Atypical cholestasis in pregnancy

NASOM, Montreal

October 2016

Florence Weber

Objectives

- Recognize atypical presentation of pruritus in pregnancy (ICP)
- Recognize diseases that mimic intrahepatic cholestasis of pregnancy (ICP)
- Use second or third line treatment for intractable pruritus in these patients

“atypical” case of ICP

- 32 year old G1, 16th weeks of gestation
  - Pruritus since week 10
  - No rash
  - ALT 88 (N 14-40)
  - Total bile acids (TBA) 15 (N<10 umol/L)

What's new/Areas uncertainty

Question 1:
Which diseases should be excluded?

Question 3:
What are the treatment options for her pruritus?

Diagnostic criteria/ Definition

Treatment

Question 2:
Which abnormal labs are necessary for diagnosis of ICP?

Question 4:
What should be the timing of delivery?

Question 1:
Which diseases should be excluded?

- Usual definition ICP: "typical"
  - Pruritus late 2nd or 3rd trimester
  - No rash
  - Elevated TBA and/or transaminase
  - Exclusion of other liver diseases
  - Post partum resolution

Question 1:
Which diseases should be excluded?

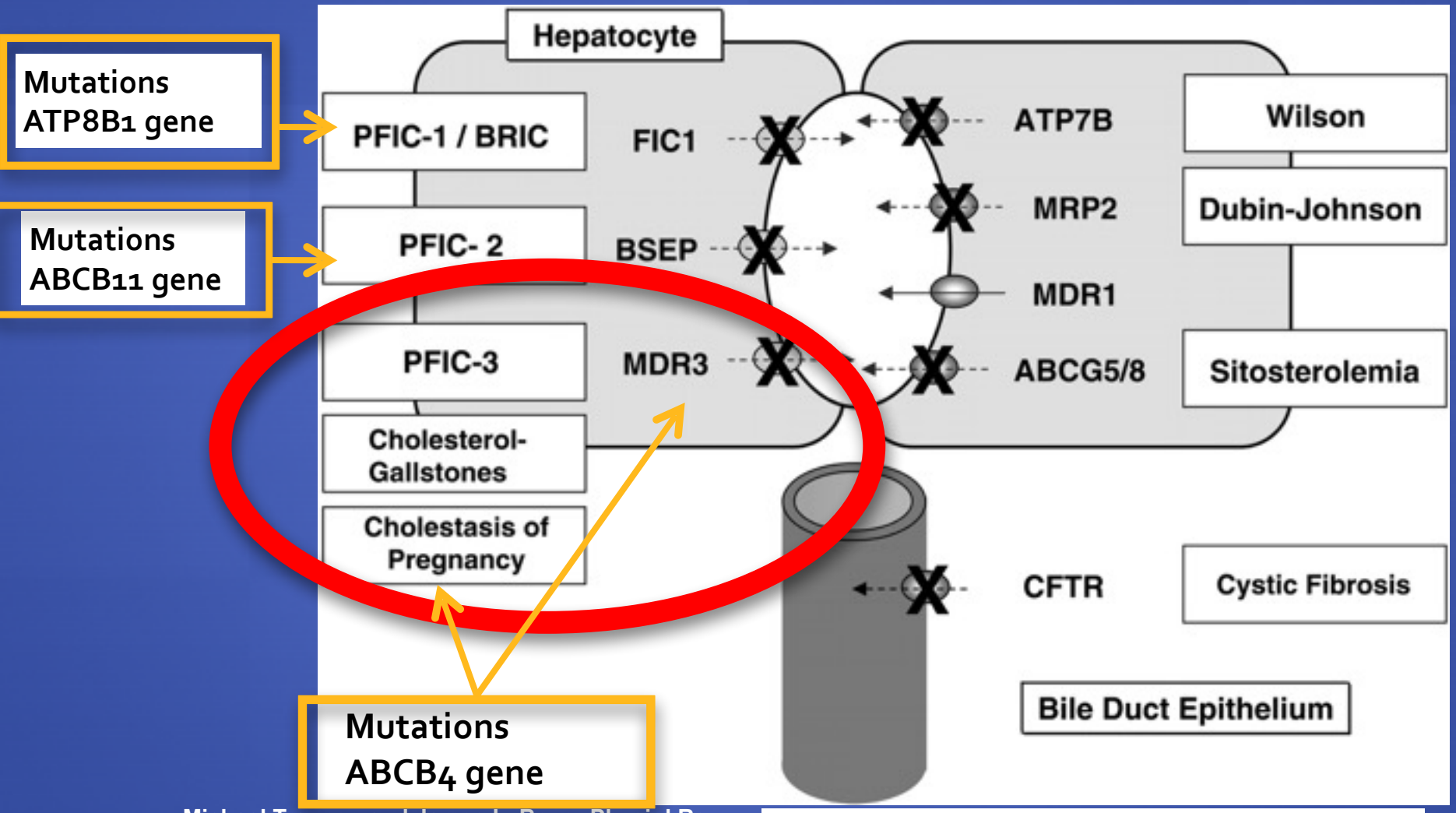
- Great variability between studies, guidelines, expert opinions. Include:
  - Virus: hepatitis A, B, C, EBV, CMV
  - Hereditary: hemochromatosis, a1 antitrypsin deficiency, Wilson's disease
  - Auto-immune: hepatitis, primary biliary cirrhosis
  - Fatty liver disease
  - Extra hepatic biliary obstruction
  - Mutations bile salt transporters

Question 2:
Which diseases should be excluded?

- Shouldn't we use the concept of:

  Primary versus secondary ICP?

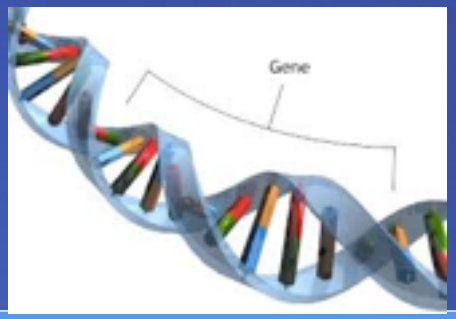
Association with genetic bile salts transporter defects



Michael Trauner, and James L. Boyer Physiol Rev 2003;83:633-671

Physiological Reviews

Genetic cause



- Large spectrum of clinical presentation of mutations including:
  - ICP
  - BRIC (Benign recurring intrahepatic cholestasis)
  - Cholesterol gallstones
  - PFIC (Progressive familial intrahepatic cholestasis)

- Bacq Y and al*:
  - Identified 4 mutations almost exclusively in 16% of Caucasians with ICP* (versus controls without ICP)

*Bacq Y, J Met Genet 2009; 46: 711-715

Genetic cause

- Bacq Y and al. Digestive and Liver disease 2016 (accepted manuscript)

	Onset pruritus	TBA concentration	TBA concentration > 40 umol/L
ABCB4 mutation 17/98	30 1/7 weeks	42,9 umol/L	35,3%
No mutation 81/98	33 2/7 weeks	24,3 umol/L	13,6%

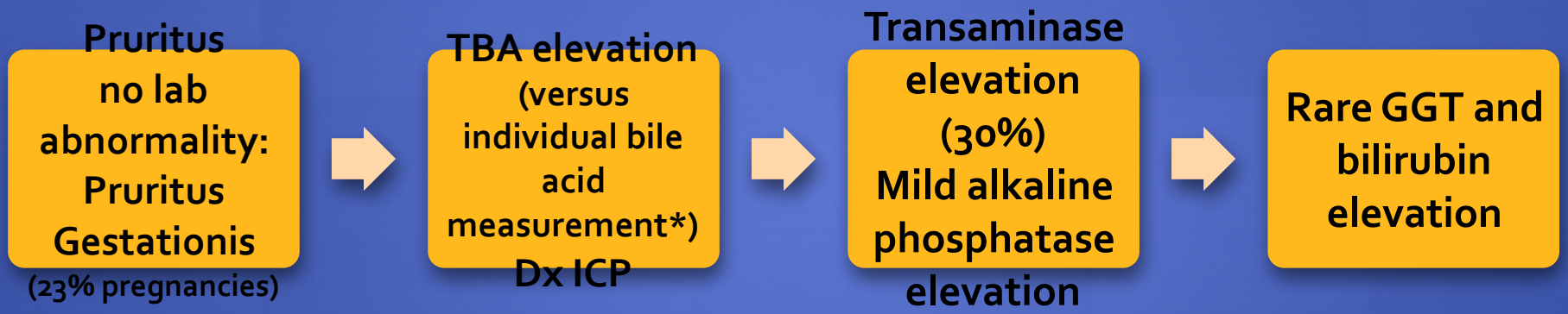
* Johnson RC and al. Journal of Perinatology 2014; 34: 711-712

Question 1:
Which diseases should be excluded?

- Great variability between studies, guidelines, expert opinions. Include:
  - Virus: hepatitis A, B, C, EBV, CMV
  - Hereditary: hemochromatosis, a1 antitrypsin deficiency, Wilson's disease
  - Auto-immune: hepatitis, primary biliary cirrhosis
  - Fatty liver disease
  - Extra hepatic biliary obstruction
  - Mutations of bile salt transporters

Question 2:
Which abnormal labs are necessary for diagnosis of ICP?

Probable sequence of abnormalities



- Why do ALT increase before GGT. Isn't this cholestasis????

*Huand WM. Am J Perinatol 2009; 26: 291

Question 2:
Which abnormal labs are necessary for diagnosis of ICP?

- Why do guidelines/experts mention elevated TBA and/or transaminase?
  - Probably because TBA levels not universally available
  - "Serum bile acids are increasingly recognized as the most definitive laboratory test for diagnosis of ICP"*
- Can we diagnose ICP if elevation of transaminase but not TBA? probably not
- Can we diagnose ICP if elevated TBA but asymptomatic? Yes

*Dixon H and Williamson C. The Pathophysiologue of intraheptaic cholestasis of pregnancy. Clinics and researsh in Hepatology and Gatroenterology 2016; 40:141-153

Back to our case

- TBA: 15 umol/L at diagnosis
- Treated with UDCA 500 mg 3 times a day
- Initially better with ALT decrease to normal
- Deterioration at 26 weeks: severe pruritus, ALT 120, TBA 50 umol/L

Question 3:
What are the treatment options for her pruritus?

Drug	Improved chemistry	Improved pruritus	Improved fetal outcome
UDCA 450-1000 mg/day**	+	+	+
SAMe	+	+	- / ?
Activated charchoal	-	-	-
Guar gum	?	+	?
Cholestyramine	+ (less than UDCA)	+(less than UDCA)	Less than UDCA
Dexamethasone (versus UDCA)	-	-	-
Rifampicin (combination with UDCA)	+	+	?

*Ovadia C and al. Clinics in dermatology 2016; 34: 327-334

**Kong X and al. Medicine 2016; 95(40)

Question 3:
What are the treatment options for her pruritus?

- Other treatment options :
  - Phenobarbital: no effet
  - Phototherapy UV-B: anecdotal
  - Plasmapheresis: case reports with success
  - Sertraline (SSRI): no data in ICP
  - Oral naltrexone (opioid antagonist): no data in ICP

Question 3:
What are the treatment options for her pruritus?

- Treatment plan for our patient:
  - UDCA (maximum dose 15 mg/kg/day)
    - Up to 3,5 g per day described*: safe?
    - plus rifampicin (caution if ALT very high).
  - Consider cholestyramine 8g/day (caution with timing)
  - If very extremely severe and <34 weeks: plasmapheresis

*Geenes V and al. Rifampicin in the treatment of severe intrahepatic cholestasis of pregnancy. Eur J Obstet Gynecol Reprod Bio 2015; 189:59-63

Question 3:
What are the treatment options for her pruritus?

- Teaser: Use of grapefruit juice
  - See poster by Dahl K and al. NASOM 2016
- 4 patients with "secondary ICP"

Question 4:
What should be the timing of delivery?

- Role of gestational age on fetal prognosis, what we know:
  - Series of 20 UIFDs: median 38 weeks, 2/20 before 37 weeks**

*Williamson C and al. BJOC 2004; 111:676

Question 4:
What should be the timing of delivery?

- 2 recent publications using different experimental approaches suggest delivery 36 weeks= best outcome*, **

- Multiple methodological flaws, do not take into account TBA, subject of debate between experts.

*Puljic A and al. Am J Obstet Gynecol 2015; 212:667
** Lo JO and al. The Jouranel of Maternal-Fetal and Neonatal Medicine 2015; 18(18): 2254-2258

Question 4:
What should be the timing of delivery?

- Position that seems most consensual: continue delivering ICP at 37 weeks unless:
  - Past history of IUFD
  - Intolerable pruritus
  - Other indication for delivery
  - Personal preference
  - **Elevated TBA**

Role of TBAs

- Role of bile acids in fetal morbidity and mortality*
  - Induction of arrhythmia/fetal heart US abnormalities**
  - Affect placental vasculature
  - Could increase preterm labor (via prostaglandin pathways)
  - Stimulate gut motility: meconium-stained amniotic fluid
  - Disrupt pulmonary surfactant in neonates
  - Long term: effect on metabolic health of teenagers

*Dixon H and Williamson C. The Pathophysiologue of intraheptaic cholestasis of pregnancy. Clinics and researsh in Hepatology and Gatroenterology 2016; 40:141-153
**Alaalla WM and al. J Mat Fetal Neonat Med 2016; 29((): 1445-1450

Role of TBAs

- Geenes V and al. Hepatology 2014; 59:1482
  - Prospective case-control
  - 669 ICP singleton pregnancies with TBA > 40 umol/L
    - Stillbirth 1,5% versus 0.5%
      - 10 stillbirths in ICP group
      - 6/10 before 37 weeks
      - 7/10 another pregnancy complication (PE, gestational diabetes)
        - Median TBA 137 umol/L (104-159) versus live births 72 umo/Ll(52-107)

Role of TBAs

- TBA > 100 umol/L: 10-15% IUFD*, **
  - Towards a new classification of ICP depending on max TBA:
    - Mild 10-39 umol/L
    - Moderate 40-99
    - Severe > 100
- Is the fetus protected if TBA > 100 and then decrease <40
  - IUFD case D**: max TBA 114, last recorded TBA 36 within 1 week of stillbirth**?

*Brouwers L and al. AJOG 2015; 212:100
**Kawakita T and al. AJOG 2015; 213:570

Conclusions

- Mutations of bile salt transporters linked to up to 15% of cases of ICP
  - Should we test every case? Selected cases?
- Notion of primary versus secondary ICP
- TBAs is the most accepted marker for diagnosis of ICP
  - Toward a new classification of ICP based on maximal recorded TBA?
    - 10-39 umol/L: mild
    - 40-99 umol/L: moderate
    - >100 umol/L: severe

Conclusions

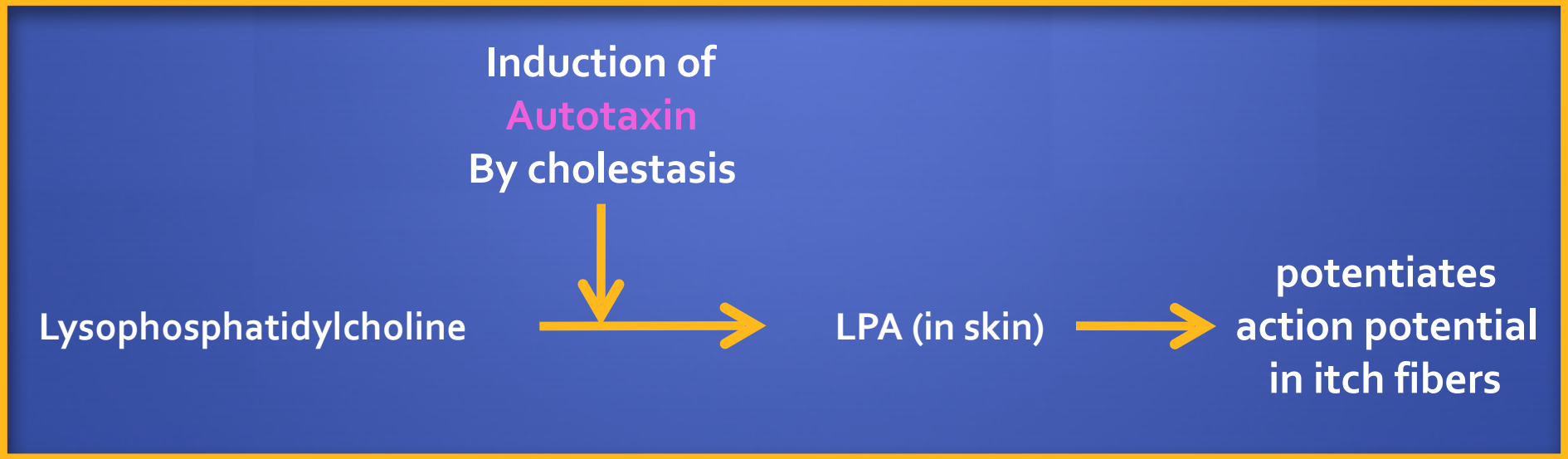
- Treatement options remain limited
  - Should always include UDCA
    - Consider: rifampicin, cholestyramine 8g/day, Grapefruit juice (500-1000 ml/day)
  - If very extremely severe and <34 weeks: plasmapheresis
  - Delivery

Conclusions

- The ideal timing of delivery is not yet known
  - Difficult question with medical legal implications, necessity of group consensus
  - Variable availability of TBA testing
  - 37 weeks or earlier if:
    - Past history of stillbirth
    - Intolerable pruritus
    - Other indication for delivery
    - Personal preference
    - TBA >40 umol/L (especially if >100)

New diagnostic tests

- Novel diagnostic avenues?
  - Measurement of sulfated progestin metabolites*
  - Measurement of autotaxin activity**



*Abu-Hayyef SA, Williamson C and al. Hepatology 2016; 63(4):1287
**Kremer AE and al. Journal of Hepatology 2015: vol 62: 897-901

Question: Why her? Risk factors

- Prior ICP (60-70% recurrence)
- Latin American:
  - ICP incidence 0,1-15%
  - Geographic variations
- Winter (selenium deficiency?)
- Twin pregnancies
- Exogenous progesterone
- Genetic predisposition

Exogenous progesterone

- Bacq Y and al. Hepatology 1997; 26: 358
  - 50 women with ICP, 64% oral natural progesterone
- Abu-Hayyef SA, Williamson C and al. Hepatology 2016; 63(4):1287:
  - In ICP: Elevated sulfated progesterone metabolites :
    - Competitively inhibit bile acid uptake and efflux: contribute to cholestasis
    - Participate to pruritus
    - Future pathway for treatment and diagnosis?

Exogenous progesterone

- Clinical significance:
- Some experts recommend avoiding progesterone supplementation if:
  - Prior ICP
  - Current ICP

Question:
Risk for other pregnancy related problems?

- Martineau MG and al. Diabetes Care 2015; 38: 243
  - 26 ICP versus 27 normal pregnancies:
    - ICP associated with impaired glucose intolerance
    - Dyslipidemia
    - Increased fetal growth

	ICP	Controls
Weeks at delivery	37,4	40,1
Birth weight (g)	3,298 (69,9 centile)	3,381 (36,1 centile)

Question:

Risk for other pregnancy related problems?

Severe intrahepatic cholestasis of pregnancy is a risk factor for preeclampsia in singleton and twin pregnancies

- Raz Y and al. Am Journal Obstet Gynecol 2015; 213: 395
  - Severe ICP (TBS>40 umol/L):
    - major risk factor for PE:
      - Singletons: 7,4% versus 1,5%
      - Twins: 33% versus 6,2%
    - Increase in severe PE
  - TBS normal in 33 patients with PE but no ICP

  - Closely follow ICP patients for PE

Question:
Risk for other pregnancy related problems?

Original Research

Postpartum Blood Loss in Women Treated for Intrahepatic Cholestasis of Pregnancy

- Furrer R and al. Obstet Gynecol; 2016: 128(5): 1048
  - Retrospective cohort case-control study:
  - 15,083 deliveries, 348 ICP (2,3%):
    - No difference between estimated blood loss and variation in hemoglobin
    - Moderate and severe ICP (TBS 40-99 and >100):
      - More meconium staining
    - Non significant difference in stillbirth (1,8% versus 0,6%)

- Reassuring, no vitamin K supplementation unless elevated INR

Question:
Are there any long term consequences?

- **Possible increases risk:**
  - **liver/biliary tract cancer (HR 3,6)**
  - **diabetes (HR 1,5)**
  - **thyroid disease (HR 1,3)**
  - **Crohn's disease (HR 1,6)**
  - **Cardiovascular disease (if associated with PE)***

- **Clinical significance?**
- **Probably more related to underlying liver disease**

*Wiktröm and al. J Hepatology 2015; 63:456