# Intrahepatic cholestasis of pregnancy

Diagnosis, Treatment, and Prevention of Stillbirth

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## I have no disclosures.

# Objectives

1. Describe the diagnosis of intrahepatic cholestasis of pregnancy including clinical presentation and laboratory testing.
2. Explain the management of pregnancy complicated by IHCP
3. Describe the risk for stillbirth associated with IHCP

# What is intrahepatic cholestasis of pregnancy (IHCP)?

- One of several liver diseases unique to pregnancy
- The flow of bile acids within the biliary tree is slowed
- Total bile acids build up within the liver
- This increase in bile acids can cause a spill-over into the bloodstream

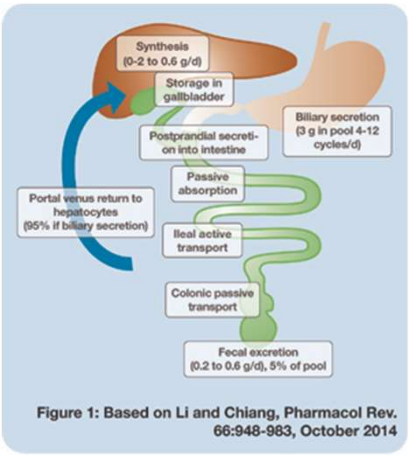
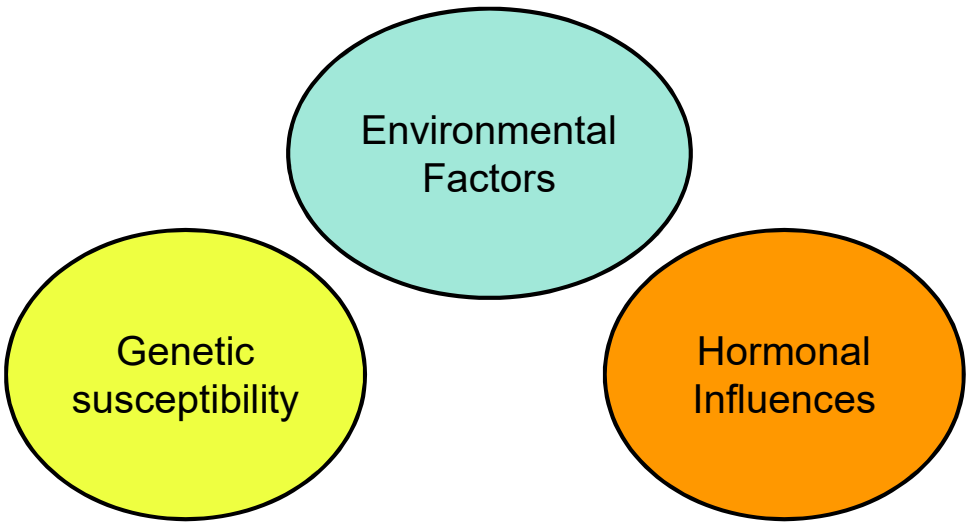



Figure 1: Based on Li and Chiang, Pharmacol Rev. 66:948-983, October 2014

# Epidemiology

- Incidence 0.2 - 2%
  - Varies widely by group studied
  - More common in Northern Europe and South America
    - Chile - approximately 4% incidence; higher in some indigenous groups
  - Prevalence increases in winter months
- Higher incidence with multiple gestation
- Increased risk in pregnancies conceived by in vitro

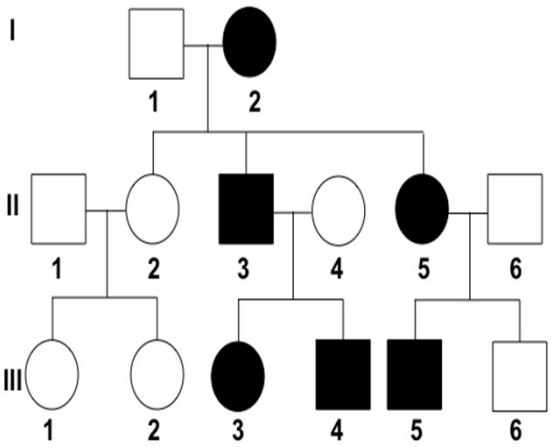
# Epidemiology gives clues to etiology



# Environmental Links

- More common in winter months
- Selenium levels
  - Dietary selenium is decreased in IHCP
  - These levels also decrease in winter
  - Found mostly in meats, dairy products, grains
  - Supplements are available
- Vitamin D deficiency
  - Also associated with increased risk of IHCP
  - Levels also decreased in winter
  - Usually found in fortified dairy
  - Supplementation available

# Genetic susceptibility




- ~14% of patients with IHCP have a positive family history
- For those with suspected "familial" cholestasis
  - Autosomal dominant inheritance is suspected
  - Sisters of affected individuals have a 12-fold increased risk
- Mutations noted in familial childhood liver disease have provided potential mechanisms

# Genetic Mutations

- Autosomal recessive cholestasis
  - Genetic mutations encoding biliary transport proteins
  - Gene encoding ABCB4 is most well studied in pregnancy
    - Codes multidrug resistance protein 3
    - Same mutation is also noted in estrogen-induced cholestasis
      - IHCP patients have increased risk for this
    - Apparent link between heterozygous women with affected children and IHCP

# Links to hormones

- Estrogen
  - Acts to decrease expression of biliary transport proteins
  - Results in internalization of bile acid transporter pump
  - A known associated condition separate from pregnancy → estrogen induced cholestasis
- Progesterone
  - Partial agonist of bile acid receptors
  - Decreases function of the receptor

# Diagnosing IHCP

## Clinical symptoms

- ITCHING!
  - Classically on palms and soles
- Importantly - no rash
  - Excoriations are common
- Often worse at night
- Gradually worsening throughout pregnancy
- Can have dark urine, light colored stools
- Jaundice is uncommon

# Diagnostic work-up

- History is key
- Physical exam may show excoriations, but rash is not present
- Labs evaluation (recommended)
  - Liver enzymes
  - Total bile acids
- Can consider
  - GGT
  - Bilirubin (total and direct)
  - Coagulation studies (INR)

# Liver function test reference ranges

| Liver Enzyme | Non-pregnant | Pregnancy | First trimester | Second Trimester | Third Trimester |
|---|---|---|---|---|---|
| ALT (IU/L) | 0-40 | | 6-32 | 6-32 | 6-32 |
| AST (IU/L) | 7-40 | | 10-28 | 11-29 | 11-30 |
| GGT (IU/L) | 11-50 | | 5-37 | 5-43 | 3-41 |
| Bilirubin (µmol/L) | 0-17 | | 4-16 | 3-13 | 3-14 |
| Bile Acids (µmol/L) | 0-14 | 0-14 | | | |

Williams and Geenes. Obstet Gynecol 24(1)

# Diagnosis

- Liver enzymes usually, but not always elevated
  - Elevated from 2x-30x
  - Can be elevated before or after elevation of bile acids
  - Poor correlation with severity of disease
  - ALT is more specific than AST
- Bile acids
  - Elevation makes the diagnosis
  - The elevation should be in total bile acids
    - If specific bile acids are used tauroconjugates are most likely to be elevated
  - Can be tested fasting or non-fasting
    - Fasting reference range: 6-10 µmol/L
    - Non-fasting reference range: 10-14 µmol/L
  - Mild elevation < 40 µmol/L
  - Moderate elevation 40-100 µmol/L
  - Severe elevation µmol/L
  - Risk appears to be dose dependent

# Additional Studies

- GGT
  - Not usually elevated but occasionally is
  - More likely to be elevated in genetic forms
- Bilirubin
  - Conjugated bilirubinemia in ~10%
- INR
  - Can be elevated but studies are conflicted
  - Should check this if there is steatorrhea with IHCP

# Imaging?

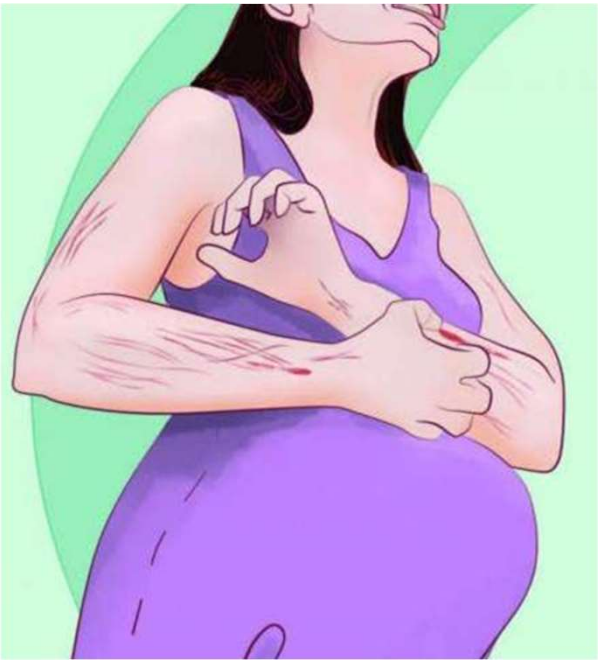
- Ultrasound
  - Not specific for diagnosis
  - Can be useful if diagnosis is in question
  - Some studies have shown an increase in fasting and ejection volumes of the gallbladder
- Probably of limited use

# IHCP Remains a Diagnosis of Exclusion

# What are the risks of IHCP?

## Risks to Mom

- Generally low risk
- VERY uncomfortable
- Very rarely jaundice
- Higher co-existing gestational diabetes and preeclampsia



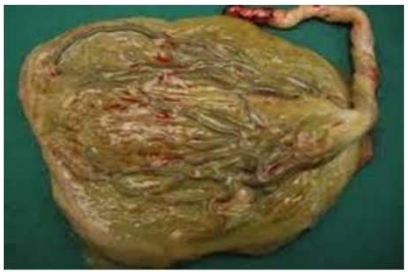
## Risks to Baby

- Spontaneous preterm birth
- Nonreassuring status in labor
- Meconium staining of amniotic fluid
- Respiratory distress syndrome (independent of gestational age)
- Stillbirth
- Dose dependent on bile acids
  - Every 1-2 µmol/L increase results in 1-2% risk in adverse outcome (Glantz et al. Hepatology 2004 Aug;40(2):467-74)
  - Does not become statistically significant until level ≥ 40 µmol/L
  - Bile acids < 40 µmol/L may not increase risk

## Pathophysiology

# Meconium staining

- Bile acids stimulate intestinal contractility
- Sheep studies infused bile acids to ewes
  - 100% of lambs exposed to bile acids passed meconium prior to delivery
  - 16% of controls passed meconium prior to delivery
- Can occur independent of non-reassuring status



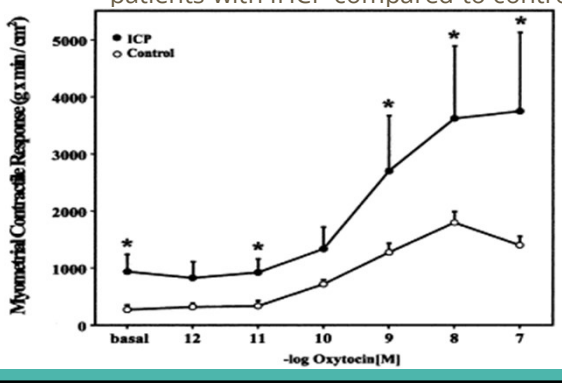
Campos et al. Acta Obstet Gynecol Scand 65:23-26

# Preterm Birth

- In rodent uteri: myometrial contractility increases in response to bile acids
- Sheep studies: shorter time to delivery when treated with bile acids
  - 20% rate of preterm delivery

# Human studies

- In vitro studies
  - Increased expression of oxytocin receptor
  - Decreased amount of oxytocin required to elicit contractions in myometrium from patients with IHCP compared to controls



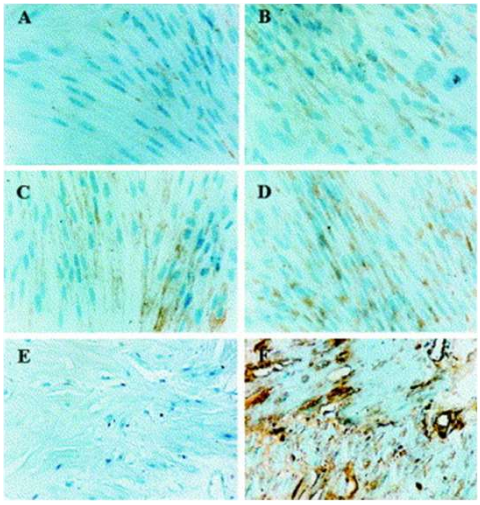
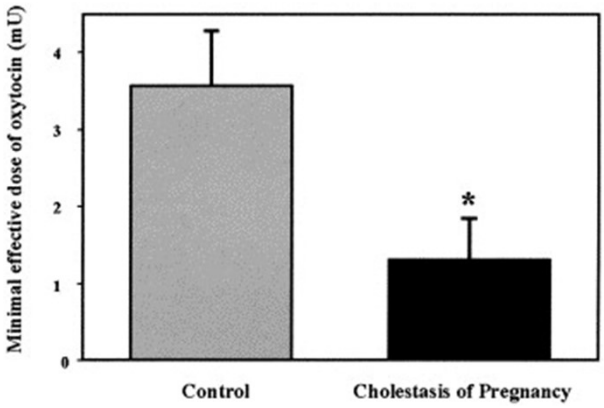




Fig 6. Immunohistochemistry of oxytocin receptor on cultured myometrial cells. A, Control. B, 2 µmol/L cholic acid. C, 20 µmol/L cholic acid. D, 200 µmol/L cholic acid. E, Negative control (myometrial sample without primary antibody). F, Positive control (term myometrium). (Stain, peroxidase antiperoxidase; original magnification, ×400).

Germaine et al Aug 2003. Am J Obstet Gynecol 189(2):577-82

# Oxytocin challenge test




- 7 nulliparous pts with IHCP and 7 nulliparous controls
- 38 week oxytocin challenge test
- Oxytocin dose increased every 30 min until 4 contractions in 10 minutes
- Contractions noted by tocometry
- Status of the baby monitored throughout

Germaine et al Aug 2003. Am J Obstet Gynecol 189(2):577-82

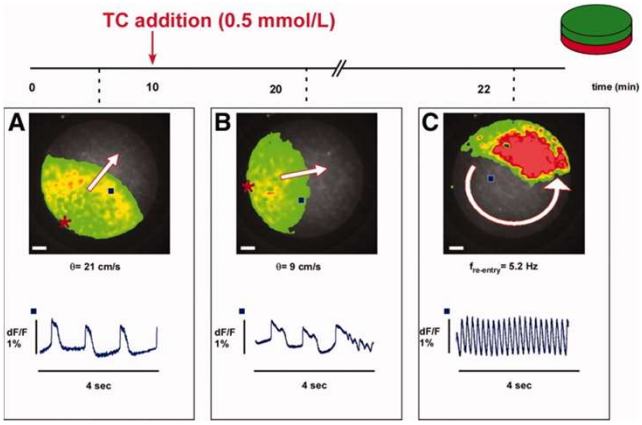
# Stillbirth and IHCP

## Bile acids in utero

- Bile acids are made starting at 12 weeks gestation
- Usually these are carried to mom due to low concentration in maternal blood
- For women with ICHP, that gradient is reversed
- Likely causes a build-up of bile acids in baby
- Does not appear to be a chronic effect on the placenta

# Why are they harmful?

- Inherently cytotoxic
- In rodent models,bile acids appear to cause arrhythmia in vitro
- At least one case report of fetal tachyarrhythmia in a case of IHCP (Al Inizi et al. Int J Gynaecol Obstet 2006;93:53-54)
- Bile acids also associated with vasoconstriction of the placental veins (Sepulveda et al Eur J Obstet Gynecol Reprod Biol 1991).




Miragoli et al. Hepatology 2011;Oct 54(4) 1282-92

# What can we do?

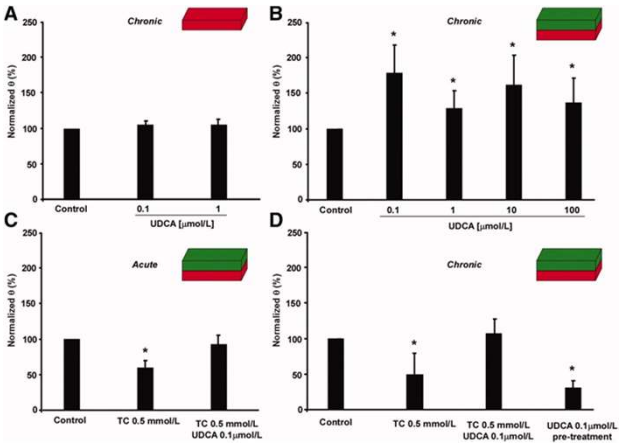
# Treatment

## Ursodeoxycholic acid (UDCA)

- Tertiary bile acid
- Present in trace amounts in human serum
- Treatment of choice
  - Decreases pruritus
  - Decreases bile acid levels
    - Maternal serum
    - Amniotic fluid
    - Colostrum
  - Mechanism of action unknown

# Ursodeoxycholic acid

- No studies powered to show benefit to stillbirth risk, but…
  - Decreased tachyarrhythmia in vitro
  - Decreased bile acid effect on uterine contractility
- Biologically plausible the stillbirth risk would decrease
- Dose: start with 300 mg BID to 300 mg TID
- Max dose: 600 mg TID
- Titrate to symptoms




Effect of exposure to UDCA on impulse propagation in the MH and FH models. (A) Chronic exposure of the MH model to UDCA did not affect conduction velocity (θ; n=7). (B) In contrast, chronic exposure of the FH model to increasing concentrations of UDCA significantly increased θ (n = 24). (C) Acute exposure of FH models to 0.5 mmol/L of taurocholic acid (TC) plus 0.1 μmol/L of UDCA inhibits slow conduction induced by TC alone (n = 7). (D) Same as (C), but following chronic exposure of FH models to TC and UDCA. Again, UDCA plus TC abolished slow conduction induced by TC alone. UDCA pretreatment for 12 hours (UDCA withdrawn before adding 0.5 mmol/L of TC for 12 hours) shows no cardioprotective effect (n = 7). Data are presented as mean ± SD.

Miragoli et. al. Hepatology 2011

# Other medications

- Rifampin
  - Antibiotic
  - Has been used in management of primary biliary sclerosis
  - No RCTs, some case reports of improvement in symptoms when added to UDCA (Lui et al. Obstet Gynecol 2018 Sept;132(3):678-681)
  - May enhance bile acid excretion
- Cholestyramine
  - Anion exchange resin
  - May improve symptom control
  - Also may impair absorption of fat soluble vitamins (mostly theoretical)
  - No improvement in bile acids or LFTs

# Other medications

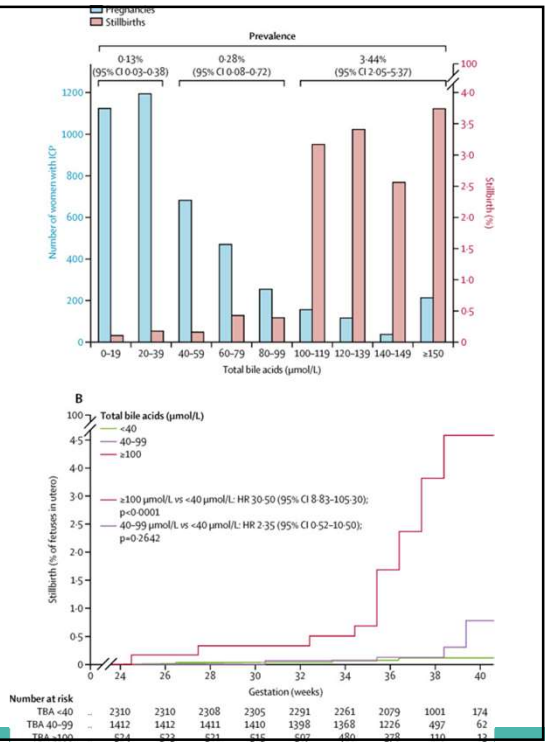
- S-adenosyl-L-methionine
  - Impares hepatic bile acid/steroid excretion
  - Requies BID IV administration
- Dexamethasone
  - No evidence for benefit
  - May decrease pruritus
- Antihistamines
  - No effect on biochemistry
  - May decrease pruritus

# Monitoring

- No specific data
- Risk for stillbirth has mostly been described at term
- Society for Maternal Fetal Medicine recommendations
  - Antenatal testing is reasonable with serial growth evaluation
  - No evidence to support any particular type or frequency
  - May not predict acute events
- Our practice
  - Serial ultrasounds for fetal growth
  - Weekly antenatal testing at 28 weeks
  - Twice weekly antenatal testing at 32 weeks

# Delivery timing

- Recent meta-analysis in Lancet (March 2019)
  - Risk of stillbirth increases dramatically if bile acids > 100 µmol/L after 36 weeks
  - Risk may not increase at all if bile acids < 40 µmol/L
  - Risk associated with highest bile acids, not after treatment




# Recommendations?

- Society for Maternal Fetal Medicine
  - 2011 last publication
  - Delivery 37-38 or sooner if documented lung maturity
- To consider:
  - If bile acids > 100 µmol/L, consider delivery at 35-36 weeks
  - Delivery of others with diagnosis at 36 - 37 weeks

Society for Maternal·Fetal Medicine

# Summary

- IHCP is a relatively benign liver disease of pregnancy for mothers, but has potential adverse effects on babies
- Diagnosis is made by clinical symptoms and elevation of total bile acids
- Stillbirth risk is associated with total bile acid level in a dose dependent fashion
- Treatment of choice is ursodeoxycholic acid (UDCA), which improves symptoms but may not improve outcome
- Antenatal testing is controversial and no consensus exists
- Delivery timing is variable, but most societies agree with early term or late preterm delivery

# Questions?