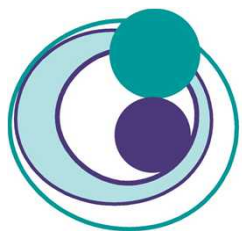




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INTRAHEPATIC CHOLESTASIS OF PREGNANCY



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Case

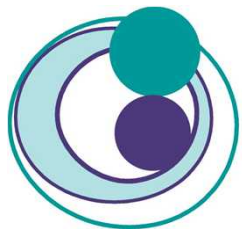


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Presentation

- Itch Itch Itch
 - Palms of hands, soles of feet
 - Trunk, limbs
- When
 - Third trimester
 - Earlier if:
 - Previous affected pregnancy
 - Multiple gestation



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- 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%

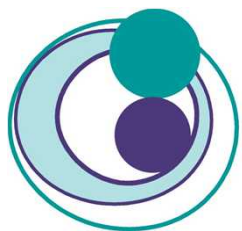
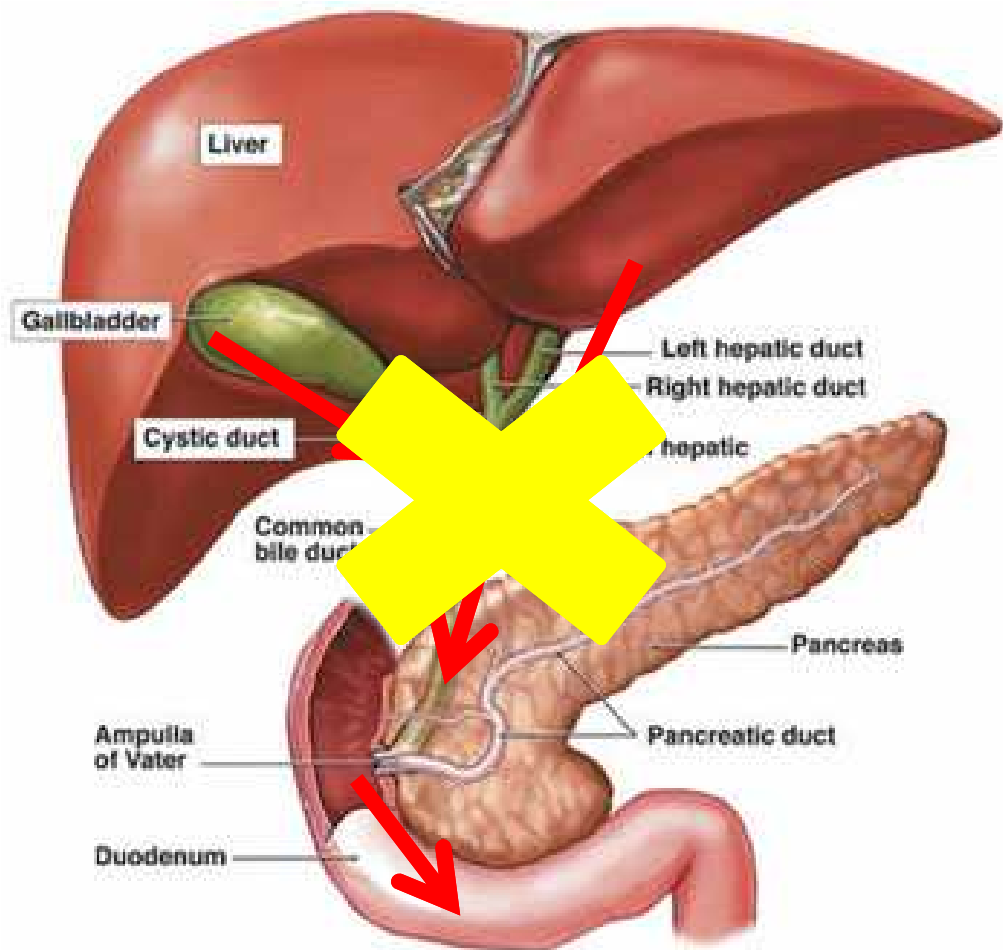
*earlier onset

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*

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 sulfonation capacity
 - Red hepatocyte membrane fluidity



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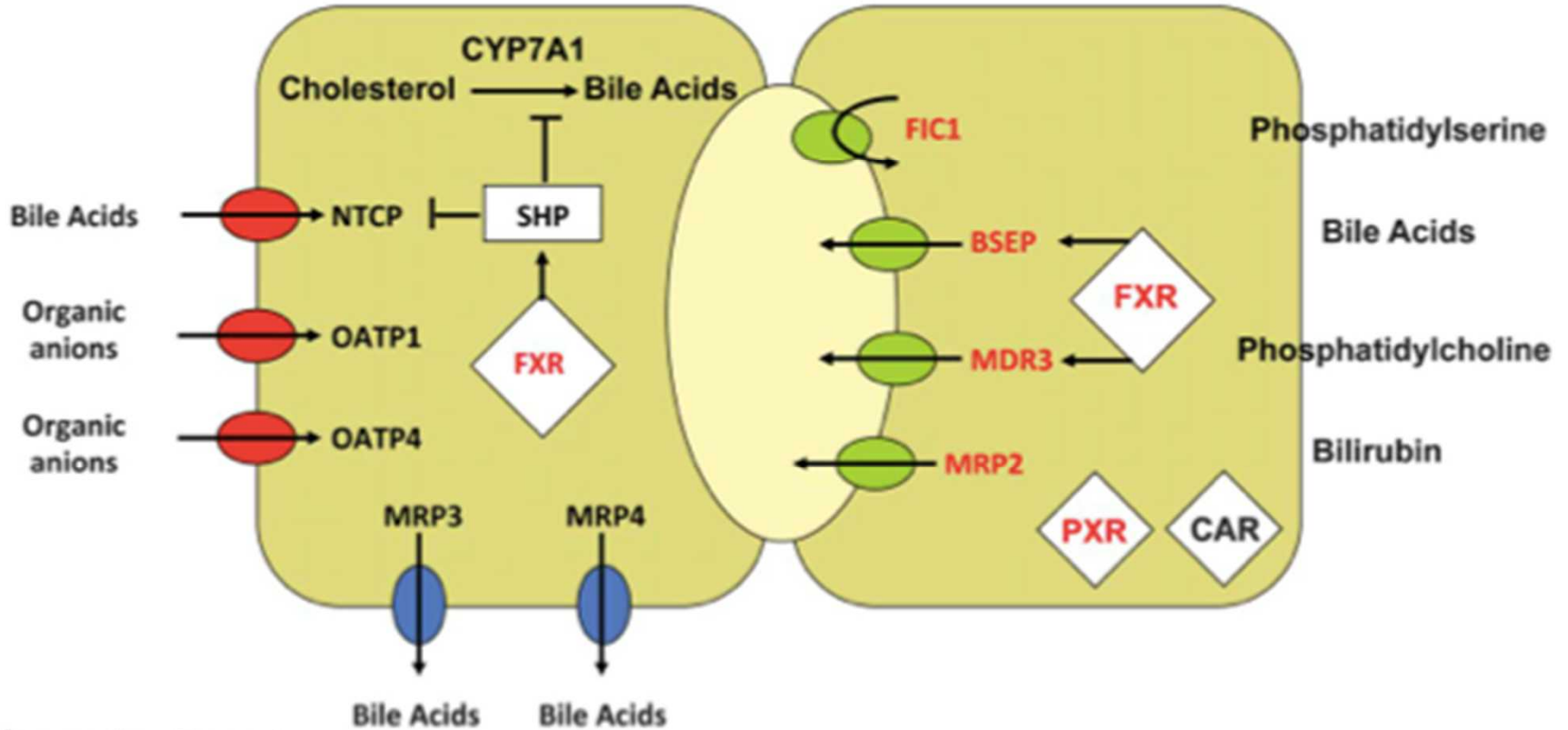
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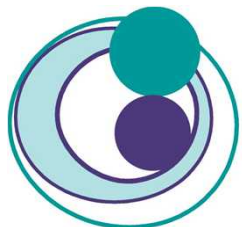
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Sinusoidal Uptake

Canalicular Export



Alternative Export



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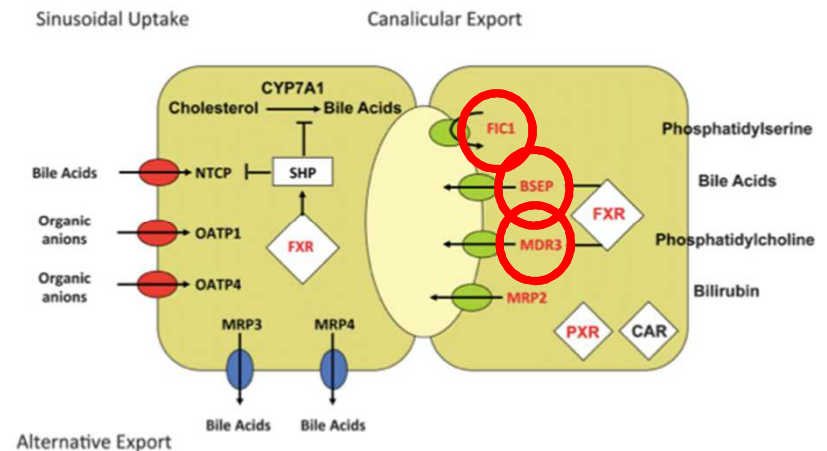
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Familial Component

- Familial clustering of disorder
- Sex-limited dominant
 - Jacquemin *et al. Lancet* 1999
- Sisters of affected women
RR= 12
 - Williamson *et al. BJOG* 2004
 - Geenes *et al. Hepatology* 2014
- 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 hyperbilirubinaemia

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

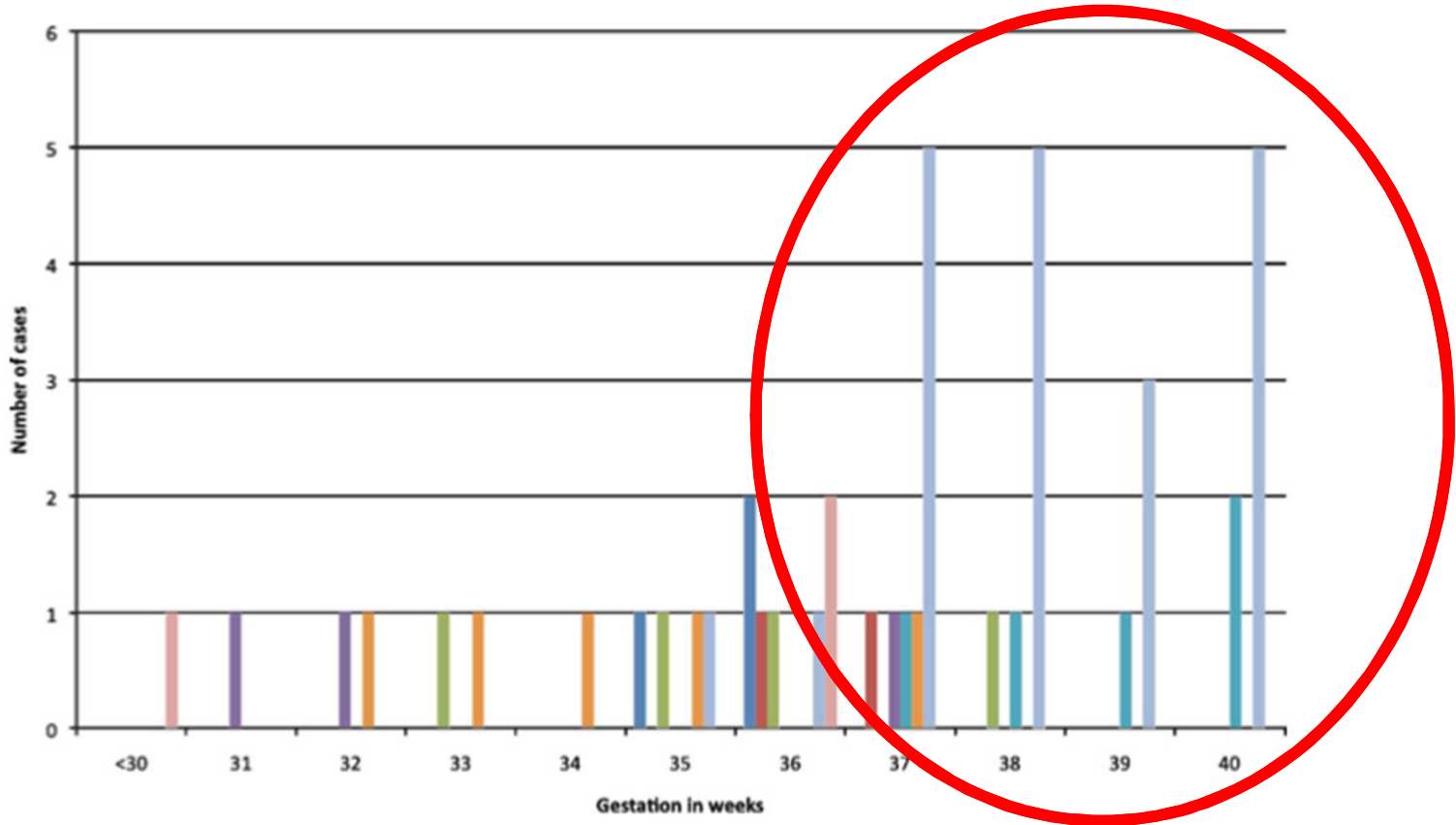
Fetal

- 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

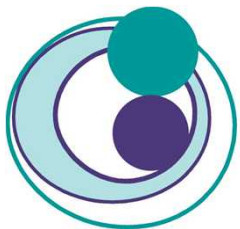
IUFD

- 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



■ Fisk 1998 (14)
 ■ Alsulyman 1996 (24)
 ■ Rioseco 1992 (5)
 ■ Laatikainen 1975(4)
■ Davies 1995 (25)
 ■ Reid 1976 (13)
 ■ Williamson 2001 (15)
 ■ Glantz 2004 (26)



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Bile Salts and IUFD

Mechanism

- Dose dependent
- Vasoconstriction
 - Placental chorionic veins
 - Abrupt reduction in O₂-ated blood flow
 - *Sepulveda et al. Eur J Obst Gynecol Reprod Biol 1991*
 - 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

Symptomatic relief

Creams

- Aqueous menthol
 - Refrigerate

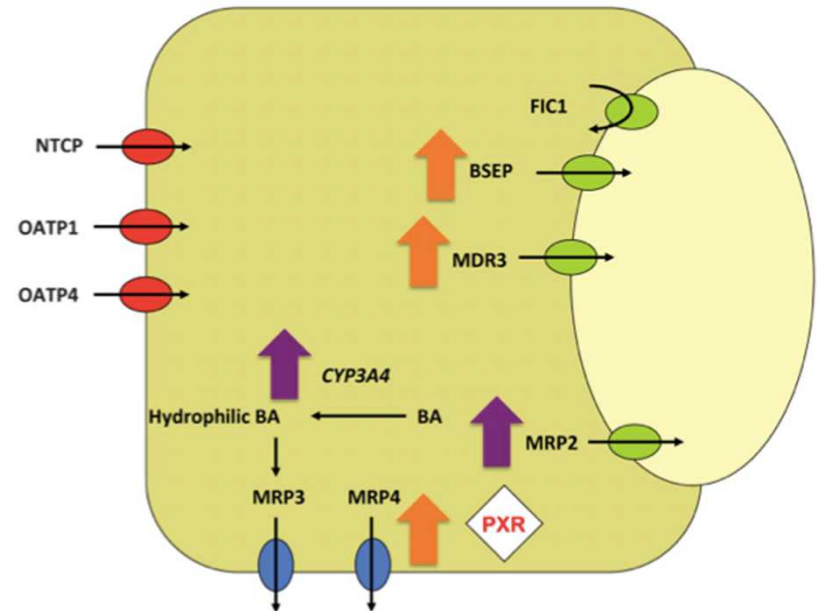
Sedating Anti-histamines

- 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

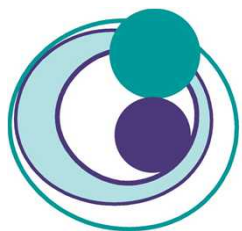
- Maternal serum
 - Umbilical cord serum

- Improved placental function

- *Geenes et al. Placenta 2011*
 - *Sewano et al Hepatol 1998*

- Side-effects

- Loose stools 16%
 - Nausea
 - Vomiting



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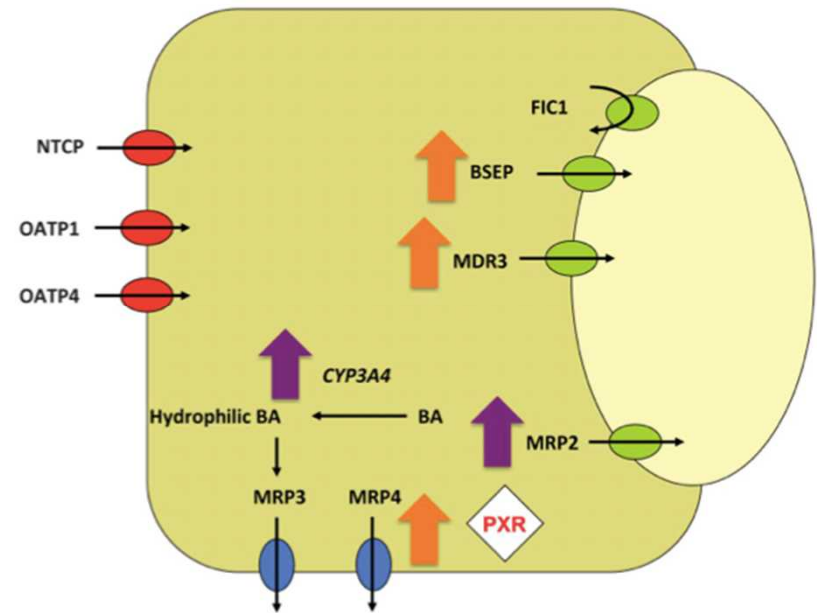
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Vitamin K

- 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

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

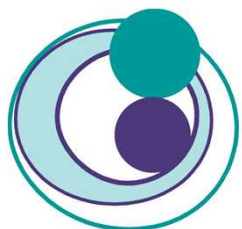
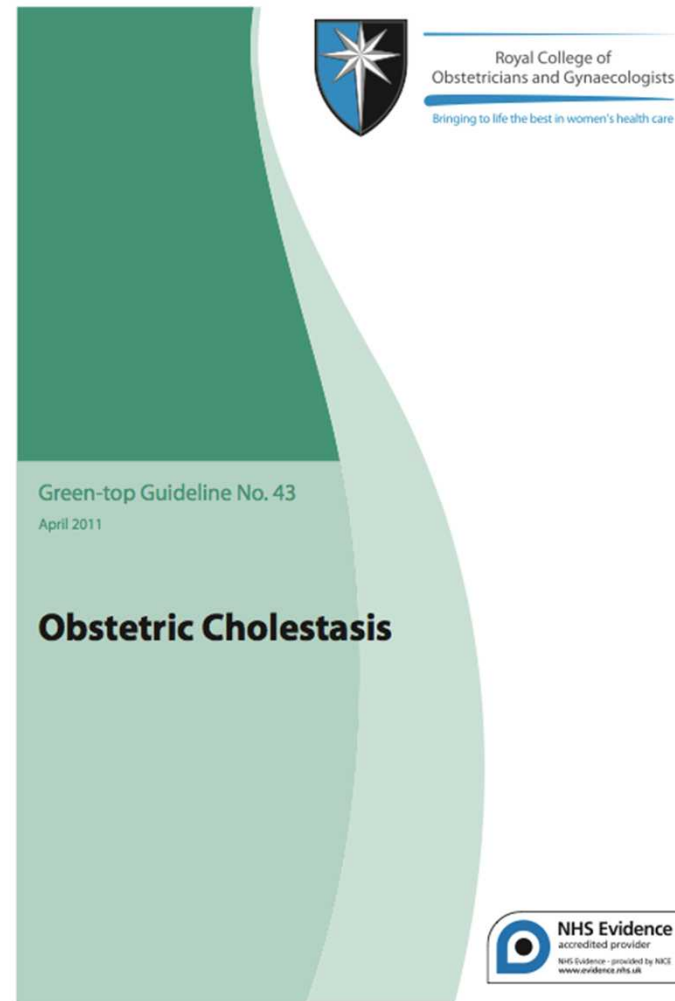
Cholestyramine

- 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

Risk Recurrence

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

Guidelines



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