INTRAHEPATIC CHOLESTASIS OF PREGNANCY
Case
Presentation

• Itch Itch Itch
  – Palms of hands, soles of feet
  – Trunk, limbs

• When
  – Third trimester
  – Earlier if:
    • Previous affected pregnancy
    • Multiple gestation
• Associated with
  – Abnormal LFTs
  – Elevated bile salts
  – Rarely
    • Steatorrhoea, dark urine, anorexia
    • Jaundice
Epidemiology

Incidence
• Overall 0.2-2%
• Variation
  – Ethnic
  – Geographical

Geographical
• Australia 0.2-1.5%
• Europe 1%
• South America 1.5-4%
• Winter months
  – Finland
  – Sweden
  – Chile
  – Portugal

Geenes V & Williamson C. World J Gastroent 2009
Risk Factors

- Previous affected pregnancy*
- Multiple pregnancy
  - Rioseco et al. AJOG 1994
- IVF
  - 2.7 vs 2%
  - Koivunova et al. Hum Reprod 2002
- Age >35 yo
  - Heinonen & Kirkinen O&G 1999
- Hep C positive*
  - Marschallet al. Hepatology 2013
- Genetic
  - FHx 35%, parous sisters 12%

Associations

- Gallstones
  - Marschallet al. Hepatology 2013
- Prolonged emesis
- More sensitive to drugs
- Low vit D
  - Reyes et al. J Hepatol 2000
- Low selenium levels
  - Wikstrom et al Acta Obst Gynecol Scand 2010

*earlier onset
Pathophysiology

• Build up of bile
  – Slower transport

• Cholestatic effect of reproductive hormones
  – Natural history
  – Studies with oral progesterone to prevent PTL
    – Bacq et al. Hepatology 1997
  – Oestrogen
    • Impairment of sulfanation capacity
    • Red hepatocyte membrane fluidity
Familial Component

• Familial clustering of disorder

• Sex-limited dominant

• Sisters of affected women RR= 12
  – Williamson et al. BJO 2004

• 3 sub-types of progressive familial ICP 1, 2 and 3
  – mutations
Diagnosis

Presentation

• Progressive itch
  – Classically
    • Palms, soles, spreads
    – Resolves 48 hrs postnatally
• No rash
  – Excoriations
• Insomnia, malaise
• Rarely
  – Dark urine, steatorrhoea, anorexia
  – Jaundice

• Abnormal LFTs
  – Mod rise transaminases
  – Inc ALP
  – Inc GGT (20%)
    • Mutation ABCB4 (MDR3)
  – 4-6 weeks PN to normalise
• Inc Bile Acids
• Rise bilirubin
  – Up to 10%
  – Mild conjugated hyperbilirubenaemia
Exclude other causes

**Obstetric-related**
- AFLP
- HELLP
- PUPPs

**Non-obstetric**
- Viral
  - Hep A/B/C
  - EBV, CMV
- Primary biliary cirrhosis
- Biliary obstruction
- Gallstones
  - Present in 13% with ICP
- Venous thrombosis
Investigations

• Liver USS
• Viral serology
• Liver autoantibodies
  – Chronic active hepatitis
  – Primary biliary cirrhosis

• Bloods
  – LFTS
  – Fasting bile acids
  – FBC
  – Coags
  – Viral serology
    • Hep A/B/C, EBV, CMV
  – Anti-smooth muscle antibodies
  – Anti-mitochondrial antibodies
Risks

Maternal

- PPH
- Vit K deficiency
- Operative delivery

Fetal

- Fetal distress 12-22%
- Meconium 25-25%
- Spontaneous preterm delivery 12-44%
- Iatrogenic preterm delivery
- RDS
  - Independent to gestation
    - Zecca et al. Pediatrics 2004
- IUFD
IUFD

• If delivered by 38 weeks
  – 11% reduced to 0.2%

• Mechanism essentially unknown
  • Possibly related to bile acids
  • Majority in women with co-existing complications
    – GDM, PET
    – ?worsen fetal prognosis
      • Geenes et al. Hepatology 2014
Clustering of Stillbirths
Bile Salts and IUFD

**Mechanism**

- Dose dependent
- Vasoconstriction
  - Placental chorionic veins
  - Abrupt reduction in O₂-ated blood flow
  - Fetal asphyxia
    - Reid et al. BMJ 1976
- Fetal arrhythmia
  - Al et al. Int J Gynecol Obst 2006
- Toxic to myocytes
  - Animal studies

**Levels**

- Glantz et al. *Hepatology* 2004
  - N=690, Swedish
  - R/ship to adverse outcomes
    - 1-2 mmol/l increase translates to a 1-2% risk in adverse outcome
    - Only stat sig if bile acids >40 mmol/L
  - Confirmed subsequently by other large cohorts
Management

**Antenatal**
- Weekly LFTS, bile acids
- Fetal surveillance
  - CTG, USS
    - Weak evidence
- Medications
- Vitamin K
  - From 32wks or diagnosis

**Intrapartum**
- Consider IOL from 37 wks
- Continuous CTG
- Active 3rd stage
Medication

First line
- Ursodeoxycholic acid
- Anti-histamines
- Vitamin K
- Menthol creams

Second line
- Dexamethasone
- Rifampicin
- Cholestyramine

www.wellingtonobstetrics.co.nz
Symptomatic relief

**Creams**
- Aqueous menthol
  - Refrigerate

**Sedating Anti-histamines**
- Promethazine
  - 25 mg PO nocte
**Ursodeoxycholic Acid**

**Action**
- 1000-2000 mg/d in divided doses (TDS)
  - Titrated to symptoms
- Tertiary bile acid present in small amount is normal human serum
- Mechanism of action poorly understood
• **Effect**
  – Improved maternal symptoms 80-90%
  – Red bile acid levels
    • Maternal serum
    • Umbilical cord serum
  – Improved placental function
    – *Geenes et al. Placenta* 2011
    – *Sewano et al Hepatol* 1998

• **Side-effects**
  • Loose stools 16%
  • Nausea
  • Vomiting
Vitamin K

- Assoc with malabsorption of fat-soluble vitamins
  - Red enterohepatic circulation of bile acids and red uptake via terminal ileum

- Start at diagnosis or 32 weeks
- Reduce risk of maternal and fetal bleeding
  - Limited data to support

www.wellingtonobstetrics.co.nz
Rifampicin

- 150 mg PO OD
- Enhances bile detoxification and excretion and bilirubin conjugation
- Improves symptoms and biochemical markers of liver injury
Dexamethasone

- 12 mg PO OD
- Suppress fetoplacental oestrogen production
- Partial clinical &/- biochemical response 70%
  - Hirvioja et al. BJOG 1992
  - Inconsistent results
    - Glantz et al. Hepatology 2005;
    - Diac et al. J O&G 2006; Kretowicz and McIntyre. ANZJOG 1994

- Side-effects
  - Restlessness
  - Sleeplessness
  - Reduced FMs
  - Glucose impairment
Cholestyramine

• 4mg PO TDS

• Bile-chelating agent

• May relieve itching

• Poorly Tolerated
  – Unpalatable
  – GI upset

• LFTs and bile salts
  – No improvement

• May reduce absorption of fat-soluble vitamins
  – Increase risk of PPH

www.wellingtonobstetrics.co.nz
Risk Recurrence

- 90%
- Earlier onset
- Lower if index pregnancy multiple gestation
- COCP
  - Seek alternative contraception
Additional References

• RCOGUK. Obstetric Cholestasis: Green-top Guideline No. 43. April 2011
• Williamson C and Geenes V. Intrahepatic Cholestasis of Pregnancy. *Obst Gynecol* 2014; 124(1): 120-133