Diagnosis and Management of Cholestasis

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PREGNANCY CARE ECHO

Intrahepatic cholestasis of pregnancy (ICP)- Definition

- Itching withOUT rash
- Elevated serum bile acids (≥ 10 µmol/L)

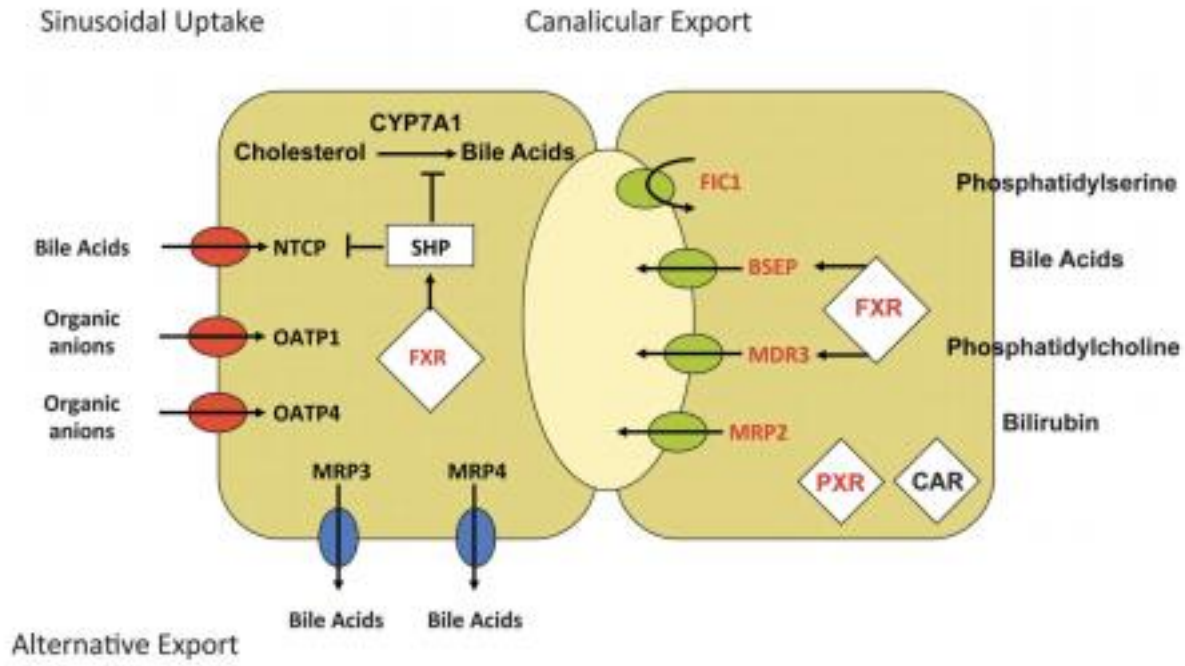
Epidemiology of ICP

- Incidence varies widely (0.1 to 15.6%)
  - In the US, 0.32-5.6%
- More common in certain ethnic groups→ Latina women
- More common in certain geographical areas→ Chile, Bolivia, Scandinavia

Pathogenesis of ICP

- **Genetic factors**→ ABCB4, ATP8B1, and ABCB11 genes found in women with ICP.
- **Hormonal factors**→ Estrogens are known to be involved as evidenced by higher incidence in twin pregnancies and increasing incidence as gestation advances.
- **Hormonal factors**→ Progesterone may saturate hepatic transport receptors for biliary excretion of bile acids.
- **Environmental factors**→ Seasonal variability has been established in some countries with higher incidence during colder months.

Pathogenesis of ICP



Risk factors for ICP

- **Previous pregnancy with ICP**
- Family history of ICP
- **Multiple gestation**
- **Underlying liver disease**
- Pregnancy conceived with fertility treatments
- **Latina women**

Differential diagnosis of ICP

Differential	Presentation	Distinguishing features
Pruritus gravidarum	Pruritus in 3rd trimester	No abnormal laboratory values
Atopic eruption	Pruritus in 1st trimester	Dry, red rash on trunk and limbs
Pruritic urticarial papules and plaques of pregnancy (PUPPS)	Pruritus in 3rd trimester	Papules, plaques, or vesicles in striae, sparing umbilicus
Pemphigoid gestationis	Pruritus in 2nd or 3rd trimester	Large, tense blisters, auto-immune with IgG antibodies
Prurigo of pregnancy	Pruritus in 3rd trimester	Red-brown papules on abdomen or limbs
Pruritic folliculitis of pregnancy	Pruritus in 3rd trimester	Acneiform eruption of shoulders, back, limbs, may be filled with pus
Psoriasis	Pruritus at any time, mostly painful	Erythematous plaques with silver scale

WILLIAMSON, ET AL. 2014

Making the diagnosis of ICP

- **Pruritus typically in the third trimester**
  - **Palms and soles** classically, but can be diffuse
- **No rash**
- Elevated serum **bile acid levels (≥ 10 µmol/L**)
  - May also have elevated hepatic transaminases
- On ultrasound (not necessary) liver and bile ducts appear normal

Laboratory findings with ICP

- **Elevated serum bile acids (≥ 10 µmol/L)**
  - May be only finding
- **Elevated hepatic transaminases**
  - May proceed abnormal bile acid levels
  - May exceed 1000 U/L
  - No evidence of coagulopathy
- **Elevated alkaline phosphatase**
  - Not specific due to elevated levels in pregnancy
- **Elevated total bilirubin**

Implications of bile acid levels

- Common classification for bile acids:
  - **Mild 10-39 µmol/L**
  - **Moderate 40-99 µmol/L**
  - **Severe >100 µmol/L**
- Most adverse pregnancy outcomes are seen at levels >40
- Stillbirth seems to be increased at levels >100

GLANTZ, ET AL, 2004. KAWAKITA, ET AL, 2015.

Treatment for ICP- Ursodeoxycholic acid (Ursodiol, Actigall, or UCDA)

- Increases bile flow and thus may increase excretion of bile acids
- Shown in a Cochrane review to be the most useful drug for decreasing maternal pruritus
- May decrease hepatic enzymes, bile acids, and bilirubin levels
- Dose:
  - Starting- 500mg PO twice daily
  - Max- 2g per day
- Fetal concentration remains low even with high doses

Treatment for ICP- other drugs

- All current therapies primarily aimed at decreasing maternal itching:
  - Hydroxyzine: Anti-histamine; 25-50mg/day
  - Cholestyramine: Bile acid eliminator; 8-16g/day
  - Rifampicin: Antibiotic with choleretic properties; reduces severe bile acid elevation; needs further study
    - May work better when combined with UCDA
  - Steroids (dexamethasone): Decreases itching, but may not improve bile acids; dosing variable
- **UCDA is current recommended first-line therapy**

WILLIAMSON, ET AL. 2014.

Maternal complications of ICP

- **Spontaneous preterm labor**
- Increased risk for gestational diabetes
- Increased risk for preeclampsia
- **Pruritis**
- Increased risk for underlying liver disease including gallbladder disease, hepatitis, and carcinoma (small)
- Increased risk for acute fatty liver of pregnancy (rare)

Fetal complications of ICP

- Meconium stained amniotic fluid
- Intrauterine demise
  - **Highest risk with bile acids >100**
  - Acute process with 2 theories for etiology:
    - Sudden cardiac death due to arrhythmia
    - Vasoconstriction of placental chorionic vessels

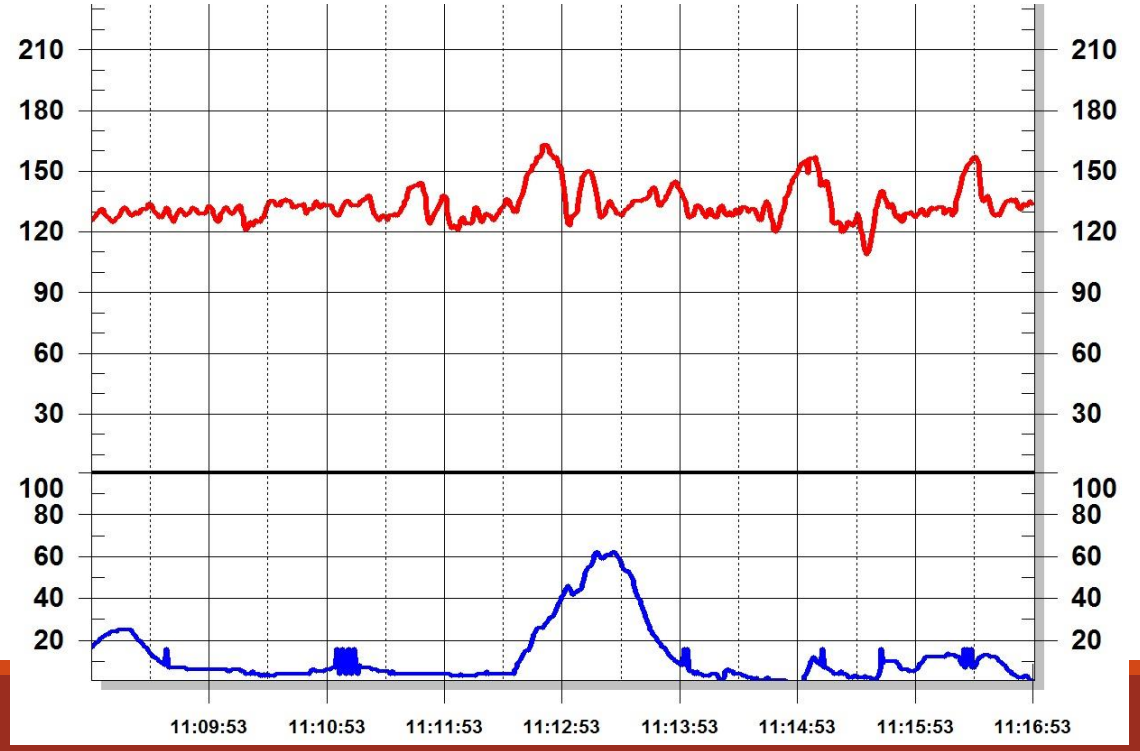
MIRAGOLI, ET AL, 2011. SEPULVEDA, ET AL, 1991.

Neonatal complications with ICP

- Morbidity associated with prematurity
- Increased risk for respiratory distress syndrome
  - After controlling for gestational age

Antenatal testing for ICP

- May not be beneficial
- Testing designed to predict fetal asphyxia from chronic conditions (i.e. placental insufficiency)
- Fetal demise (stillbirth) from ICP thought to be acute and unpredictable
- Prescriptions for testing vary widely
  - When to start?
  - How frequent?



Antenatal testing for ICP

	Twice Weekly N=118	Weekly N=35	Less than Weekly N=46	None/Unknown N=226	P-Value
Delivery gestational age (weeks)	**36.8 (1.2)**	**37.4 (1.1)**	**37.2 (1.0)**	**37.5 (1.5)**	**<0.001**
Composite neonatal morbidity	3 (2.5)	0 (0)	1 (2.2)	4 (1.8)	0.942
Abnormal NST prompting delivery	2 (1.5)	2 (4.7)	0 (0)	NA	0.541
At least one BPP ordered	**20 (16.9)**	**3 (8.6)**	**3 (6.5)**	**3 (1.3)**	**<0.001**
NICU admission	25 (21.2)	2 (5.7)	8 (17.4)	42 (18.6)	0.220
RDS	12 (10.2)	1 (2.9)	2 (4.3)	12 (5.3)	0.312
Stillbirth	0 (0)	0 (0)	0 (0)	2 (0.9)	0.706

Timing of delivery?

- Some experts advocate for early delivery (36-37 weeks)
- Others recommend delaying delivery until closer to term (39 weeks)
- Perhaps a case-by-case approach?
  - **Women with mild disease (bile acids <40) could be expectantly managed until 38-39 weeks**
  - **Women with moderate disease (bile acids 40-99) could be delivered at 37-38 weeks**
  - **Women with severe disease (bile acids >100) could be delivered at 36-37 weeks**
  - **All of the above +/- antenatal testing**

WILLIAMSON, ET AL 2014. LO, ET AL. 2014

Follow-up after ICP

- Discuss recurrence risk (60-90%)
- Repeat bile acids, liver function tests to ensure normalization
  - Consider right upper quadrant ultrasound or referral to GI if abnormal
- Avoid high estrogen-containing contraceptives
  - Most OCPs are acceptable
  - Warn women that symptoms may recur with hormonal birth control

WILLIAMSON, ET AL. 2014.

Questions?