“ITCHY MOMS”: INTRAHEPATIC CHOLESTASIS OF PREGNANCY

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INTRAHEPATIC CHOLESTASIS OF PREGNANCY (IHCP): DEFINITION

- Pregnant, usually 3rd trimester
- Pruritus, usually severe
- NO RASH
- Elevated bile acids
- Elevated liver functions

IHCP: EPIDEMIOLOGY

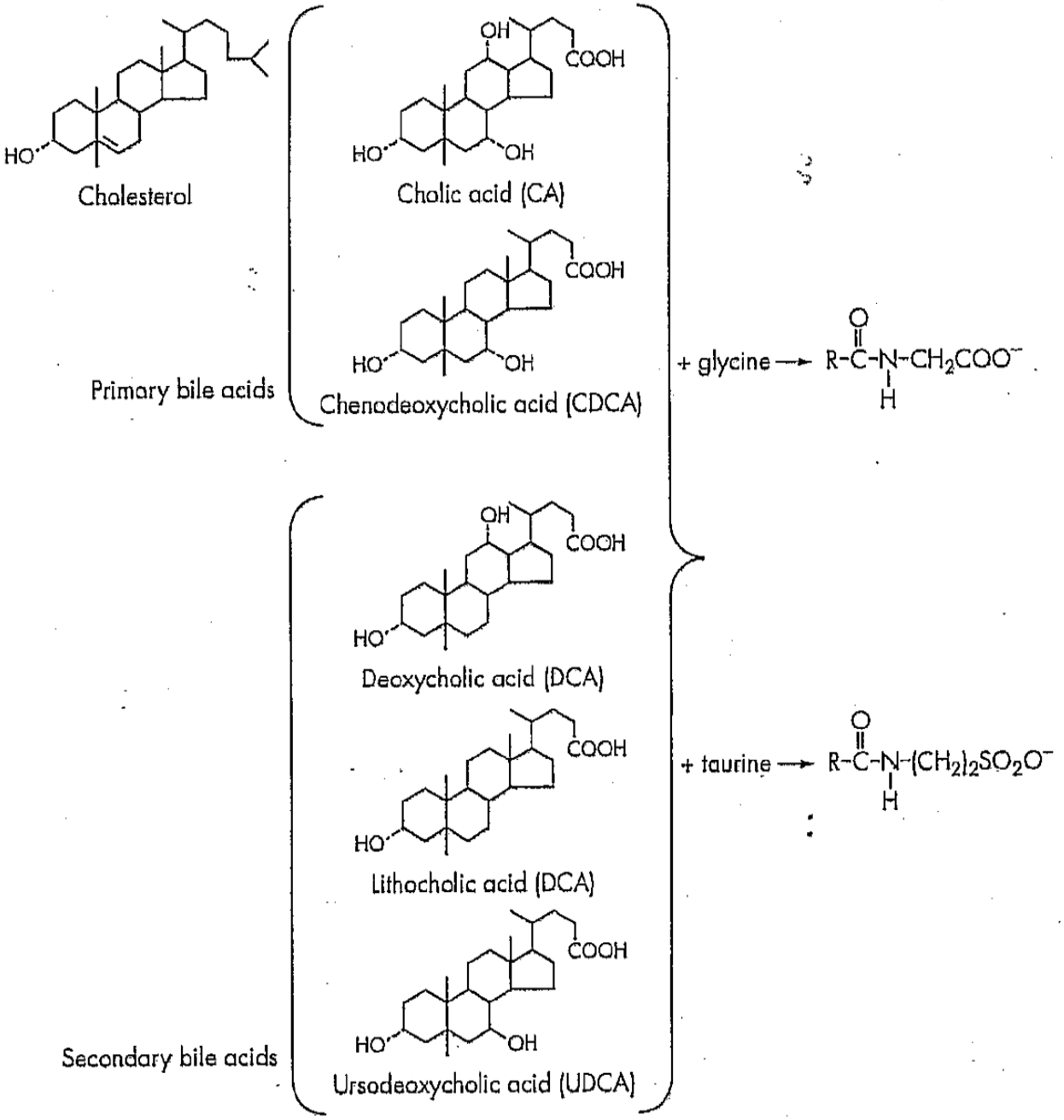
- High incidence in certain ethnicities:
  - Scandinavian
  - Araucana (Chile)
  - Aymara (Bolivia)
  - Yup'ik/Inupiaq (Alaska/Greenland)
  - Hispanic (Mex-Am in USA)

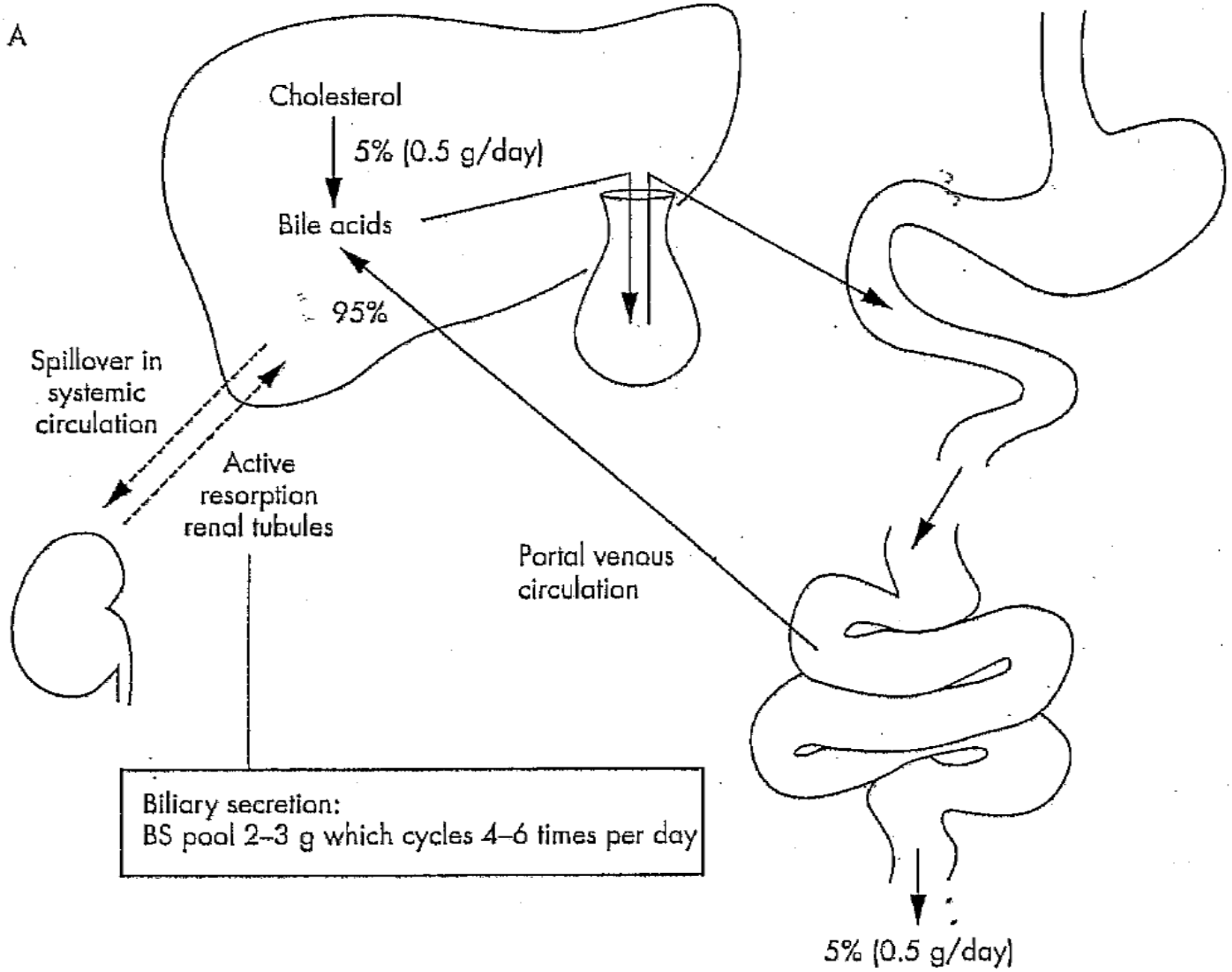
IHCP: Pregnancy Complications

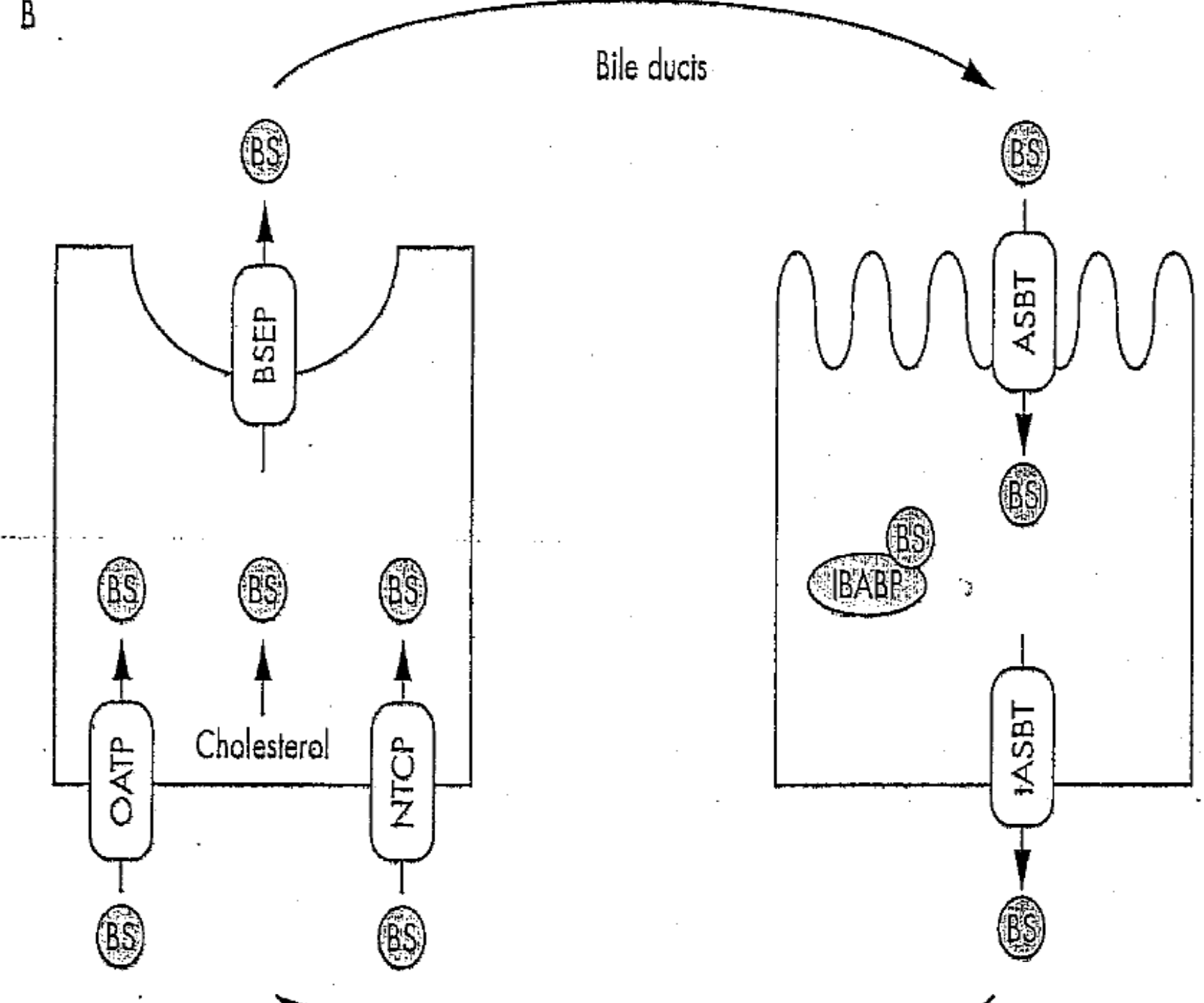
- Severe (intolerable) pruritus: 100%
- Preterm birth: 10-35%
- Stillbirth: 1-9%
- Meconium, NRFS in labor
- Cholelithiasis
- PPH
- Recurrence (next pg): 40-70%

Bile Physiology

- Bile acids (BA) are cholesterol breakdown products and are toxic
- BA are conjugated to bile salts and excreted, where they act as emulsifiers in the gut to enable fat digestion
- Basically, bile salts + phosphatidyl choline = bile
- Bile salts are transported back to the liver via the enterohepatic circulation


Cholesterol
Primary bile acids
Cholic acid (CA)
Chenodeoxycholic acid (CDCA)
Secondary bile acids
Deoxycholic acid (DCA)
Lithocholic acid (DCA)
Ursodeoxycholic acid (UDCA)
+ glycine
+ taurine

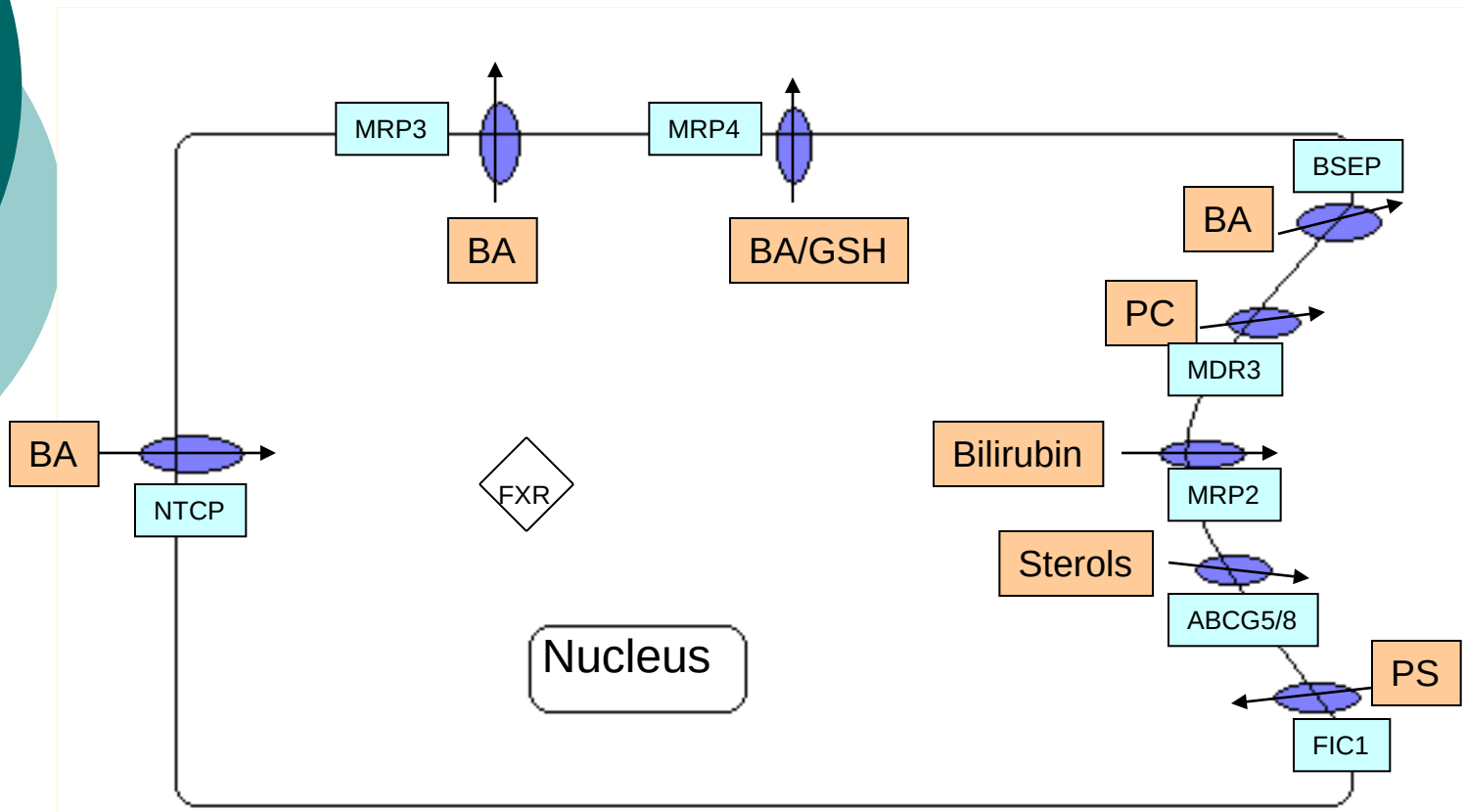

A
Cholesterol
5% (0.5 g/day)
Bile acids
95%
Spillover in systemic circulation
Active resorption renal tubules
Portal venous circulation
Biliary secretion:
BS pool 2–3 g which cycles 4–6 times per day
5% (0.5 g/day)


B
Bile ducts
BS
BSEP
OATP
Cholesterol
NTCP
ASBT
IBABP
tASBT

IHCP: Genetics

- Genetically heterogeneous in different populations
- Mutations in the bile acid (BA) transporter genes (that control export of BA from hepatocyte to biliary canaliculus)
- Mutations in these transporters result in familial cholestasis syndromes
- E2 and P4 can up-regulate the genes that result in reduced BA transport in susceptible women

Alternative Export



Uptake

BILE

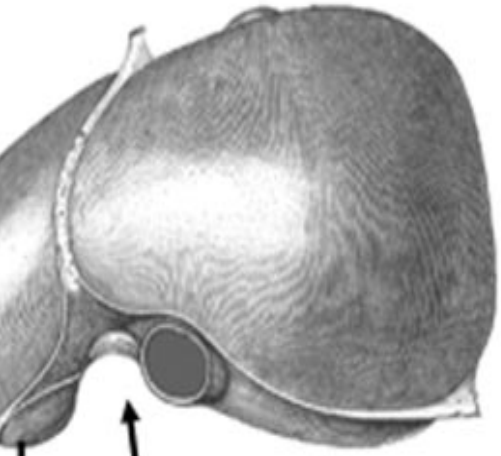
A link between FAO and IHCP?

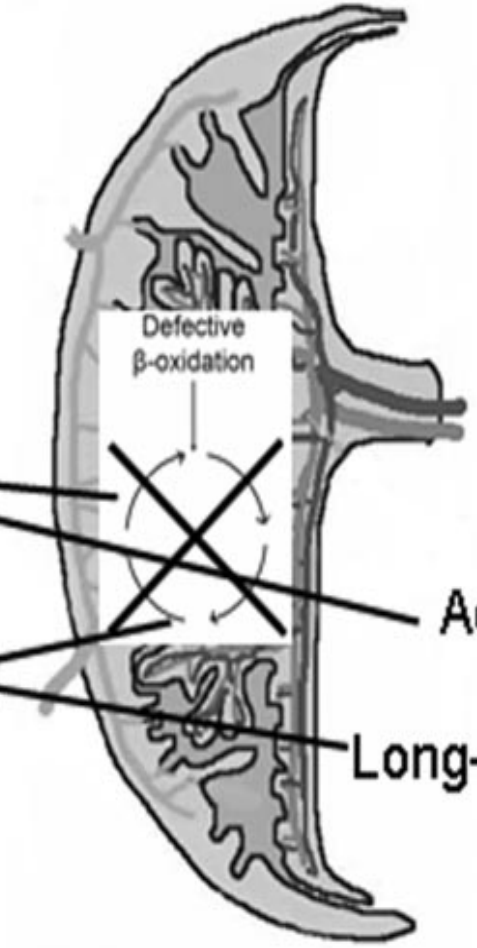
- FAO = fatty acid oxidation disorders
- LCHAD and acute fatty liver of pg
- CPT-1 deficiency and IHCP?
- CPT-1 deficiency most common gene disorder in our population (allele frequency 0.70 in Eskimos)
- Evolutionary response to the traditional ketogenic high-fat diet
- Is IHCP a side effect?

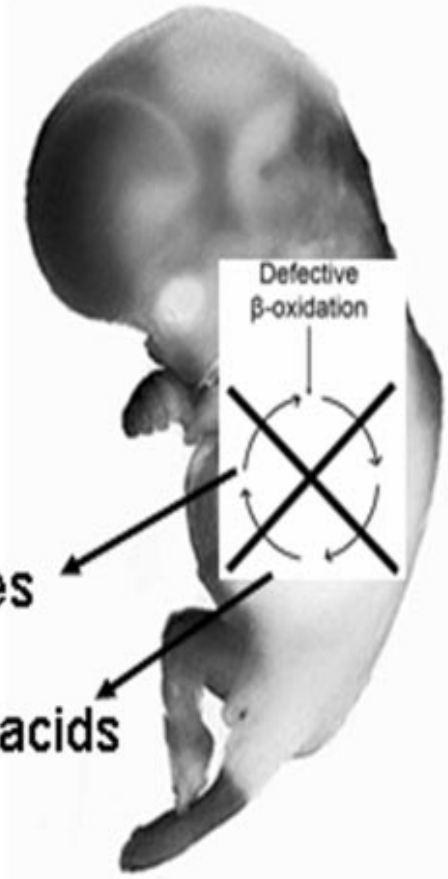
plo-insufficient Mother

Homozygous Placenta

Affected Fetus







Acyl-carnitines

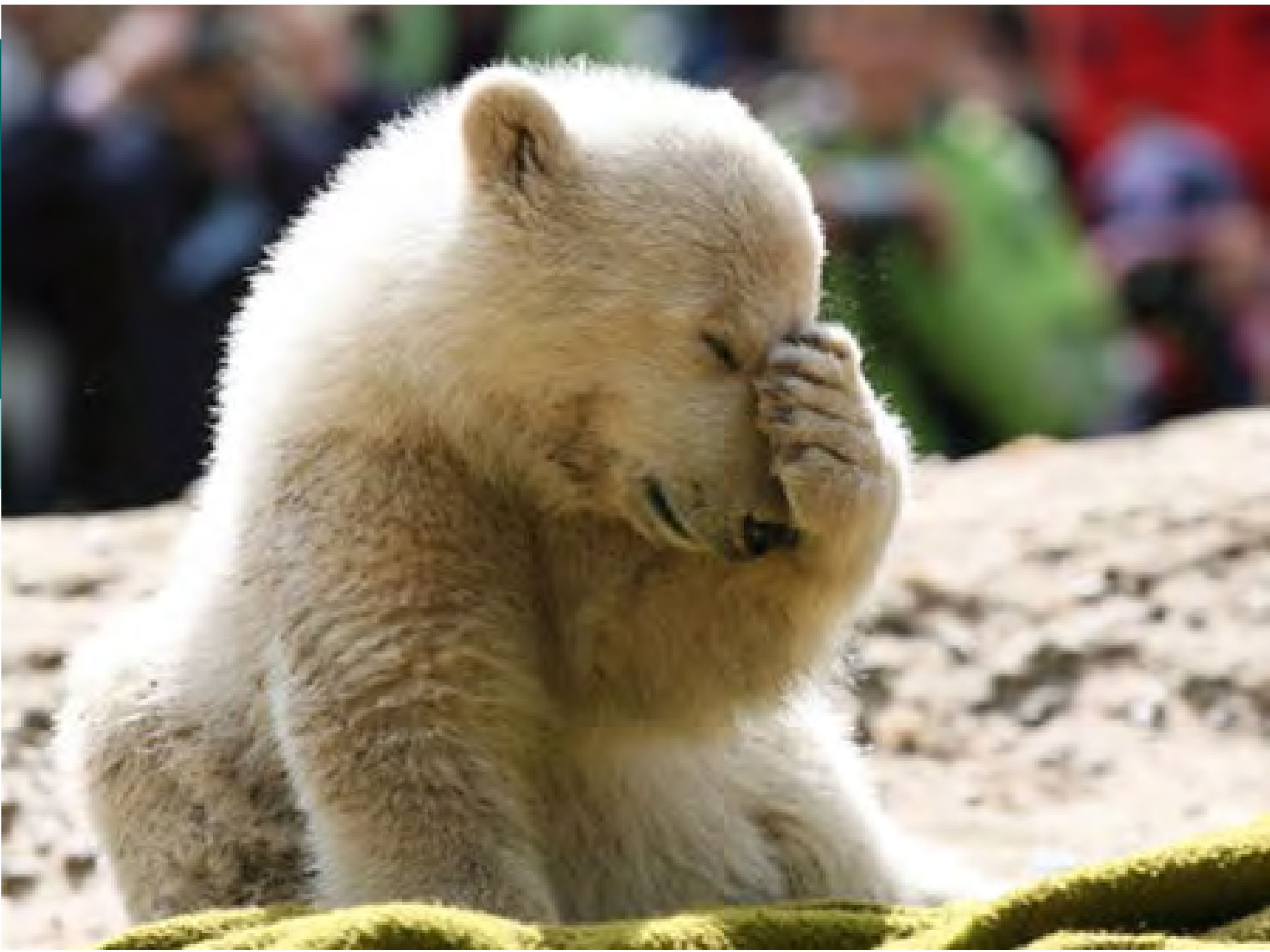
Long-chain fatty acids

Acyl-carnitines

Long-chain fatty acids

LP syndrome

P



IHCP: Diagnosis (Clinical)

- Intractable itching, particularly palms and soles
- NO RASH
- Patient scratching constantly during exam
- Pruritus usually precedes elevated bile acids
- May have had in a prior pregnancy

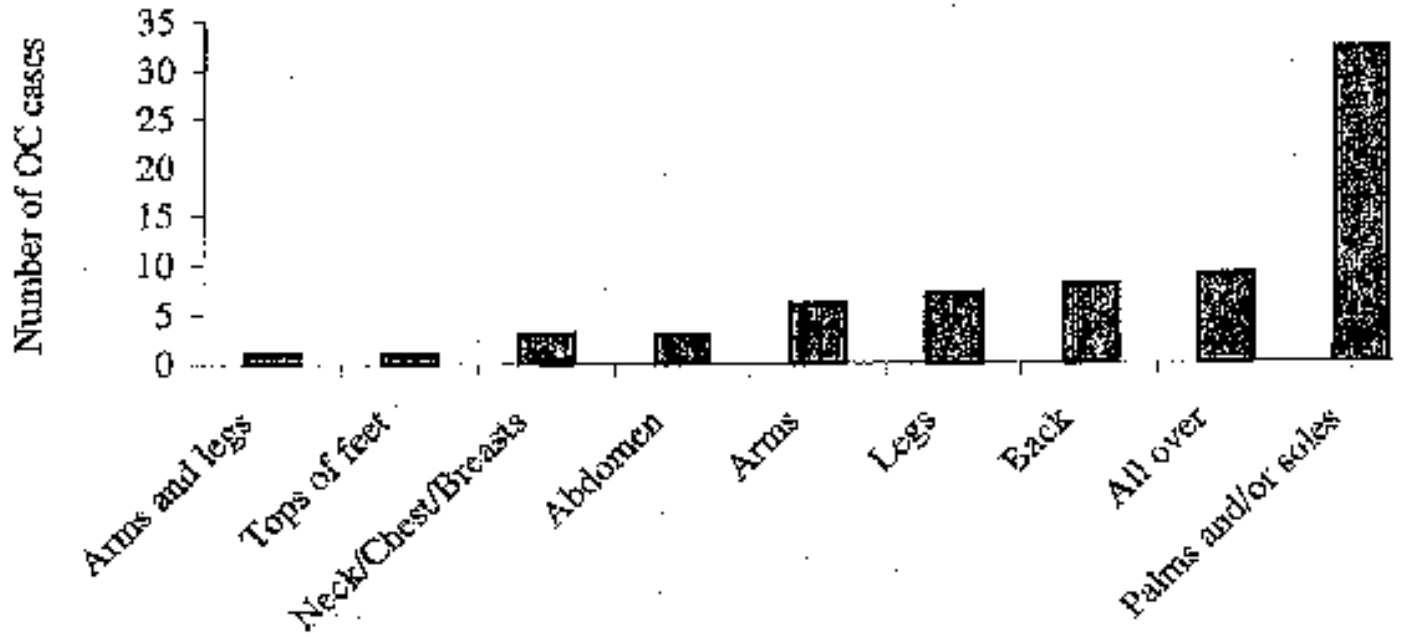
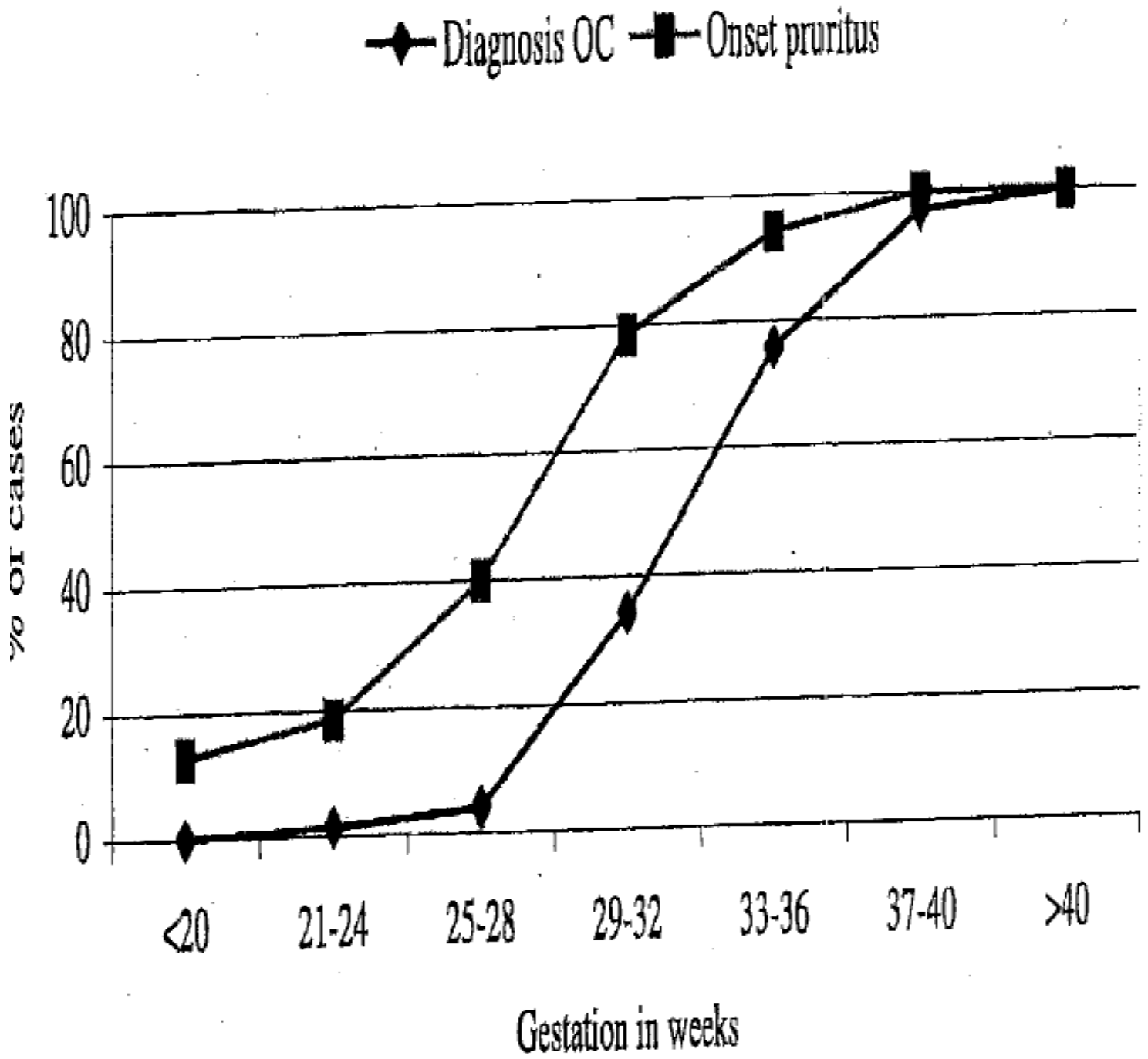


Fig. 2. Location of most severe pruritis.


Diagnosis OC
Onset pruritus
% of cases
100
80
60
40
20
0
<20
21-24
25-28
29-32
33-36
37-40
>40
Gestation in weeks

Diagnosis (Laboratory)

- Total bile acids >10 (7)mmol/L
- Cholic acid >3 mmol/L
- ALT/AST > 35 U/L
- Alk ptase >200 U/L
- Occasionally (1-3%) elevated bili and clinical jaundice

Diagnosis of IHCP
Bile Acids “In’s and Out’s”

- In pregnancy, >10mmol/L is considered abnormal
- (Non-pregnant>19 mmol/L)
- If itching but nl BA, repeat in 2 wks, but treat as if IHCP!
- Cholic a. elevated first (>3mmol/L)
- CA:CDCA ratio>1.9 (most sensitive)
- BA drawn fasting or postprandial

IHCP – Maternal issues

- Increased PPH (decreased vit K?)
- Increased GBD (22% in one study)
- Generally resolves within 48 hr PP
- Not a contraindication to hormonal contraception PP
- Increased preterm birth
- Increased stillbirth

IHCP – Fetal Issues

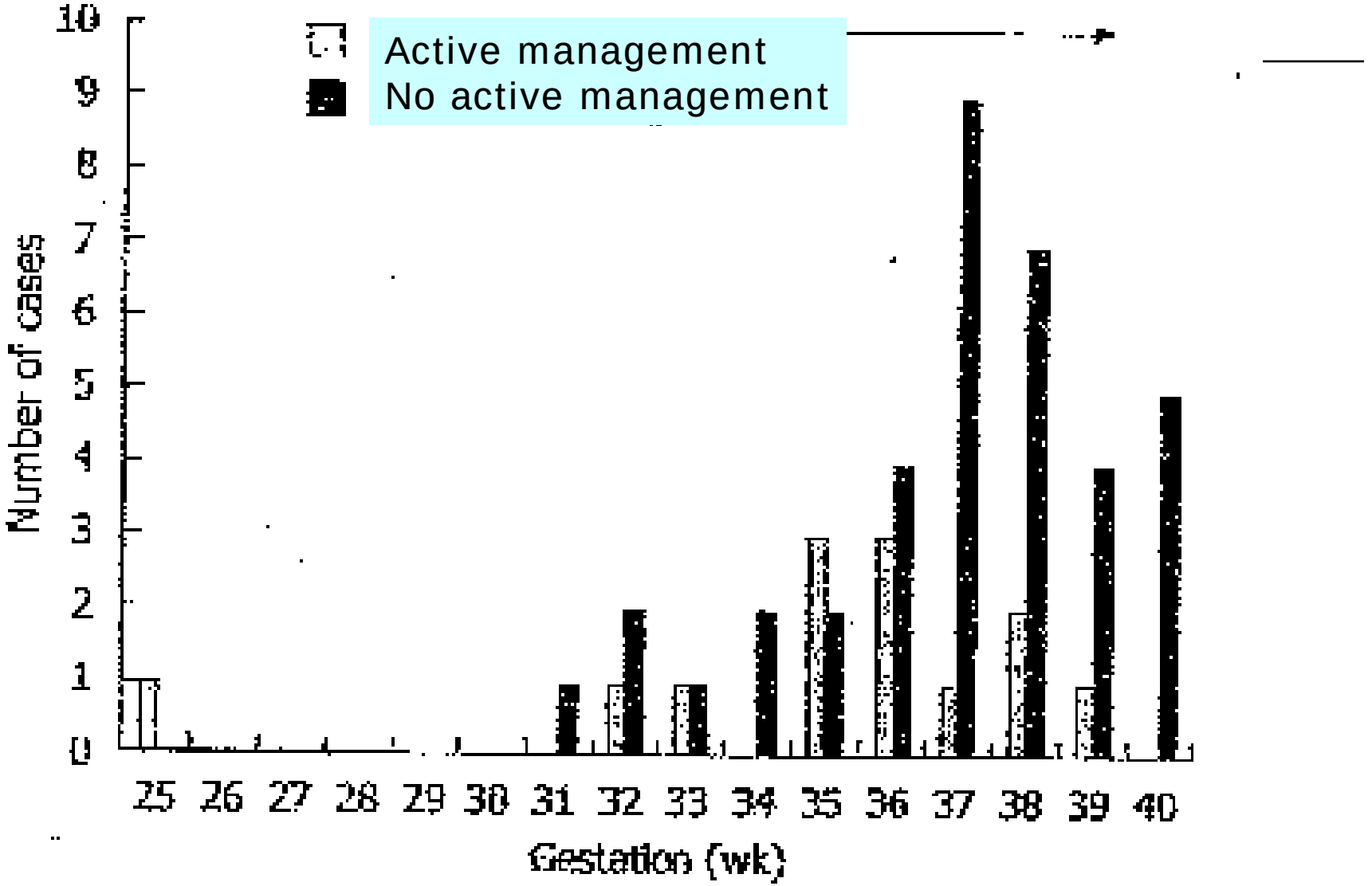
- IUFD
- Mechanism unknown
  - Acute hypoxic injury at autopsy
  - Elevated BA in meconium
  - Placental vasoconstriction
  - Maternal BA>40 umol/L predictive?

IHCP – Fetal Issues

- BA increases myometrial sensitivity to oxytocin (PTB?)
- BA increases colonic motility (meconium?)
- BA directly toxic to cardiomyocytes (sudden IUFD?)

IHCP – Fetal Issues
Data from 5 studies (n=550)

- NRFS 8 - 14%
- Meconium 16 – 44%
- PTB 3 - 16%
- IUFD 2 – 23%
- NND 1 – 2%


Active management
No active management
Number of cases
0
1
2
3
4
5
6
7
8
9
10
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
Gestation (wk)

IHCP – Active Management

- Fetal surveillance
  - 2x/wk NST
  - Weekly BPP and AFI
  - FKC TID
  - Dopplers?
  - Early delivery at 37 weeks

IHCP – Active Management

- Ursodiol
  - Works mainly in EHC; <10% absorbed
  - Stimulates bile secretion by regulating BSEP and MRP4
  - Normalizes CA:CDCA ratio
  - Reduces BA and ALT levels
  - Rarely any side effects (diarrhea)

IHCP – Active Management

- Ursodiol
- Initial dose: 15 mg/kg/d ÷ BID
- If no relief: 25 mg/kg/d ÷TID/QID
- Give enough!

IHCP - Management

- Treatments of unproven value:
  - Steroids
  - Vitamin K
  - SAMe
  - Anti-histamines
  - Cholestyramine

IHCP - Management

- What to do for the itching?
- Anti-histamines not effective
- Steroids not effective
- Anti-histamines may allow sleep if taken in large doses at h.s.
- Eucerin cream after cool shower
- Delivery!

IHCP – ANMC Data (2007-2010)

- Clinical Characteristics (n=206)
- Maternal Age (yrs) 26.7±6.7
- Parity 2 (0-12)
  - (primigravidas (n=50) (24.4%)
- Weight (kg) 82.5±16.5

IHCP – ANMC Data (2007-2010)

- Ethnicity (n=206)
- Yup'ik 43%
- Inupiaq 31%
- Athabaskan 7%
- Aleut 4%
- "Other" 15%

IHCP –ANMC Data (2007-2010)

- Clinical Characteristics (n=206)
- GA at diagnosis (wks) 33.6±3.8
- GA at delivery (wks) 36.9±1.5
- Recurrence (%) 43/199 (21%)
  - (37 x1, 5 x2, 1 x4)

IHCP –ANMC Data (2007-2010)

- Preterm Birth 48/198 (24%)
- Age at PTB (wks) 35.1±1.6
- NICU admits 23 (11%)
  - no neonatal deaths
  - no MAS cases
  - 3 infants born at 37 wks (1.45%)

IHCP – ANMC Data (2007-2010)

- Stillbirths
- Prior IUFD 11/195 (5.6%)
- IUFD this pg 3/206 (1.45%)
- GA at IUFD 36.5 wks

IHCP with IUFD – Current Group

- Case #1
- 21 y/o G4P2 presented with absent FM at 38.1 wks
- “I had itching with all my babies, and I thought it was normal, so I didn’t bother the doctor”
- PP bile acids 79 umol/L

IHCP with IUFD – Current Group

- Case #2
- 20 y/o G1P0 c/o itching since 32 wks, BA not drawn
- IUFD at 36.5 wks
- “The doctors told me itching was normal in pregnancy, and that I should take Benadryl”
- PP bile acids 28 umol/L

IHCP with IUFD – Current Group

- Case #3
- 29 y/o G3P1 with pruritus at 32 wks and begun on ursodiol
- Bile acids returned normal (6.6) and itching got better, so urso stopped
- Itching resumed, BA not repeated, given Benadryl
- IUFD at 37.0 weeks
- PP bile acids 169 umol/L

IHCP-ANMC Data (2007-2010)

- Clinical Presentation
- Pruritus 99%
  - 2 pts had h/o IHCP-→ asx but BA up
- Jaundice (5) 2.4%

- Your guess: What was the leading identifiable dx of those pts w/ itching who didn't have IHCP?? (_____)

IHCP – ANMC Data (2007-2010)

- Lab abnormalities (bile acids):
- Total bile acids (umol/L) 39±58
- Cholic acid (umol/L 23±45

- Normal (<10 umol/L) 39.5%
- >40 umol/L 25.4%
- >200 umol/L 4.9%

IHCP – ANMC Data (2007-2010)

- Laboratory abnormalities
- ALT (U/L) 61±94
- AST (U/L) 43±49
- Alk ptase (U/L) 221±105
- Alk ptase >300 22%
- Bilirubin (mg/dL) .58±.49

IHCP – ANMC Data (2007-2010)

- Laboratory abnormalities
- Normal ALT(<35) 61%
- Normal AST(<35) 65%
- Women w/ 1+abn lab 77%
- Women w/ no abn lab 23%
- Problem:
- “pruritus gravidarum” vs. IHCP?

IHCP – ANMC Data (2007-2010)

- Neonatal outcomes
- Weight (g) 3166±619
- Apgar @ 5 min 9 (0-10)
- Twins 8 sets (4%)
- NICU admit 11% (3>37 wks)
- Meconium 16%
- IRDS 4%

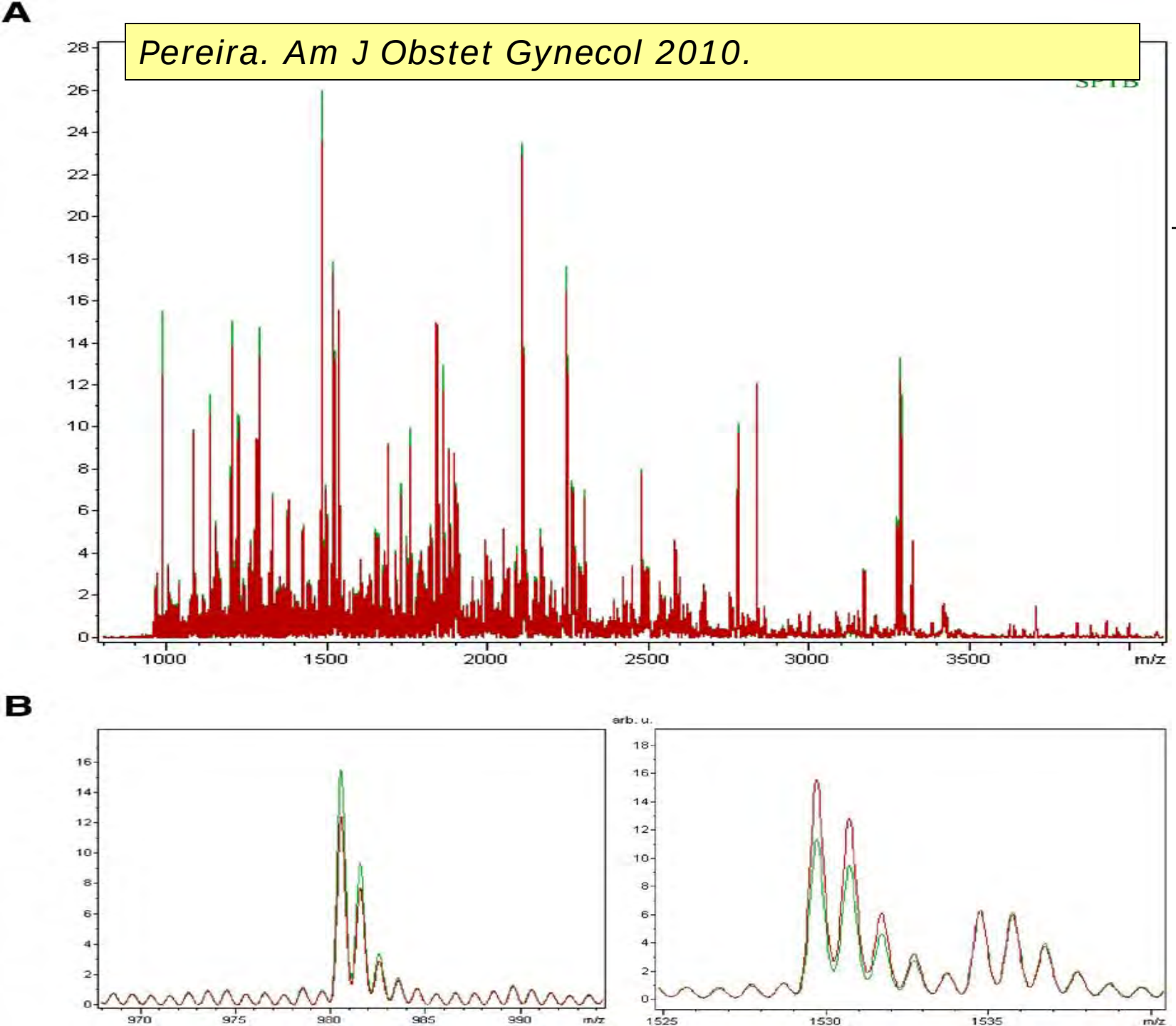
Diagnosis of IHCP
We Need a More Sensitive Marker!

- Candidate Lab Tests:
- Glutathione-S Transferase (GST)
- Proteomic profiling
- Gene (or gene product) testing
- Liver ultrasound for fat?
- Dopplers?
- Are CPT-1 and IHCP connected??

Proteomic Biomarkers for Diagnosis

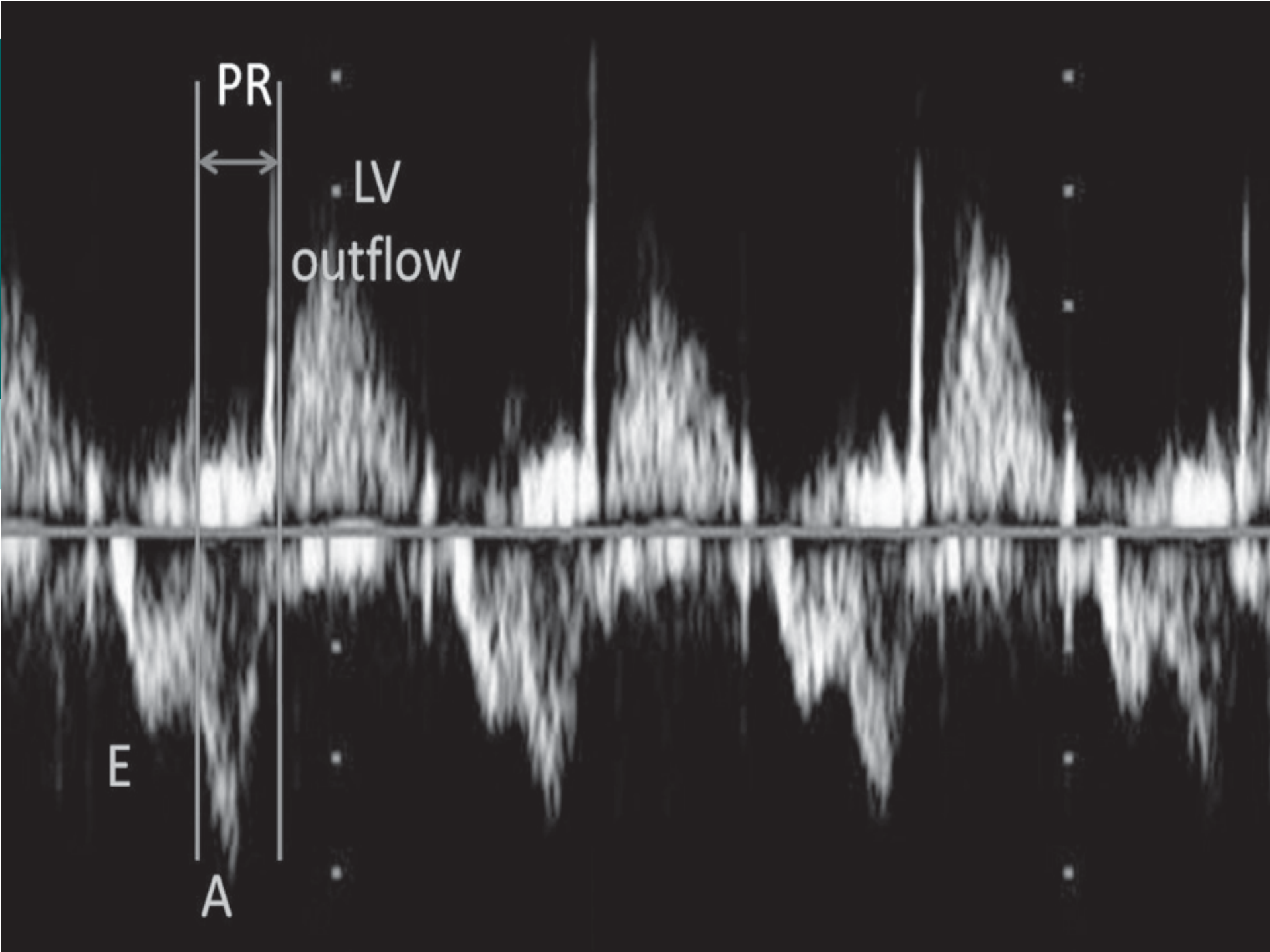
- Proteomic profiling of amniotic fluid in preterm labor. JMFNM 2008.
- Noninvasive diagnosis of amnionitis: proteomic biomarkers in vaginal fluid. AJOG 2010.
- Application of proteomics for diagnosis of fetal aneuploidies. JProteomics 2009.
- Proteomic profiling of urine biomarkers of preeclampsia. AJOG 2009.
- Proteomic profiling to detect fatty liver disease. Gut 2009.

Pereira. Am J Obstet Gynecol 2010.



ICP and IUFD: Is the mechanism cardiac?

- IUFD is usually sudden/unexpected
- In vitro experiments with murine cardiomyocytes show an arrhythmogenic effect of bile acids
- Mechanism might be an effect on the fetal conduction system (as DM)
- Fetal PR interval prolonged in fetus with ICP


PR
LV
outflow
E
A

GOT QUESTIONS?