# Pregnancy Cholestasis: Diagnosis, management, & delivery timing

- Jim Thornton
  - Nottingham

# Intrahepatic cholestasis of pregnancy

- Definitions
- Names
- Cause
- Risks and associations
- Drug treatment
- Delivery timing

# Intrahepatic cholestasis of pregnancy

- 0.7%
- Itching, esp. palms and soles
- Raised bile acids (Normal fasting <10)

- Clinical risks
  - Preterm birth?
  - Stillbirth?

# 352 cases detected via a patient support group

BJOG: an International Journal of Obstetrics and Gynaecology
July 2004, Vol. 111, pp. 676–681

DOI: 10.1111/j.1471-0528.2004.00167.x

## Clinical outcome in a series of cases of obstetric cholestasis identified via a patient support group

Catherine Williamson,[a,b] Laura M. Hems,[a] Dimitrios G. Goulis,[a] Ian Walker,[c] Jennifer Chambers,[a] Oscar Donaldson,[a] Michael de Swiet,[b] Desmond G. Johnston[a]

**Objective** To explore the clinical features of obstetric cholestasis pregnancies in UK white Caucasians.

**Design** A questionnaire survey.

**Setting** Study coordinated at Queen Charlotte's Hospital.

**Population** Clinical features of 352 affected pregnancies in 227 Caucasian women identified via a patient support group.

**Methods** Evaluation of the gestation at which prematurity and intrauterine death occur, and recording of additional clinical features in pregnancies complicated by obstetric cholestasis.

**Main outcome measures** The timing of pregnancies complicated by intrauterine death and prematurity.

**Results** Among the affected pregnancies, 23 (7%) were complicated by intrauterine death (20 singletons and 3 twins) and 133 (38%) were delivered prematurely (56 spontaneous and 77 iatrogenic). Eighteen of the 20 singleton intrauterine deaths occurred after 37 weeks. All three intrauterine deaths in twin pregnancies occurred before 37 weeks. Pruritus started earlier in pregnancies complicated by spontaneous prematurity, but not in those complicated by intrauterine death.

**Conclusions** Intrauterine death in singleton pregnancies complicated by obstetric cholestasis death mainly occurs after 37 weeks. The gestation at which pruritus is first reported may help to predict spontaneous prematurity.

# Intrauterine fetal death

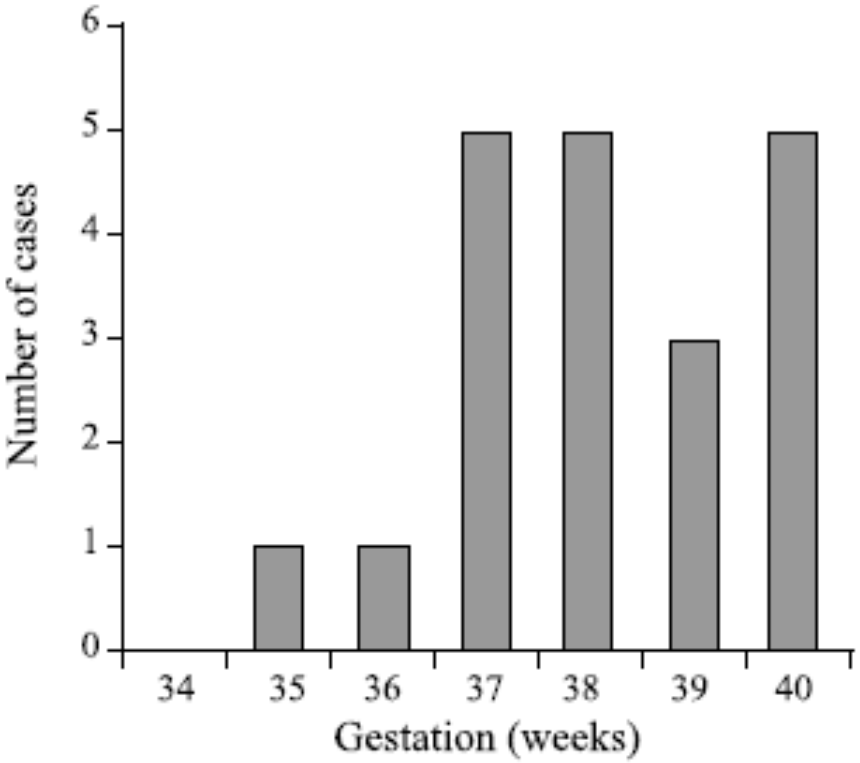



**Fig. 2.** Gestational week at which intrauterine death occurred in singleton pregnancies complicated by obstetric cholestasis.

# Severe disease Bile acid > 40 UKOSS

HEPATOLOGY

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

AUTOIMMUNE, CHOLESTATIC AND BILIARY DISEASE

## Association of Severe Intrahepatic Cholestasis of Pregnancy With Adverse Pregnancy Outcomes: A Prospective Population-Based Case-Control Study

Victoria Geenes,[1] Lucy C. Chappell,[2] Paul T. Seed,[2] Philip J. Steer,[3] Marian Knight,[4] and Catherine Williamson[1,2]

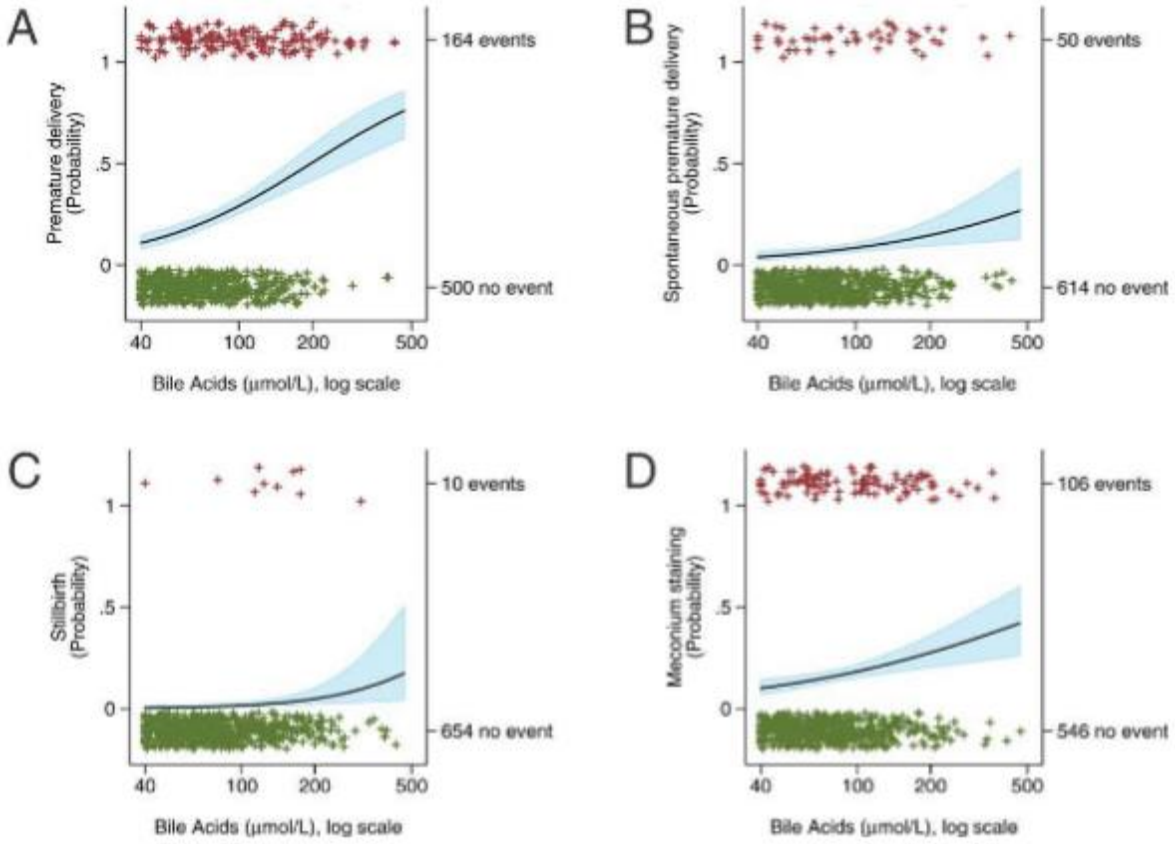
Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-specific liver disease, characterized by maternal pruritus and raised serum bile acids. Our objectives were to describe the epidemiology and pregnancy complications associated with severe ICP and to test the hypothesis that adverse perinatal outcomes are increased in these women. A prospective population-based case-control study with national coverage was undertaken using the UK Obstetric Surveillance System (UKOSS). Control data for comparison were obtained from women with healthy pregnancy outcome through UKOSS (n = 2,232), St Mary's Maternity Information System (n = 554,319), and Office for National Statistics (n = 668,195). The main outcome measures investigated were preterm delivery, stillbirth, and neonatal unit admission. In all, 713 confirmed cases of severe ICP were identified, giving an estimated incidence of 9.2 per 10,000 maternities. Women with severe ICP and a singleton pregnancy (n = 669) had increased risks of preterm delivery (164/664; 25% versus 144/2200; 6.5%; adjusted odds ratio [OR] 5.39, 95% confidence interval [CI] 4.17 to 6.98), neonatal unit admission (80/654; 12% versus 123/2192; 5.6%; adjusted OR 2.68, 95% CI 1.97 to 3.65), and stillbirth (10/664; 1.5% versus 11/2205; 0.5%; adjusted OR 2.58, 95% CI 1.03 to 6.49) compared to controls. Seven of 10 stillbirths in ICP cases were associated with coexisting pregnancy complications.

# Bile acid > 40

| | OR (95% CI) |
|---|---|
| Preterm delivery | 5.4 (4.2 – 7.0) |
| Spontaneous PTD | 2.2 (1.5 - 3.3) |
| Iatrogenic PTD | 8.8 (6.2 – 12) |
| Stillbirth | 2.6 (1.0 - 6.4) |
| Birth wt <C10 | .70 (.54 - .91) |

# Pre-term delivery, stillbirth & meconium

Probability in relation to bile acid level.



# Treatment

- Antihistamines
- Emollient creams
- Activated charcoal
- Urso-deoxy-cholic acid (UDCA)

- Early delivery

# Cochrane review

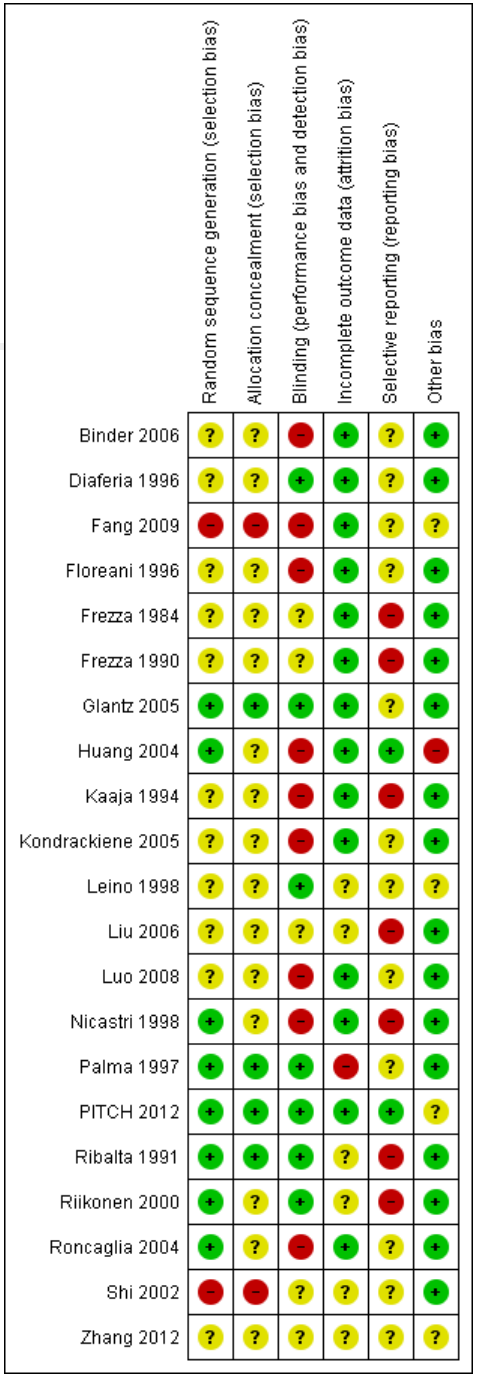
**Interventions for treating cholestasis in pregnancy (Review)**

Gurung V, Stokes M, Middleton P, Milan SJ, Hague W, Thornton JG

THE COCHRANE COLLABORATION®

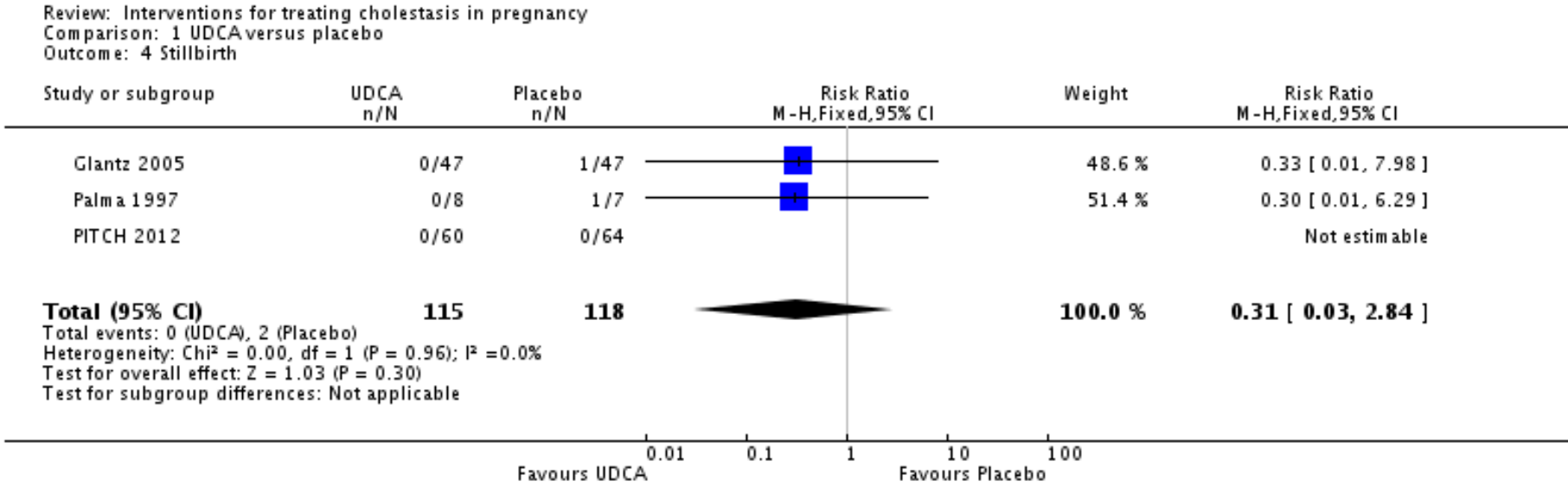
# Cochrane review

- 21 trials. 1197 women
- Treatments
  - **Ursodeoxycholic acid**
  - S-adenosylmethionine
  - Guar gum
  - Activated charcoal
  - Dexamethasone
  - Chinese remedies



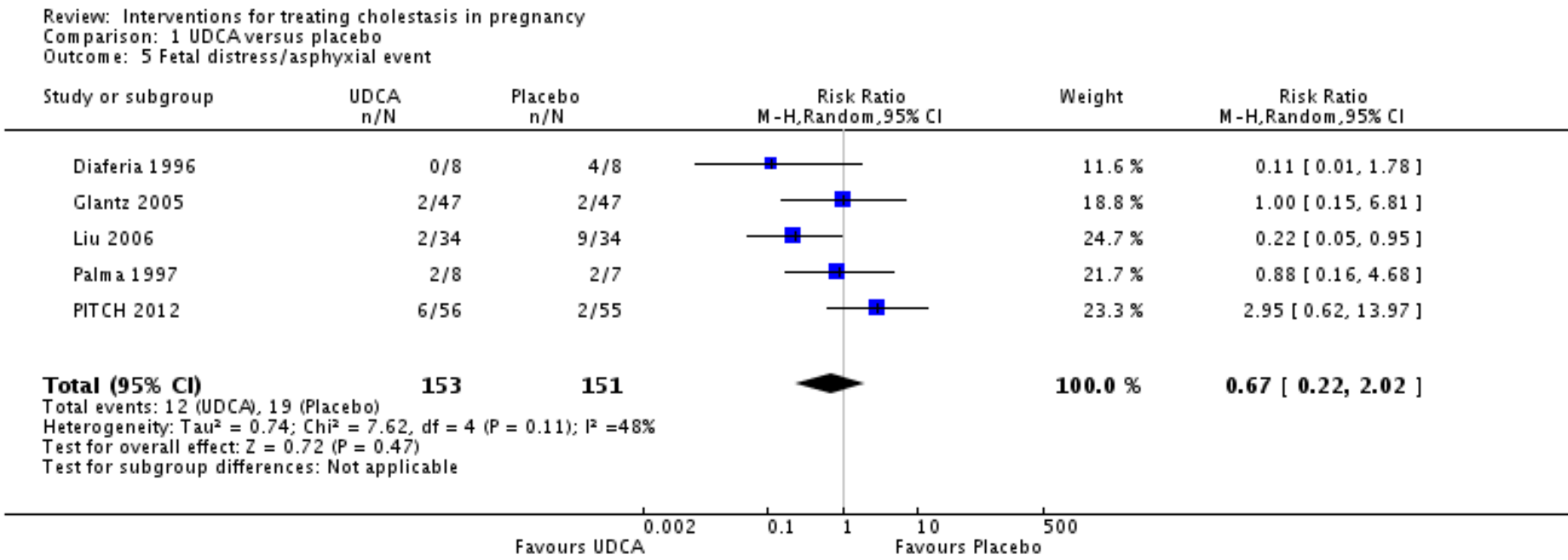
# UDCA v placebo

- On stillbirth



# IDCA v placebo

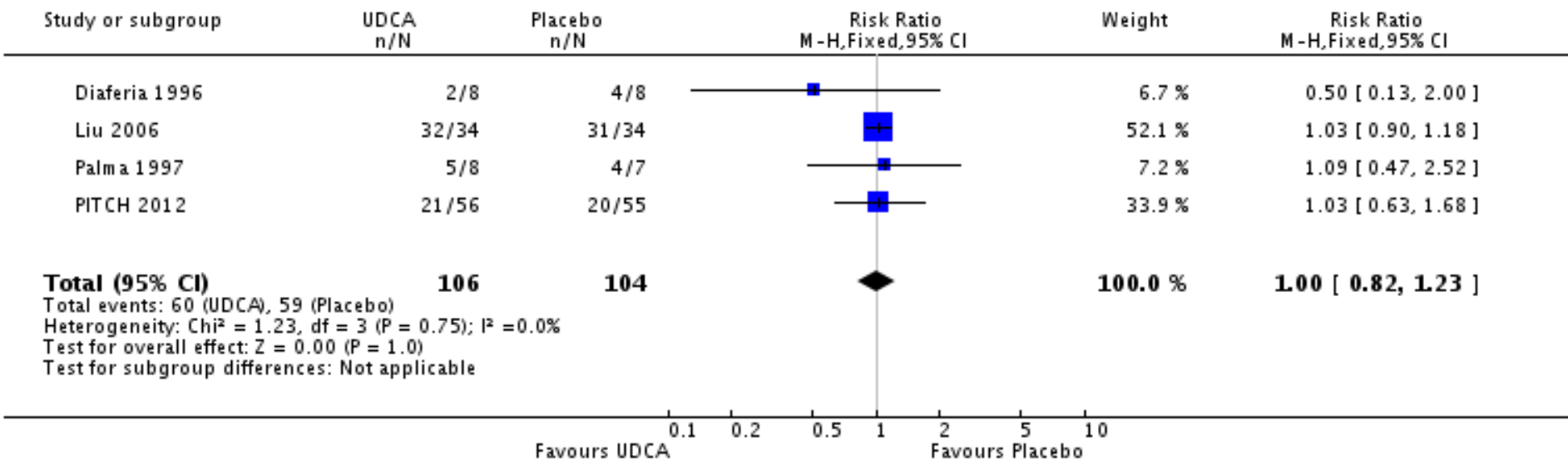
- On fetal distress/asphyxial event



# UDCA v placebo

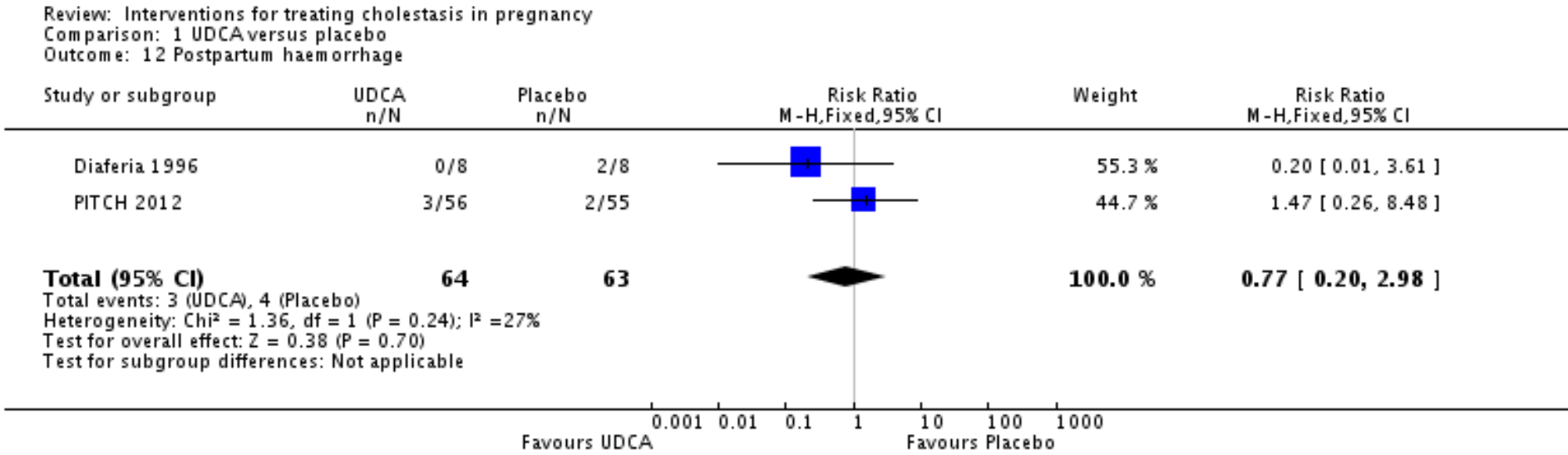
- On Caesarean section

Review: Interventions for treating cholestasis in pregnancy
Comparison: 1 UDCA versus placebo
Outcome: 11 Caesarean section



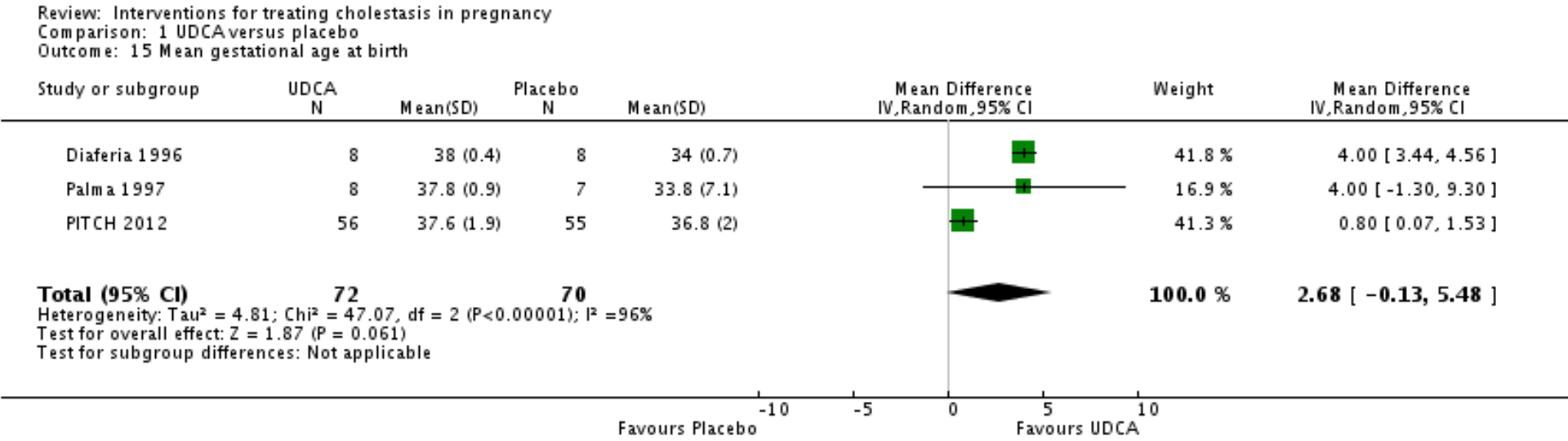
# UDCA v placebo

- On post partum haemorrhage



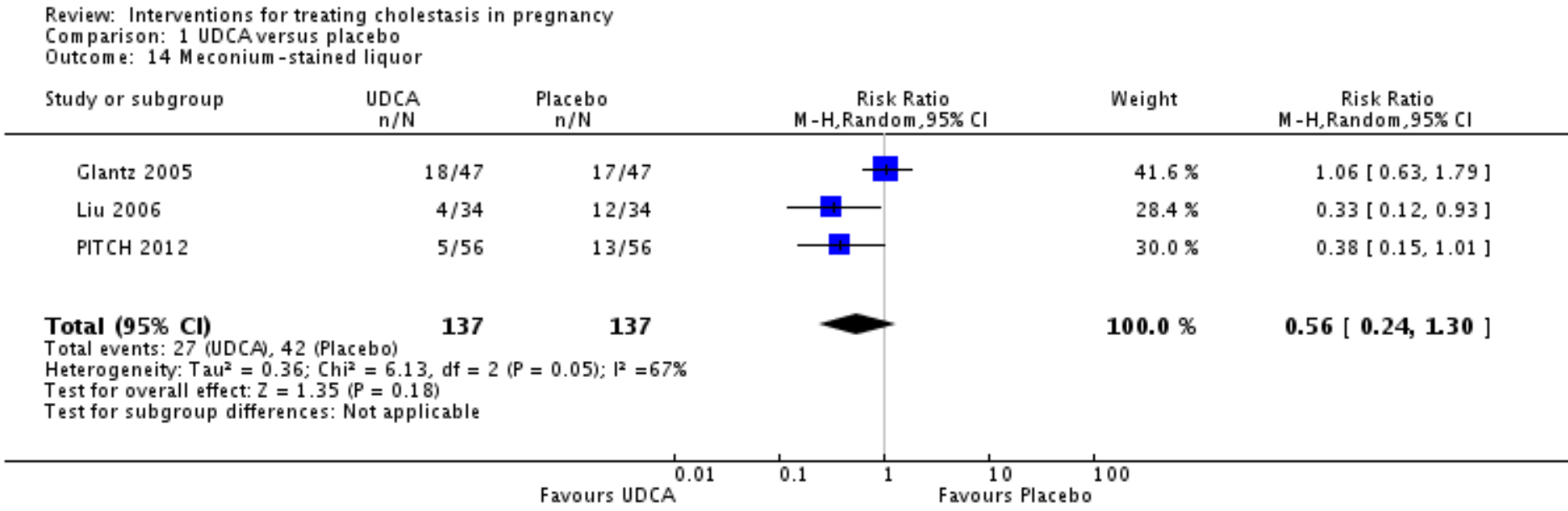
# UDCA v placebo

- On mean gestational age



# UDCA v placebo

- On meconium stained liquor



# The PITCH trial

BMJ

*BMJ* 2012;344:e3799 doi: 10.1136/bmj.e3799 (Published 13 June 2012)



RESEARCH

## Ursodeoxycholic acid versus placebo, and early term delivery versus expectant management, in women with intrahepatic cholestasis of pregnancy: semifactorial randomised clinical trial



Lucy C Chappell *clinical senior lecturer in maternal and fetal medicine*[1], Vinita Gurung *specialist trainee in obstetrics and gynaecology*[2], Paul T Seed *senior lecturer in medical statistics*[1], Jenny Chambers *clinical trial coordinator*[3], Catherine Williamson *professor of obstetric medicine*[3], James G Thornton *professor of obstetrics and gynaecology*[4], on behalf of the PITCH Study Consortium

# Factorial Trial

| **UDCA + Early delivery** | **Placebo + Early delivery** |
| --- | --- |
| UDCA + Delayed delivery | Placebo + Delayed delivery |

# UDCA v placebo on pruritus

100mm scale. 0 = no itching. 100 = worst posible
Control = 60mm.
Minimum clinically important difference = 30mm improvement

| Outcomes | UDCA | Placebo | Difference (95% CI) | P value |
|---|---|---|---|---|
| **Maternal outcomes** | n=56 | n=55 | | |
| Mean (SD) worst episode of itch over past 24 hours (mm on VAS) | 49.0 (24.8) | 61.9 (27.2) | −16.2 (−26.5 to −5.9) | 0.003 |

UDCA reduces pruritus but the benefit is not worth the bother/risk

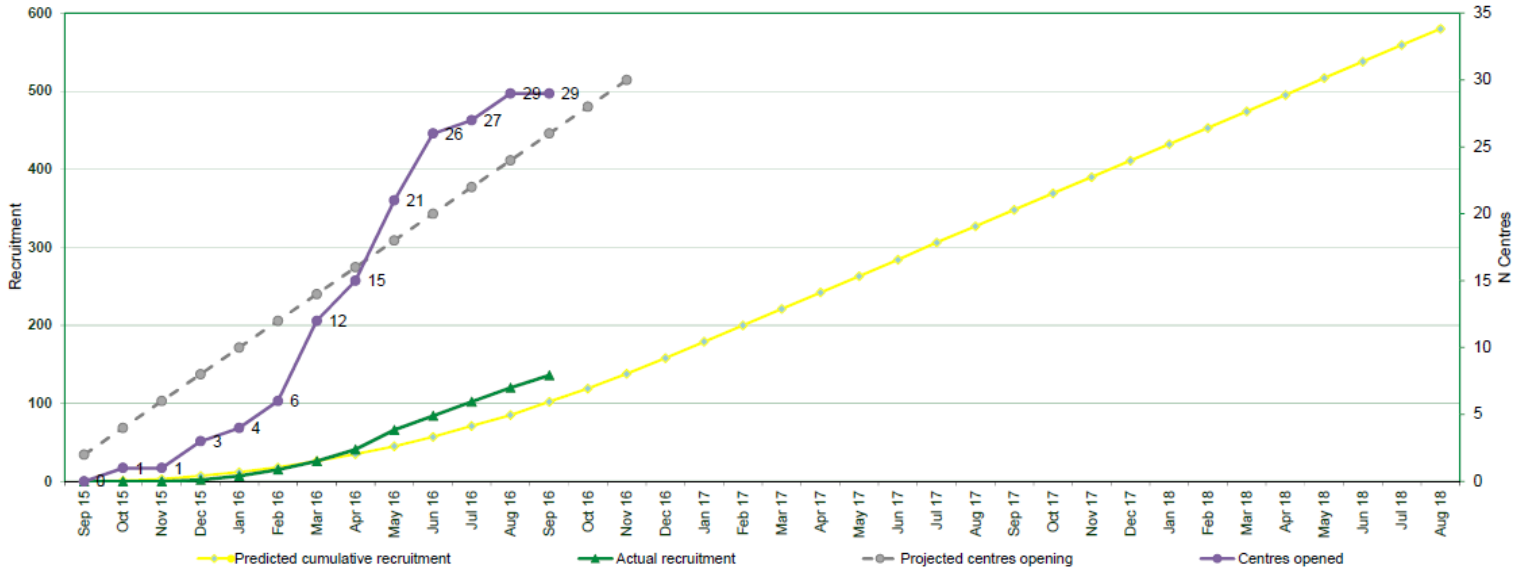
# Early delivery v delay

| | Early delivery n= 30 | Delay n = 32 | Relative risk (95% CI) |
|---|---|---|---|
| Caesarean | 7 | 11 | 0.7 (0.3 to 1.6) |
| Live birth | 30 | 33 (1twins) | |
| Apgar <7 at 5mins | 1 | 1 | |
| Meconium | 3 | 6 | 0.71 (0.23 to 2.2) |
| Admission to NNU | 1 | 2 | |
| Ventilation | 0 | 1 | |
| Jaundice | 2 | 0 | |
| Convulsions | 0 | 0 | |

# PITCHES

- Phase III trial in IntrahepaTic CHolestasis of pregnancy (ICP) to Evaluate urSodeoxycholic acid in improving perinatal outcome
  - P- Pregnant women with obstetric cholestasis
  - I – UDCA
  - C – placebo
  - O - Perinatal death/ admission to NICU
  - 612 participants

# PITCHES trial progress Sept 2016




| | | Sep 15 | Oct 15 | Nov 15 | Dec 15 | Jan 16 | Feb 16 | Mar 16 | Apr 16 | May 16 | Jun 16 | Jul 16 | Aug 16 | Sep 16 | Oct 16 | Nov 16 | Dec 16 | Jan 17 | Feb 17 | Mar 17 | Apr 17 | May 17 | Jun 17 | Jul 17 | Aug 17 | Sep 17 | Oct 17 | Nov 17 | Dec 17 | Jan 18 | Feb 18 | Mar 18 | Apr 18 | May 18 | Jun 18 | Jul 18 | Aug 18 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Predicted Recruitment | Centres Open | 2 | 4 | 6 | 8 | 10 | 12 | 14 | 16 | 18 | 20 | 22 | 24 | 26 | 28 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 | 30 |
| | Monthly Recruitment | | 1 | 2 | 4 | 5 | 6 | 8 | 9 | 10 | 12 | 14 | 14 | 17 | 17 | 19 | 20 | 21 | 21 | 21 | 21 | 21 | 21 | 22 | 21 | 21 | 21 | 21 | 21 | 21 | 21 | 21 | 22 | 21 | 21 | 21 |
| | Cumulative Recruitment | | 1 | 3 | 7 | 12 | 18 | 26 | 35 | 45 | 57 | 71 | 85 | 102 | 119 | 138 | 158 | 179 | 200 | 221 | 242 | 263 | 284 | 306 | 327 | 348 | 369 | 390 | 411 | 432 | 453 | 474 | 495 | 517 | 538 | 559 | 580 |
| Actual Recruitment | Centres Open | | 1 | 1 | 3 | 4 | 6 | 12 | 15 | 21 | 26 | 27 | 29 | 29 | | | | | | | | | | | | | | | | | | | | | | | |
| | Monthly Recruitment | | | | 2 | 5 | 8 | 11 | 15 | 25 | 18 | 18 | 18 | 16 | | | | | | | | | | | | | | | | | | | | | | | |
| | Cumulative Recruitment | | | | 2 | 7 | 15 | 26 | 41 | 66 | 84 | 102 | 120 | 136 | | | | | | | | | | | | | | | | | | | | | | | |
| | % of Target | | | | 29% | 58% | 83% | 100% | 117% | 147% | 147% | 144% | 141% | 133% | | | | | | | | | | | | | | | | | | | | | | | |

# Conclsıon

- Associatıon wıth preterm labour and stıllbırth for bıle acıd > 40
- UDCA reduces ıtchıng by a small amount
- No other proven benefit
- Delıvery by 39 weeks

# Spontaneous preterm delivery

Relation to bile acid level