ICP

- jaundice in pregnancy
- recurrent jaundice in pregnancy
- idiopathic jaundice of pregnancy
- obstetric hepatosis
- hepatosis gestationalis
- obstetric cholestasis
History

- 1883 Ahlfeld
  - Recurrent jaundice in pregnancy that resolved following delivery

- 1950s
  - Severe pruritus with or without jaundice reported
  - Resolution after delivery
  - High recurrence rate

Current Definition

- pruritus with onset in pregnancy
- associated with abnormal liver function in the absence of other liver disease
- resolves following delivery
Epidemiology

- Geographic variation
  - Most common in South America
    - particularly Chile and Bolivia - 5-15%
    - Scandanavia 2%
    - USA and other European countries <1%
  - More common in winter months
- Twins
- IVF

Maternal Presentation

- Usually occurs in 3rd trimester
  - 80% after 30 weeks
  - But has been reported as early as 8 weeks
- Pruritis
  - Often generalized
  - Predominates on palms and soles of feet
  - Worse at night
Maternal Presentation

- Deranged LFTs
  - Elevated bile acid
- Jaundice – 10-15%
- Coagulation usually normal
  - Subclinical steatorrhoea → Vit K deficiency
- Resolves postpartum
  - LFTs normalize within 2-8 weeks

Fetal Concerns

- Meconium stained fluid
- Preterm birth
- FHR abnormalities
- Stilbirth
Meconium Staining of Amniotic Fluid (MSAF)

- 15% among normal pregnancies
- 15-68% in ICP
- Among IUFD cases – meconium staining 100%
- The frequency of MSAF is greater in pregnancies with higher levels of maternal serum bile acids

MSAF and Bile acid

Greene et al 2009
World J Gastro 2009 May;15(17):2049-2066
Preterm Labor

- Most report a rate of 30-40%
- More recent studies report higher rate of iatrogenic preterm delivery
  - Studies 1988-1990 – 7%
  - Studies 1999-2001 – 11%
  - Studies 1999-2003 – 22%

Rate of PTB and Bile acid

Greene et al 2009
World J Gastro 2009 May7;15(17):2049-2066
Respiratory Distress Syndrome

- Zecca et al
  - Demonstrated there is increased risk of RDS with ICP in a retrospective cohort study
  - Further confirmed high levels of bile acids in the broncho-alveolar lavage of 10 infants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP</td>
<td>2.578 (1.445–4.600)</td>
<td>.001</td>
</tr>
<tr>
<td>Gestational age</td>
<td>0.826 (0.700–0.975)</td>
<td>.024</td>
</tr>
<tr>
<td>Males</td>
<td>1.682 (1.031–2.743)</td>
<td>.037</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>1.368 (0.683–2.740)</td>
<td>.377</td>
</tr>
</tbody>
</table>


**FHR Abnormality**

- Antepartum and intrapartum
- Reduced fetal heart rate variability, tachycardia and bradycardia (< 100 bpm)
- More recently, a case report has described fetal tachyarrhythmia (220-230 bpm) leading
IUFD

- Older studies 10-15%
- Newer studies <3.5%
- Seems to cluster around 37 weeks

Greene et al. 2009
World J Gastro 2009 May;15(17):2049-2066
IUFD

- Thought to be increased with bile acid level
- Glantz et al find fetal complication rate increased with bile acid <40 µmol/dL
  - Analysis done for PTB, MSAF and “asphyxial event”
  - Same study has 3 IUFD – one of which bile acid was 27 µmol/dL
- Other case reports IUFDs with lower bile acid levels of 21 and 15 µmol/dL

Investigations

- Liver Function Tests
- AST & ALT
  - Transaminases located with hepatocytes. Elevations indicative of damage
  - May precede elevation of bile acid
  - ALT thought to be more sensitive (2-10x more increase than AST)
  - NOTE normal values in pregnancy are 20% lower than non-pregnant women
LFTS

- **Bilirubin**
  - Tends to be normal
  - If elevated, more likely to be conjugated

- **GTT**
  - Most likely normal
  - If elevated, more severe disease

- **Alkaline phosphatase (ALKP)**
  - May increase
  - Placental isoforms limit its use

LFTs

- **Bile acids**
  - Cholic acid (CA) and Chenodeoxycholic acid (CDCA). Both are end products of cholesterol metabolism.
  - In normal pregnancy
    - CDCA same
    - CA ? Increase
    - Overall should still be < 1.5 µmol/dL
Bile Acid in ICP

- Most suitable marker
- Upper limit of normal 10-14 µmol/dL
- No consensus if rise precedes symptoms
- Fetal bile acid also increased
- No consensus if fasting value is better

Other Investigations

- Liver Ultrasound
  - Gallstones more common (up to 13%)
  - Probably not causal
- Liver biopsy
  - Rarely necessary
  - Cholestasis without inflammation, and bile plugs in hepatocytes and canaliculi predominate in zone 3
Etiology of Maternal Disease

- Not well understood
- Genetic component
  - Ethnic and geographic variation
  - Relative risk for parous sisters of affected women is 12
  - Insights into the genetic etiology come from studies of the familial cholestasis syndromes progressive familial cholestasis (PFIC) and benign recurrent cholestasis (BRIC).

Genes associated with ICP

- ABCB4 gene
  - Most studied in ICP
  - Encodes the multidrug resistance protein 3 (MRP3)
  - Homozygous mutations result in a spectrum of phenotypes that include PFIC type 3 and cholelithiasis
  - 1999 heterozygous single nucleotide deletion (1712 delT)
  - ABCB4 haplotype which is associated with the "severe" phenotype of serum bile acids > 40 µmol/L.
Genes associated with ICP

- **ABCB11 gene variation**
  - bile salt export pump (BSEP)
  - BSEP is located exclusively in the hepatocyte canalicular membrane and is the primary export pump for bile acids

- **ABCC2 gene variation**
  - encodes the multidrug resistance related protein 2 (MRP2)
  - MRP2 exports organic anions including bilirubin into the bile

- **NR1H4 variation**
  - Encodes farnesoid X receptor
  - responsible for the regulation of bile acid synthesis and transport within the liver

Hormonal Factors

- More common in multiple than singleton pregnancies (20.9% vs 4.7% in one study)

- Symptoms may recur in a subgroup of affected women when taking the combined oral contraceptive pill

- Symptoms of ICP in the third trimester when estrogen and progesterone levels are highest
Hormonal Factors

- **Estrogen**
  - Depot estrogen increase bile acid level
  - In vitro, 17-β-estradiol glucuronide to rats causes endocytic internalization of BSEP

- **Progesterone**
  - Bacq 1995 observed a high rate of ICP among pregnant women on natural progesterone
  - May be due to build up of metabolites
    - Increase level of disulfated progesterone seen in maternal urine and cord blood
    - In vitro progesterone metabolites decrease bile flow in rat

Environmental factors

- **Selenium**
  - Lower levels seen among ICP vs control
  - Low dietary intake in Finland and Chile

- **Seasonal**
  - More common in Winter in Scandanavia and Chile
  - Interestingly selenium is higher in summer months

*Reyes H et al Selenium, zinc and copper plasma levels in intrahepatic cholestasis of pregnancy normal pregnancies and in healthy individuals, in Chile Hepatol 2000; 32: 542-549*
What makes the skin itch?

- Bile acid
  - Levels do not correlate well with symptoms
  - Onset of pruritis precede lab abnormalities

- Sulfated progesterone metabolites
  - UCDA decreases its excretion which correlates better to resolution of symptoms

Etiology of Fetal Problem

- Probably related to bile acids levels
  - Glantz et al showed bile acid levels correlate well with fetal complications
  - 1-2% increase risk of (PTL/MSAF/asphyxia) for every µmol/dL increase in bile acid levels

- Related to duration of exposure
  - Ozetkin el at 2009
  - Both level and duration of exposure to BA is associated with “fetal asphyxia”
Etiology of Fetal Problem

- Meconium
  - Injection of cholic acid caused MSAF in lambs
  - ? Stress
  - Bile acid also increases bowel motility

- Abnormal EFM
  - Cholic acid cause less contractions in rat cardiomyocytes

- Preterm delivery
  - Rodent myometrium increases contractility with bile acid
  - CA infused lamb deliver early
  - Some obervation of increased response to pitocin among patients with ICP

- RDS
  - Bile acid related
  - ? bile acids in the fetal circulation cause a reversal of the action of phospholipase A2, thereby causing the degradation of phosphatidylycholine and a lack of surfactant.
Etiology to Fetal Problem

- IUFD
  - Poorly understood
  - Usually normally growth fetus
  - 100% MSAF among stillbirth
    - Meconium (but not heat treated meconium) can cause vasoconstriction in placental and placental vessel
    - Placental vasocinstriction due to MSAF or bile acid


Management Options

- Fetal Monitoring
  - Many reported cases of normal NST or fetal movement hours preceding a demise
Management Options

- Elective delivery
  - Delivery at 37-38 weeks
  - ? Later if bile acid < 40 µmol/dL
- Amniocentesis to check lung maturity
  - But RDS is more common
  - Reports of severe RDS despite reassuring FLM among ICP cases
- No good evidence to guide management
Medications

- Ursodeoxycholic acid (UDCA)
  - UDCA stimulates biliary secretion by post-transcriptional regulation of BSEP and the alternative exporters MRP4 and MRP3.
  - It has antiapoptotic effects on hepatocytes
    - To reduce the mitochondrial membrane permeability to ions and cytochrome c expression.
  - Lowers serum levels of a major cholestatic metabolite of estrogen - ethinyl-estradiol 17α-glucuroniden

**UCDA**

**Dosing**
- The starting dose 300 mg twice daily.
- If symptoms persist after 1 week, the evening dose can be increased to 600 mg.
- If symptoms still persist, the total daily dose can be increased to 600 mg twice daily.

**Gantz et al 2005**
- Double blinded RCT
- UCDA vs Dexamethasone vs placebo
- Treatment group UCDA 1g/day for 3 weeks
- Treatment group Dexa 12g/day for 1 week then placebo for 3 weeks
- N=130
- Underpowered (supposedly need 240 to detect 33% decrease in fetal complications)
UCDA

Results

- UDCA reduced ALT and bilirubin, but not bile acids or pruritus, in women with ICP.
- In patients with bile acid levels exceeding 40 mol/L, treatment with UDCA was more effective in alleviating pruritus and reducing bile acids, aminotransferases and bilirubin, compared with treatment with dexamethasone and placebo.

Intrahepatic cholestasis of pregnancy: A randomized controlled trial comparing dexamethasone and ursodeoxycholic acid

Hepatology
Volume 42, Issue 6, pages 1399-1405, 29 Nov 2005 DOI: 10.1002/hep.20952
UCDA vs Dexa vs Placebo

Currently there is no direct evidence that UCDA improves fetal outcomes

Need bigger study to detect differences

Indirect evidence

- UDCA treatment has been shown to reduce the bile acid level in cord blood, amniotic fluid and colostrum
- It reduced cord blood bilirubin levels in one study
- UDCA also protects cardiomyocytes from bile acid-induced arrhythmias in an in vitro model

Table 2A. Fetal Complication Rates and Outcomes of Pregnancies: ITT Analysis

<table>
<thead>
<tr>
<th></th>
<th>All Included n = 130</th>
<th>UDCA n = 47</th>
<th>Desmopressin n = 36</th>
<th>Placebo n = 47</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm delivery</td>
<td>24 (18.5%)</td>
<td>8 (17%)</td>
<td>9 (25%)</td>
<td>7 (14.9%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Asphyxia</td>
<td>8 (6.2%)</td>
<td>2 (4.3%)</td>
<td>4 (11.1%)</td>
<td>2 (4.3%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Meconium passage</td>
<td>46 (36.9%)</td>
<td>18 (38.3%)</td>
<td>13 (36.1%)</td>
<td>17 (34%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Green staining of placenta/membranes</td>
<td>31 (23.8%)</td>
<td>14 (29.8%)</td>
<td>8 (22.2%)</td>
<td>9 (19.1%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Pretermity, total</td>
<td>34 (26.2%)</td>
<td>12 (25.6%)</td>
<td>11 (30.6)</td>
<td>11 (23.4%)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Elective delivery, total</td>
<td>45 (34.4%)</td>
<td>15 (31.9%)</td>
<td>12 (33.3%)</td>
<td>18 (38.3%)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Table 2B. Fetal Complication Rates and Outcomes of Pregnancies: Subanalysis of ICP Women With Bile Acids ≥40 μmol/L

<table>
<thead>
<tr>
<th></th>
<th>All n = 36 (%)</th>
<th>UDCA n = 12 (%)</th>
<th>Desmopressin n = 11 (%)</th>
<th>Placebo n = 11 (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm delivery</td>
<td>12 (35.3)</td>
<td>4 (33.3)</td>
<td>3 (27.3)</td>
<td>5 (45.5)</td>
<td>n.s.</td>
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<tr>
<td>Asphyxia</td>
<td>2 (5.9)</td>
<td>0</td>
<td>1 (9.1)</td>
<td>1 (9.1)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Meconium passage</td>
<td>17 (41.1)</td>
<td>6 (50)</td>
<td>4 (36.4)</td>
<td>5 (45.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Green staining of placenta/membranes</td>
<td>15 (41.1)</td>
<td>6 (50)</td>
<td>4 (36.4)</td>
<td>7 (63.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Pretermity, total</td>
<td>17 (41.1)</td>
<td>6 (50)</td>
<td>4 (36.4)</td>
<td>7 (63.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Elective delivery, total</td>
<td>12 (35.3)</td>
<td>5 (41.7)</td>
<td>3 (27.3)</td>
<td>4 (36.4)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>
Medications

- **Dexamethasone**
  - Evidence conflicting
  - RCT showed not effective

- **Cholestyramine**
  - 8-16g/day
  - Binds to bile acid in gut thereby increasing fecal excretion
  - Helps pruritis but does not affect bile acid or LFTs
  - May decrease fat soluble vitamins eg Vit K

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Medications

- **SAMe**
  - RCT SAMe vs UCDA (1)
    - SAMe 500mg BID / UCDA 300mg BID
    - UCDA is more effective than S-adenosyl-l-methionine at improving the concentration of serum bile acids and other tests of liver function,
    - both therapies are equally effective at improving pruritus.
  - RCT SAMe +UCDA (2)
    - Combo is more effective

Medications

- Topical
  - aqueous cream with 2% menthol (Dermacool)
  - Camphor/menthol (SARNA)
- Vitamin K
  - ICP is associated with malabsorption of Vitamin K – hence theoretical risk of hemorrhage in newborn and mother
  - No evidence to support or refute this practice

Summary

- ICP is associated with risks with the mother and more so to the fetus
- The pathophysiology of ICP is still not well
  - Multifactorial: genetic, hormonal, environmental
- UCDA is the drug of choice
- So-called “active management” is associated with better outcome
  - Based on currently available data, an evidence-supported approach for antenatal care and timing of delivery is not available