Intrahepatic Cholestasis of Pregnancy

Danny Wu MBChB
Kaiser Permanente
10/2011

ICP

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

Outline

- Epidemiology
- Clinical Presentation
- Risks
  - Maternal
  - Fetal
- Investigations
- Possible Etiologies
- Management Options
History

- 1883 Ahfeld
  - Recurrent jaundice in pregnancy that resolved following delivery
- 1950s
  - Severe pruritis 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%
    - Scandinavia 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
- Stillbirth

**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**

![Graph showing the relationship between MSAF and bile acid levels.](image)

Greene et al. 2009
World J Gastro 2009 May;7(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%

Respiratory Distress Syndrome

- Zecca et al
  - Demonstrated there is increased risk of RDS with ICP in a case-controlled study
  - N=77 with 427 controls
  - Rate of RDS was 28.6% vs 14%
  - Further confirmed high levels of bile acids in the broncho-alveolar lavage of 10 infants with RDS and ICP

Rate of PTB and Bile acid


ICP and RDS

<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>

RDS and ICP


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 to atrial flutter

IUFD

- Older studies 10-15%
- Newer studies <3.5%
- Seems to cluster around 37-39 weeks

IUFD

Greene et al 2009
World J Gastro 2009 May;7(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 phenotypes related to PFIC type 3 and cholelithiasis
  - 1999 heterozygous single nucleotide deletion (1712 del T)
  - ABCB4 haplotype is associated with the "severe" phenotype - bile acids > 40 µmol/L
Genes associated with ICP

- ABCB11 gene variation:
  - BSEP (bile salt export pump) is located exclusively in the hepatocyte canalicular membrane and is the primary export pump for bile acids.
- ABCC2 gene variation:
  - Encodes MRP2 (multidrug resistance related protein 2) which 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.

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.

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 \( \mu\text{mol/dL} \) increase in bile acid levels
- Related to duration of exposure
  - Ozetkin et al 2009
  - Both level and duration of exposure to BA is associated with “fetal asphyxia”

- Meconium
  - Injection of cholic acid caused MSAF in lambs
  - Stress
  - Bile acid also increases bowel motility
- Abnormal EFM
  - Cholic acid decreases contractility of rat cardiomyocytes

Etiology of Fetal Problem

- Preterm delivery
  - Rodent myometrium increases contractility with bile acid
  - CA infused lambs deliver early
  - Some observation of increased response to pitocin among patients with ICP
- RDS
  - Bile acid related
  - Bile acids in the fetal circulation
    - reversal of the action of phospholipase A2
    - the degradation of phosphatidylcholine and a lack of surfactant
Etiology to Fetal Problem

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


Management Options

- Fetal surveillance
- Early delivery
- Medications

Management Options

Fetal Monitoring

- Many reported cases of normal NST or fetal movement hours preceding a demise

Lee R et al (Obstet Gynecol 2009;113:528-31)
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

IUFD

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
    - By reducing the mitochondrial membrane permeability to ions and cytochrome c expression.
  - Lowers serum levels of a major cholestatic metabolite of estrogen - ethinyl-estradiol 17α-glucuronide

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.

UCDA

- 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)

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 Dexamethasone vs Placebo

Fetal Outcomes
UCDA

- 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

Medications

- Dexamethasone
  - Evidence conflicting
  - RCT showed not effective

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

Medications

- SAMe (S-adenosyl-L-methionine)
  - RCT SAMe vs UCDA (1)
    - SAMe 500mg BID / UCDA 300mg BID
  - UCDA is more effective than SAMe 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

  1) Roncaglia N et al. BJOG. 2004;111(1):17-21

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