results

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total TBA concentration (μmol/L)</td>
<td>6.2</td>
<td>4.5-19.2</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>17</td>
<td>6.0-40.0</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>21</td>
<td>10.0-30.0</td>
</tr>
</tbody>
</table>
True or False?

The patient does not have ICP because she has normal TBA concentration and serum transaminases.
Clinical Pearl

The onset of pruritus may precede abnormalities in the total serum bile acid concentration or transaminases by several weeks.

Adapted from:
If a patient has the clinical symptoms of ICP and her initial labs are normal:

1) It does not exclude ICP
2) Repeat the labs, serially if necessary
You repeat the laboratory tests again in 2 weeks…

<table>
<thead>
<tr>
<th>Case</th>
<th>Value</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total TBA concentration (µmol/L)</td>
<td>12.7</td>
<td>4.5-19.2</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>20</td>
<td>6.0-40.0</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>27</td>
<td>10.0-30.0</td>
</tr>
</tbody>
</table>

She still has pruritus.

Does she have ICP?
Normal laboratory reference ranges published by your laboratory may not represent normal values in pregnancy.
LAC+USC TBA data

<table>
<thead>
<tr>
<th>Laboratory provided reference</th>
<th>Pregnancy (n=211)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBA (µmol/L)</td>
<td>≤ 19.2</td>
</tr>
</tbody>
</table>

We use a TBA concentration of >8.5 µmol/L to make the diagnosis of ICP.
You inform the patient she has ICP. She asks you what are the risks of having ICP?
Adverse effects of ICP

- Preterm birth
- Meconium passage
- Postpartum hemorrhage
- Fetal death
This risk appears higher with higher total serum bile acid concentrations.
Spontaneous preterm delivery
Meconium staining of amniotic fluid
Green staining of placenta and membranes
Asphyxial events

- TBA < 10 µmol/L
- TBA 10-39 µmol/L
- TBA ≥ 40 µmol/L

Keck School of Medicine of USC
Question:
What is the risk for fetal death in ICP?

a) 0%
b) 1-1.5%
c) 10-20%
d) 30-40%
Clinical Pearl

The risk for fetal demise with ICP is approximately 0.6-1.5%

Henderson CE et a. Primum non nocere: how active management became modus operandi for ICP. Am J Obstet Gynecol 2014 Sep; 211 (3)
TBA concentrations $\geq 100\mu$mol/L may have a much higher risk of stillbirth

<table>
<thead>
<tr>
<th>Ref</th>
<th>10-39</th>
<th>40-99</th>
<th>$\geq 100$</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brouwers et al</td>
<td>2/267 (0.9)</td>
<td>0/8 (0)</td>
<td>0/86 (0)</td>
<td>2/21 (9.5)</td>
</tr>
<tr>
<td>Kawakita et al.*</td>
<td>--</td>
<td>0/152 (0)</td>
<td>0/55 (0)</td>
<td>4/26 (15.4)</td>
</tr>
</tbody>
</table>

*Deaths at 34 1/7, 35 3/7, 35 5/7, and 37 1/7.
*Highest TBA before birth between 114-509 µmol/L
Clinical Pearl

Although adverse outcomes correlate with higher bile acid concentrations adverse outcomes are still seen with lower bile acid concentrations.
### Complications

- Fetal distress
- Respiratory distress
- Meconium aspiration
- Pneumonia
- Meconium stained amniotic fluid
- Sepsis

No fetal deaths occurred

### Table: Complications by TBA Concentration

<table>
<thead>
<tr>
<th>TBA concentration</th>
<th>Complications</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 (n=18)</td>
<td>5 (28%)</td>
<td>Ref</td>
</tr>
<tr>
<td>10-40 (n=34)</td>
<td>10 (29%)</td>
<td>1.09 (0.30-3.85)</td>
</tr>
<tr>
<td>40-100 (n=16)</td>
<td>3 (19%)</td>
<td>0.54 (0.12-3.05)</td>
</tr>
<tr>
<td>&gt;100 (n=5)</td>
<td>3 (60%)</td>
<td>3.90 (0.49-50.76)</td>
</tr>
</tbody>
</table>

Adverse outcomes occur with TBA <40 µmol/L

Fetal Death with TBA <40

Fetal Death in a Patient With Intrahepatic Cholestasis of Pregnancy

Loïc Sentilhes, MD, Eric Verspyck, MD, PhD, Patrick Pia, MD, and Loïc Marpeau, MD, PhD

- 28 week nullipara
- TBA 58 µmol/L
- AST 470 U/L, ALT 991 U/L
- Treated with cholestyramine then ursodeoxycholic acid

• Marked improvement in liver function tests
• Bile acids decreased to 13 µmol/L
• Expectant management
• IUFD at 39 weeks 3 days
• Normal non-stress test the day before
A tracing of a fetal death

- 29 year old G1 P0 at 33 ½ weeks of pregnancy
- Intense pruritus
- Serum bile acid concentration of 79 µmol/dL
- AST 62 U/L, ALT 91 U/L
- Pt complaining of contractions
- Admitted for corticosteroids

Lee RH Miller DA Incerpi MH Pathak B Goodwin TM. Obstet Gynecol 2009;113 (pt2):528-531
On admission
8 hours after admission
Fetal bradycardia not noticed for 35 minutes

The doctor is called in

Bedside ultrasound confirmed bradycardia
Delivery
Fetal death

Delivery occurred 13 minutes after confirmation by MD

Male fetus 2,465 grams Apgars 0 and 0

Thick meconium

Normal appearing fetus and placenta

Patient declined autopsy
What causes fetal death in ICP?

We don’t know
What medications are given for ICP

- Ursodeoxycholic acid
- Cholestyramine
- S-Adenosyl-L-Methionine
- Rifampin
Ursodeoxycholic acid (UDCA)

- Improves pruritus and LFTs
- Increases bile flow
- 300 mg po tid
- Not FDA approved for ICP
- FDA-class B

Clinical Pearl

No medication for ICP has reduced adverse outcomes
Is there a role for antepartum testing?

Several reports of normal non-stress tests days prior to fetal death

We utilize twice weekly antepartum testing in the rare case there may be fetal compromise leading to immediate delivery

Lee RH Miller DA et al. Obstet Gynecol 2009;113 (pt2):528-531
The patient asks you at what gestational age she should be delivered. You respond:

- a) ICP is not an indication for induction
- b) 39-40
- c) 37-38
- d) 36
- e) 34
Clinical Pearl

Deliver patients with ICP at 36 weeks’ gestation
Timing of fetal death

- 352 pregnancies
- 23 (7%) deaths (20 singletons and 3 twins)
- 18 of 20 singleton IUFDs occurred at or after 37 weeks gestation

Williamson et al. BJOG 2004;111(7):676-81
Obstetric cholestasis, outcome with active management: a series of 70 cases

Anna P. Kenyon\textsuperscript{a}, C. Nelson Piercy\textsuperscript{b}, J. Girling\textsuperscript{c}, C. Williamson\textsuperscript{d}, R.M. Tribe\textsuperscript{a}, A.H. Shennan\textsuperscript{a,\textasteriskdash}*

- Pruritus and abnormal liver function tests
- Antihistamine
- Ursodeoxycholic acid (900mg/day, max 2gm/day)
- Vitamin K (10mg daily starting 34 weeks)
- Every other day non-stress test
- Weekly AFI measurement
- Delivery at 37-38 weeks
- No fetal deaths

Kenyon et al. BJOG 2002; 109: 282-288
## USC data

<table>
<thead>
<tr>
<th></th>
<th>Mild ICP N=34</th>
<th>Moderate ICP N=39</th>
<th>Severe ICP N=49</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBA (µmol/L)</td>
<td>12.8 ± 4.5</td>
<td>28.9 ± 5.3</td>
<td>90.8 ± 49.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Meconium Passage</td>
<td>0 (0)</td>
<td>6 (15.4)</td>
<td>10 (20.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Asphyxial events</td>
<td>1 (2.9)</td>
<td>1 (2.6)</td>
<td>1 (2.0)</td>
<td>0.97</td>
</tr>
<tr>
<td>Antepartum fetal death</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2.0)</td>
<td>0.47</td>
</tr>
</tbody>
</table>

Prospective cohort data

- ICP and TBA >40 µmol/L
  - Fetal death rate 1.5% (10/669)
  - 6 of 10 deaths occurred before 37 weeks’ gestation
  - Median 36 wks ± 2 days
  - Median TBA 137µmol/L
Infant death per 10,000 live births with ICP
Risk of expectant management per 10,000 with ICP

Question:

Are there times you offer delivery prior to 36 weeks’ gestation?
Delivery prior to 36 weeks’

1) TBA concentration >100µmol/L at any point
2) Prior IUFD from ICP with recurrent ICP
3) Unbearable pruritus
4) Jaundice or abnormalities in coagulation profile

Discuss:
- Risks of prematurity
- Lack of substantial data that delivery outweighs risks of prematurity
- Limits of amniocentesis
Key learning points

1. Most common presentation is a complaint of total body itching
2. Pruritus may precede biochemical abnormalities by several weeks
3. Risk of fetal death is 1.2-1.5%
4. Risk of fetal death may be higher with bile acids above 100µmol/L
Key learning points

5. Ursodeoxycholic acid
6. No medication has been shown to reduce adverse outcomes
7. Deliver at 36 weeks of gestation
8. Delivery before 36 weeks in select cases