Intrahepatic Cholestasis of Pregnancy

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Disclosures

• I have no relevant financial relationships to disclose or conflicts of interest to resolve.

• I will not discuss any unapproved or off label, experimental or investigational use of a product, drug, or device.
Intrahepatic Cholestasis of Pregnancy

• Typically occurs in the second and third trimesters
• Characterized by:
  – Pruritus and elevation in serum bile acid concentrations
• Wide variation of incidence geographically
• ICP is increased in Bolivia and is highest among the Araucanos Indians in Chile
  – 5.5% overall; 14% recurrence
• “We propose that an ethnic predisposition to develop intrahepatic cholestasis of pregnancy is present in Araucanian women and that the high prevalence of the disease in Chile is mainly influenced by ethnic admixture with this South American Indian (ethnic) group”
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Pathogenesis

• **Cause is unknown**

• Hypothesized that multiple factors involved:
  
  – Genetic:
    
    • ABCB4 gene mutations found in familial cases. Found in up to 16% Caucasian cases
  
  – Hormonal:
    
    • Estrogen: induces cholestasis clinically and experimentally. Higher levels and prevalence in twins; 20.9 v. 4.7% J Hepatol Gonzalez MC et al; 1989.
    
  
  – Environmental
    
    • Seasonal effect on prevalence in Scandinavia and Chile
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Epidemiology

• Sweden
  • 1.2 million births reviewed
  • 1997-2009
  • Incidence of 1/200
  • women with ICP more likely to have GDM (aOR, 2.81) and pre-eclampsia (aOR 2.62), spontaneous (aOR 1.60) and iatrogenic (aOR 5.95) preterm delivery, however, this actively managed cohort of ICP cases was not at increased risk of stillbirth (aOR 0.92, 95% CI 0.52-1.62). Infants in ICP deliveries were more likely to have a low (<7) 5-minute Apgar score (aOR 1.45) and be LGA at birth (aOR 2.27).

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Epidemiology

• USA
  – **Bridgeport Hospital**
    – Jan ‘97-August ‘99
    – 0.32% of live births
    – Mean EGA at sx onset: 31 wks (13-38.4)
  – **Los Angeles**
    – Latina population
    – LA County / USC
    – Third trimester L and D admits had blood drawn for bile acids (1-580 micromol/l; mean 10.4)
    – N=340
    – 7.1% >20 micromol/l
    – 19.7% pruritis score >4
    – Prevalence of ICP was 5.6%; 19/340
    – Higher rates of chorio and thick mec
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Clinical Manifestations

• Typically initiates with intense pruritis
• Generalized, but palms and soles predominate
• Worse at night
• Symptoms may present prior to lab abnormalities
• Encephalopathy, abdominal pain or other stigmata of liver failure unusual

• Physical Exam
  – Excoriations
  – Jaundice <10% cases
    • Jaundice without pruritis: Search for other etiology
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Laboratory Evaluation

- Serum Total Bile Acid concentrations INCREASE w/ ICP
- May be only lab finding
- Cholic acid > Chenodeoxycholic acid
  - Elevated ratio
  - Obtaining ratio does not enhance diagnostic accuracy
- Alk phos, 5’nucleotidase, total and direct bili
  - May be elevated
- Bilirubin: typically <6 mg/dl
- GGT / gamma-glutamyl transpeptidase
  - Normal or at most modest elevation
- Aminotransferases also may increase to levels >1000 u/L
  - Must rule out hepatitis
- PT typically normal
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**DIAGNOSIS**

- Diagnosis based on presence of
  - Pruritus ASSOCIATED WITH
    - Elevated total serum bile acids
    - AND/OR
    - Elevated Aminotransferases
    - AND
    - Absence of disease that may produce similar findings
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Treatment

• Goals:
  – Reduce symptoms
  – Prevent maternal and fetal complications
• Ursodeoxycholic Acid
  – Most promising treatment
  – Increases bile flow
  – Has been used to treat other cholestatic disease
    • Primary biliary cirrhosis
  – Found to:
    • Improve pruritus and liver tests
    • No adverse perinatal effects
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Treatment / Ursodeoxycholic acid

• Meta-analysis support use
  – 9 RCTs evaluated / pooled
  – 454 Urso treated patients
  – Better outcomes than alternative treatment
    • Cholestyramine, dexamethasone, S-adenosyl-methionine
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Treatment / Ursodeoxycholic acid

Maternal Clinical and Biochemical Parameters

Bacq Y et al. Gastroenterology 2012
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Treatment / Ursodeoxycholic acid

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Treatment / Ursodeoxycholic acid

• IUFD x 2: Both in PLACEBO groups

• 3 Conclusions:
  – 1. UDCA improves pruritis symptoms and liver tests in women with IHCP
  – 2. Suggest improved perinatal outcomes
  – 3. Confirms previous reports of safety

Bacq Y et al. Gastroenterology 2012
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Treatment / Ursodeoxycholic acid

- 84 symptomatic patients randomized
  - UDCA vs. cholestyramine x 14 days
  - Pruritus onset average 31-32 weeks.
  - Treatment started approx 34 wks
  - Pruritus reduced more effectively in the UDCA group vs. Cholestyramine
  - More term deliveries w/ UDCA
  - LFTs and Bile Acid levels improved more in the UDCA group.
  - No adverse UDCA effects
  - 12 pts with treatment related adverse effects with cholestyramine

Kondrackiene J et al. Gastroenterology 2005
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Treatment / Ursodeoxycholic acid

• Other study findings:
  – Treatment restores serum bile acid composition
  – Meconium bile acid concentrations not affected by maternal UDCA tx
  – UDCA restores transport capabilities of the placenta which are altered in pts with ICP
  – Normalizes serum bile acid pattern in babies
  – Low accumulation of UDCA in AF and cord blood even w/ high doses
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Ursodeoxycholic acid

- Therefore, UDCA considered FIRST LINE THERAPY
- Optimal dose to be determined
- Typically prescribed at 300 mg TID until delivery
- Individualize Adjunct Meds Controversial:
  - Hydroxyzine, Cholestyramine, SAMe, Rifampicin
- Disappointing results with DEX, phenobarbital, charcoal, UV light
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Maternal Prognosis

- Maternal prognosis is good
- No increased risk for PPH
- No routine assessment of coagulation required
- No routine use of Vit K
- Pruritus typically resolves first few days after delivery with normalization of bile acids
- Possible increased risk for sequelae:
  - Gallstones, hepatitis, fibrosis, cholangitis
- Follow labs through 6 wk postpartum for resolution; otherwise refer GI
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Maternal Prognosis

- 1973-2009 Swedish Birth Registry
- 11,388 women w/ ICP vs. 113,893 controls
- RR 2.62 for later hepatobiliary disease
- RR 5.11 for Hep C / Chronic hepatitis
- RR 2.72 for gallstone disease or cholangitis
- “Women w/ ICP substantially increased risk for later hepatobiliary disease....advocate for Hep C testing in women with ICP.”
- RR 3.6 liver and biliary cancer
- RR 1.3 Immune-mediated diseases (DM 1.47, thyroid 1.30, psoriasis 1.27, arthritis 1.32, Crohn’s 1.55
- RR 1.12 CV disease in ICP women w/ preeclampsia
Hormonal Contraception

• Combination pill rarely results in recurrent cholestasis
• Low dose estrogen OCP not contraindicated
• Acceptable choice per CDC
• If cholestasis thought due to estrogen effect, choose progestin only contraceptive or alternative.
• ICP not a contraindication to breastfeeding
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Recurrence Risk

• 60-70% recurrence risk
• Variable in severity
• Increased cholelithiasis risk with recurrent disease
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Fetal Prognosis

- Significant risk of adverse fetal outcomes
- PREMATURITY: 6-60%
  - sPTB, IOL, Twins
  - Earlier onset of pruritus noted w/ sPTB
- MECONIUM STAINED AF
- IUFD
- RDS
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Fetal Prognosis

• SPONTANEOUS FETAL DEATH
• After excluding other attributable causes of IUFD:
  -- Preeclampsia, DM, IUGR, anomalies
• RISK OF FETAL DEMISE
  -- 1.2%
• Higher risk likely with higher bile acid levels
• Higher risk likely with advancing EGA
  -- Series of 20 IUFDs and ICP, median EGA at IUFD was 38 wks; only 2 IUFD <37 wk.
• Pathophysiology of IUFD:
  -- Bile acid induced Arrhythmia vs. Vasospasm
• No perfect protocol of antepartum testing surveillance for ICP
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Fetal Prognosis

• BILE ACID LEVELS:
• N= 693 ICP women
• Fetal complications = PTD, asphyxia, mec
  – Probability directly related to bile acid levels
  – Statistically increased at >40 micromol/L
• IUFD RISK
  – Greatest risk at >100 micromol/L
  – 10-15%
• IUFD reported at <40
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IUFD

- UK OB SURVEILLANCE SYSTEM
- > 2,000 healthy controls
- 713 ICP cases: Pruritus AND Bile Acid >40
- Largest prospective cohort study
- Incidence 9.2/10,000 deliveries
- Outcome evaluated:
  - PTD, IUFD, NICU admit
- >75% pharmacologic therapy
- 87% had FHR monitoring
- 65% growth ultrasounds

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669 ICP singletons v. controls

All adverse outcomes increase with rising bile acids

1.5% v. 0.5%

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IUFD

• 6/10 Stillbirths occurred before 37 wks
• Median EGA at delivery 36 2/7 wks
  – Vs. 30 5/7 wk in controls
• Not SGA
• 3 were LGA; none w/ GDM
• Among ICP IUFDs; Bile Acid Median 137
  – Vs. 72 among ICP Livebirths

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Antepartum Testing

- Value to prevent IUFD w/ ICP unproven
- No increase in abnormal tests among those who did have IUFD
- Reports of IUFD within few days of reactive NSTs
- Likely a sudden event rather than chronic placental vascular pathology
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Timing of Delivery

- Balancing the risks
  - Fetal Death
  - Prematurity
- General consensus: Deliver at 36 – 36 6/7 wks
- Deliver at diagnosis after 37 wk
- No amnio recommendation
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Timing of Delivery

- Determine the risk of perinatal mortality (IFUD + infant death) stratified by ega of 34-40 wks
- The risk of infant and fetal death by each additional week of expectant management in intrahepatic cholestasis of pregnancy by gestational age
- California birth database 2005-2008
- 1,604,386 singleton nonanomalous pregnancies between 34-40 wks w/ and w/o ICP
- Risk of IUFD evaluated
  - Puljic A et al. AJOG 2015
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Timing of Delivery

• Among women with ICP
  – Risk of delivery is lower than risk of expectant mgmt at 36 weeeks
    • 4.7 v. 19.2 / 10,000
  – Risk of expectant mgmt remains higher than delivery and continues to rise by week of gestation beyond 36 wks.
    – Risk of expectant mgmt is lowest at 35 wks (9/1/10,000) and rises at 36 wk (19.2/10,000)
• Conclusion: delivery at 36 wks would reduce the perinatal mortality risk as compared with expectant management.

Puljic A et al. AJOG 2015
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Timing of Delivery

- **Considerations** for delivery PRIOR TO 36 wks
- Individualization of therapy
- Extensive counseling regarding risks/benefits/lack of data
- As long as possible beyond 34 wks
- Antenatal steroids
  - Unrelenting severe pruritus not responsive to pharmacotherapy
  - Jaundice
  - Past hx of IUFD prior to 36 weeks w/ recurrent ICP in current pregnancy
  - Total Serum Bile Acids >100 micromol/L
• 2nd/3rd TMs
• Pruritus + Elevated Bile Acids
• Increased risks for fetal morbidity and mortality
• Good maternal prognosis but some increased long-term risks
• Tx goal is pruritus reduction and prevention of complications
• Ursodeoxycholic acid is first line therapy
• Delivery at 36 wks
• Reevaluate Bile Acids and LFTs 6-8 wk postpartum
• 60-70% recurrence risk