réseau sécurité naissance
NAÎTRE ENSEMBLE

26e Journées Scientifiques

# Cholestase gravidique

RECOMMANDATIONS POUR LA PRATIQUE CLINIQUE

PARI(S) SANTÉ FEMMES 2023

DR VINCENT DOCHEZ

SERVICE DE GYNÉCOLOGIE-OBSTÉTRIQUE – CHU NANTES

23/11/2023

PARI(S) SANTÉ FEMMES

CNGOF

G Model
GOFS-3708; No. of Pages 18

ARTICLE IN PRESS

Gynécologie Obstétrique Fertilité & Sénologie xxx (xxxx) xxx–xxx

Disponible en ligne sur
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

Recommandations pour la pratique clinique

# La cholestase gravidique : recommandations pour la pratique clinique du Collège national des gynécologues obstétriciens français

## *Intrahepatic cholestasis of pregnancy: French College of Obstetricians and Gynecologists guidelines for clinical practice*

L. Sentilhes [a,*], M.-V. Sénat [b], H. Bouchghoul [a], P. Delorme [c], D. Gallot [d], C. Garabedian [e], H. Madar [a], N. Sananès [f], F. Perrotin [g], T. Schmitz [h]

# 3 articles

- ESSAI PITCHES (RCT) : 2019
- META-ANALYSE : OVADIA 2019
- COCHRANE 2020

# ESSAI PITCHES

Lancet 2019; 394: 849–60

## Ursodeoxycholic acid versus placebo in women with intrahepatic cholestasis of pregnancy (PITCHES): a randomised controlled trial

Lucy C Chappell, Jennifer L Bell, Anne Smith, Louise Linsell, Edmund Juszczak, Peter H Dixon, Jenny Chambers, Rachael Hunter, Jon Dorling, Catherine Williamson*, Jim G Thornton*, for the PITCHES study group†

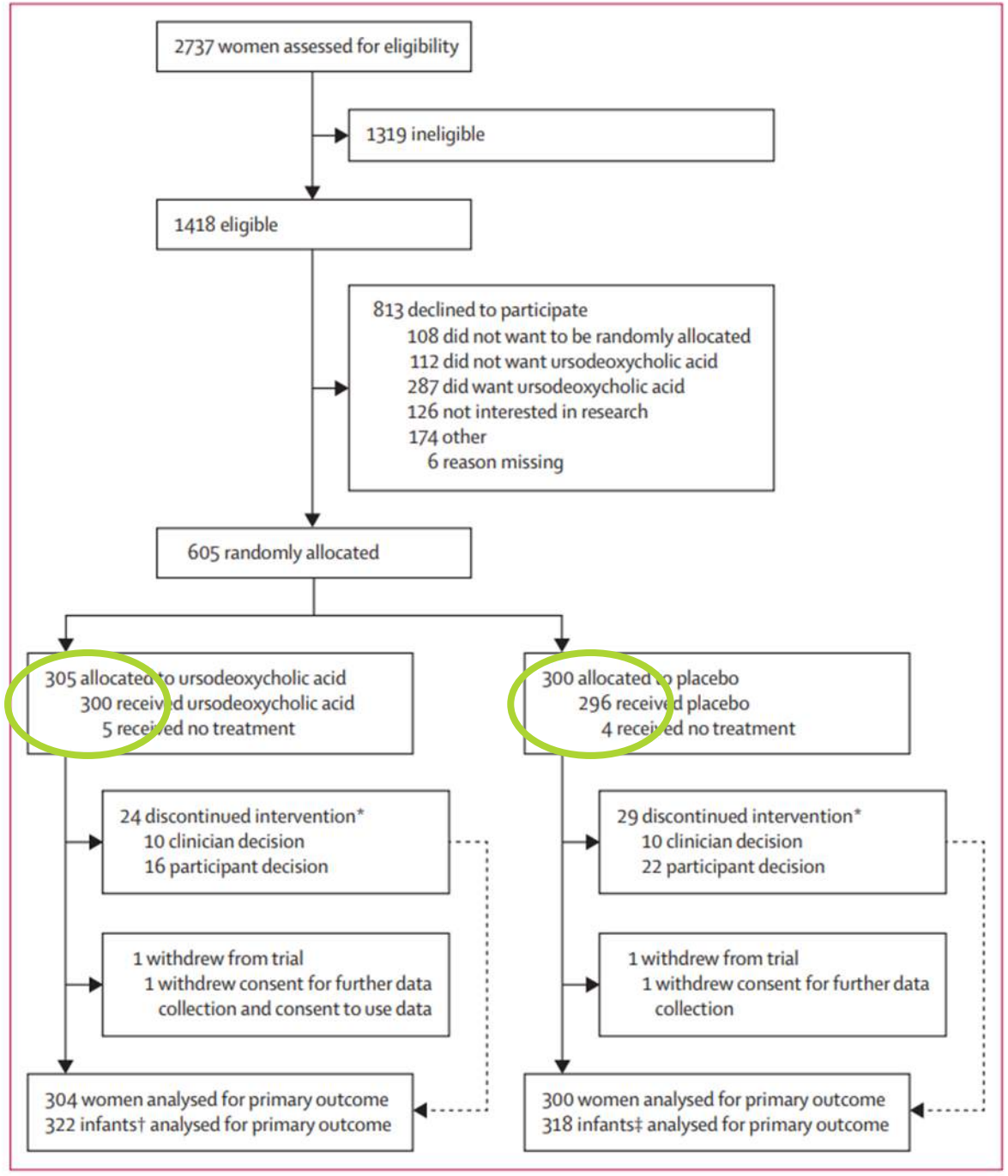



***Figure 1:*** **Trial profile**

| | Ursodeoxycholic acid (n=304) | Placebo (n=300) |
|---|---|---|
| Age, years | 30·5 (5·6) | 30·8 (5·3) |
| Ethnic group | | |
| White | 247 (81%) | 246 (82%) |
| Black | 10 (3%) | 7 (2%) |
| Asian | 34 (11%) | 40 (13%) |
| Other | 11 (4%) | 7 (2%) |
| Not known | 2 (1%) | 0 |
| Body-mass index at start of pregnancy (kg/m²), mean (SD) | 27·4 (6·4) | 26·9 (6·1) |
| Smoked at start of pregnancy | 33 (11%) | 44 (15%) |
| Indices of Multiple Deprivation score: quintile 5*, n/N (%) | 76/289 (26%) | 81/286 (28%) |
| Not defined, n | 15 | 14 |
| Previous pregnancy of ≥24 weeks' gestation | 178 (59%) | 193 (64%) |
| Previous stillbirth | 2 (1%) | 2 (1%) |

| | Ursodeoxycholic acid (n=304) | Placebo (n=300) |
|---|---|---|
| (Continued from previous page) | | |
| History of intrahepatic cholestasis of pregnancy, n/N (%) | 92/175 (53%) | 90/190 (47%) |
| Missing, n | 3 | 3 |
| Pre-pregnancy liver disease | 3 (1%) | 6 (2%) |
| Liver ultrasound at randomisation, n/N (%) | 79/293 (27%) | 78/292 (27%) |
| Normal, n/N (%) | 65/77 (84%) | 57/77 (74%) |
| Gallstones, n/N (%) | 9/77 (12%) | 12/77 (16%) |
| Other abnormality, n/N (%) | 3/77 (4%) | 8/77 (10%) |
| Missing result, n | 2 | 1 |
| Previous operation for gallstones | 20 (7%) | 17 (6%) |
| Pre-pregnancy diabetes | 4 (1%) | 4 (1%) |
| Gestational age (weeks), median (IQR)† | 34·4 (32·1–35·9) | 34·4 (31·5–36·0) |
| <34 weeks | 133 (44%) | 131 (44%) |
| 34 to <37 weeks | 141 (46%) | 141 (47%) |
| ≥37 weeks | 30 (10%) | 28 (9%) |
| Twin pregnancy† | 18 (6%) | 19 (6%) |
| Gestational diabetes | 32 (11%) | 25 (8%) |
| Itch score, mean (SD)‡ | 57·1 (25·1) | 59·5 (25·1) |
| Medication for pruritus§, n/N (%) | 146/298 (49%) | 137/297 (46%) |
| Antihistamine, n/N (%) | 121/298 (41%) | 119/297 (40%) |
| Topical emollient, n/N (%) | 102/298 (34%) | 101/297 (34%) |
| Ursodeoxycholic acid, n/N (%) | 15/298 (5%) | 13/297 (4%) |
| Missing, n | 6 | 3 |
| Highest baseline serum concentration before randomisation | | |
| Bile acid (μmol/L), geometric mean (95% CI)† | 28·1 (26·0–30·3) | 26·9 (24·9–29·0) |
| <40 μmol/L | 232 (76%) | 228 (76%) |
| ≥40 μmol/L | 72 (24%) | 72 (24%) |
| Alanine transaminase, N | 286 | 286 |
| Alanine transaminase (U/L), geometric mean (95% CI) | 70·0 (61·5–79·6) | 59·5 (52·0–68·1) |
| Aspartate transaminase, N | 47 | 48 |
| Aspartate transaminase (U/L), geometric mean (95% CI) | 49·0 (38·4–62·5) | 61·6 (46·8–81·0) |

| | Ursodeoxycholic acid (n=304) | Placebo (n=300) |
|---|---|---|
| (Continued from previous page) | | |
| History of intrahepatic cholestasis of pregnancy, n/N (%) | 92/175 (53%) | 90/190 (47%) |
| Missing, n | 3 | 3 |
| Pre-pregnancy liver disease | 3 (1%) | 6 (2%) |
| Liver ultrasound at randomisation, n/N (%) | 79/293 (27%) | 78/292 (27%) |
| Normal, n/N (%) | 65/77 (84%) | 57/77 (74%) |
| Gallstones, n/N (%) | 9/77 (12%) | 12/77 (16%) |
| Other abnormality, n/N (%) | 3/77 (4%) | 8/77 (10%) |
| Missing result, n | 2 | 1 |
| Previous operation for gallstones | 20 (7%) | 17 (6%) |
| Pre-pregnancy diabetes | 4 (1%) | 4 (1%) |
| Gestational age (weeks), median (IQR)† | 34·4 (32·1–35·9) | 34·4 (31·5–36·0) |
| <34 weeks | 133 (44%) | 131 (44%) |
| 34 to <37 weeks | 141 (46%) | 141 (47%) |
| ≥37 weeks | 30 (10%) | 28 (9%) |
| Twin pregnancy† | 18 (6%) | 19 (6%) |
| Gestational diabetes | 32 (11%) | 25 (8%) |
| Itch score, mean (SD)‡ | 57·1 (25·1) | 59·5 (25·1) |
| Medication for pruritus§, n/N (%) | 146/298 (49%) | 137/297 (46%) |
| Antihistamine, n/N (%) | 121/298 (41%) | 119/297 (40%) |
| Topical emollient, n/N (%) | 102/298 (34%) | 101/297 (34%) |
| Ursodeoxycholic acid, n/N (%) | 15/298 (5%) | 13/297 (4%) |
| Missing, n | 6 | 3 |
| Highest baseline serum concentration before randomisation | | |
| Bile acid (μmol/L), geometric mean (95% CI)† | 28·1 (26·0–30·3) | 26·9 (24·9–29·0) |
| <40 μmol/L | 232 (76%) | 228 (76%) |
| ≥40 μmol/L | 72 (24%) | 72 (24%) |
| Alanine transaminase, N | 286 | 286 |
| Alanine transaminase (U/L), geometric mean (95% CI) | 70·0 (61·5–79·6) | 59·5 (52·0–68·1) |
| Aspartate transaminase, N | 47 | 48 |
| Aspartate transaminase (U/L), geometric mean (95% CI) | 49·0 (38·4–62·5) | 61·6 (46·8–81·0) |

| | Ursodeoxycholic acid (n=304) | Placebo (n=300) |
|---|---|---|
| (Continued from previous page) | | |
| History of intrahepatic cholestasis of pregnancy, n/N (%) | 92/175 (53%) | 90/190 (47%) |
| Missing, n | 3 | 3 |
| Pre-pregnancy liver disease | 3 (1%) | 6 (2%) |
| Liver ultrasound at randomisation, n/N (%) | 79/293 (27%) | 78/292 (27%) |
| Normal, n/N (%) | 65/77 (84%) | 57/77 (74%) |
| Gallstones, n/N (%) | 9/77 (12%) | 12/77 (16%) |
| Other abnormality, n/N (%) | 3/77 (4%) | 8/77 (10%) |
| Missing result, n | 2 | 1 |
| Previous operation for gallstones | 20 (7%) | 17 (6%) |
| Pre-pregnancy diabetes | 4 (1%) | 4 (1%) |
| Gestational age (weeks), median (IQR)† | 34·4 (32·1–35·9) | 34·4 (31·5–36·0) |
| <34 weeks | 133 (44%) | 131 (44%) |
| 34 to <37 weeks | 141 (46%) | 141 (47%) |
| ≥37 weeks | 30 (10%) | 28 (9%) |
| Twin pregnancy† | 18 (6%) | 19 (6%) |
| Gestational diabetes | 32 (11%) | 25 (8%) |
| Itch score, mean (SD)‡ | 57·1 (25·1) | 59·5 (25·1) |
| Medication for pruritus§, n/N (%) | 146/298 (49%) | 137/297 (46%) |
| Antihistamine, n/N (%) | 121/298 (41%) | 119/297 (40%) |
| Topical emollient, n/N (%) | 102/298 (34%) | 101/297 (34%) |
| Ursodeoxycholic acid, n/N (%) | 15/298 (5%) | 13/297 (4%) |
| Missing, n | 6 | 3 |
| Highest baseline serum concentration before randomisation | | |
| Bile acid (μmol/L), geometric mean (95% CI)† | 28·1 (26·0–30·3) | 26·9 (24·9–29·0) |
| <40 μmol/L | 232 (76%) | 228 (76%) |
| ≥40 μmol/L | 72 (24%) | 72 (24%) |
| Alanine transaminase, N | 286 | 286 |
| Alanine transaminase (U/L), geometric mean (95% CI) | 70·0 (61·5–79·6) | 59·5 (52·0–68·1) |
| Aspartate transaminase, N | 47 | 48 |
| Aspartate transaminase (U/L), geometric mean (95% CI) | 49·0 (38·4–62·5) | 61·6 (46·8–81·0) |

| | Ursodeoxycholic acid (n=304) | Placebo (n=300) |
|---|---|---|
| (Continued from previous page) | | |
| History of intrahepatic cholestasis of pregnancy, n/N (%) | 92/175 (53%) | 90/190 (47%) |
| Missing, n | 3 | 3 |
| Pre-pregnancy liver disease | 3 (1%) | 6 (2%) |
| Liver ultrasound at randomisation, n/N (%) | 79/293 (27%) | 78/292 (27%) |
| Normal, n/N (%) | 65/77 (84%) | 57/77 (74%) |
| Gallstones, n/N (%) | 9/77 (12%) | 12/77 (16%) |
| Other abnormality, n/N (%) | 3/77 (4%) | 8/77 (10%) |
| Missing result, n | 2 | 1 |
| Previous operation for gallstones | 20 (7%) | 17 (6%) |
| Pre-pregnancy diabetes | 4 (1%) | 4 (1%) |
| Gestational age (weeks), median (IQR)† | 34·4 (32·1–35·9) | 34·4 (31·5–36·0) |
| <34 weeks | 133 (44%) | 131 (44%) |
| 34 to <37 weeks | 141 (46%) | 141 (47%) |
| ≥37 weeks | 30 (10%) | 28 (9%) |
| Twin pregnancy† | 18 (6%) | 19 (6%) |
| Gestational diabetes | 32 (11%) | 25 (8%) |
| Itch score, mean (SD)‡ | 57·1 (25·1) | 59·5 (25·1) |
| Medication for pruritus§, n/N (%) | 146/298 (49%) | 137/297 (46%) |
| Antihistamine, n/N (%) | 121/298 (41%) | 119/297 (40%) |
| Topical emollient, n/N (%) | 102/298 (34%) | 101/297 (34%) |
| Ursodeoxycholic acid, n/N (%) | 15/298 (5%) | 13/297 (4%) |
| Missing, n | 6 | 3 |
| Highest baseline serum concentration before randomisation | | |
| Bile acid (μmol/L), geometric mean (95% CI)† | 28·1 (26·0–30·3) | 26·9 (24·9–29·0) |
| <40 μmol/L | 232 (76%) | 228 (76%) |
| ≥40 μmol/L | 72 (24%) | 72 (24%) |
| Alanine transaminase, N | 286 | 286 |
| Alanine transaminase (U/L), geometric mean (95% CI) | 70·0 (61·5–79·6) | 59·5 (52·0–68·1) |
| Aspartate transaminase, N | 47 | 48 |
| Aspartate transaminase (U/L), geometric mean (95% CI) | 49·0 (38·4–62·5) | 61·6 (46·8–81·0) |

# META-ANALYSE – Ovadia 2019

Lancet 2019; 393: 899-909

## Association of adverse perinatal outcomes of intrahepatic cholestasis of pregnancy with biochemical markers: results of aggregate and individual patient data meta-analyses

Caroline Ovadia, Paul T Seed, Alexandros Sklavounos, Victoria Geenes, Chiara Di Illio, Jenny Chambers, Katherine Kohari, Yannick Bacq, Nuray Bozkurt, Romana Brun-Furrer, Laura Bull, Maria C Estiú, Monika Grymowicz, Berrin Gunaydin, William M Hague, Christian Haslinger, Yayi Hu, Tetsuya Kawakita, Ayse G Kebapcilar, Levent Kebapcilar, Jūratė Kondrackienė, Maria P H Koster, Aneta Kowalska-Kańka, Limas Kupčinskas, Richard H Lee, Anna Locatelli, Rocio I R Macias, Hanns-Ulrich Marschall, Martijn A Oudijk, Yael Raz, Eli Rimon, Dan Shan, Yong Shao, Rachel Tribe, Valeria Tripodi, Cigdem Yayla Abide, Ilter Yenidede, Jim G Thornton, Lucy C Chappell*, Catherine Williamson*

# Ovadia et *al.* 2019

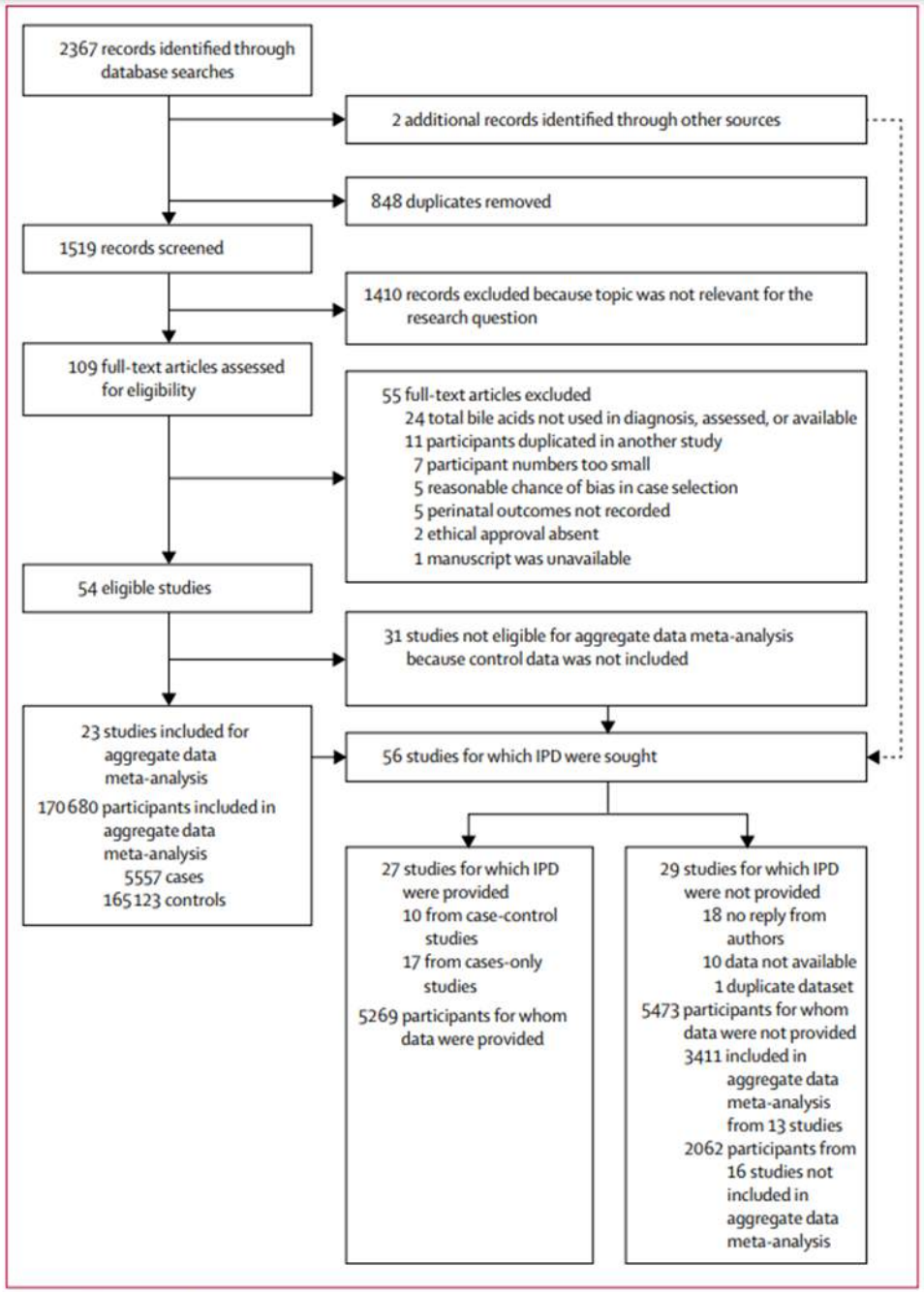



***Figure 1:*** **Flow chart of search results**
IPD=individual patient data.

# Ovadia et *al.* 2019

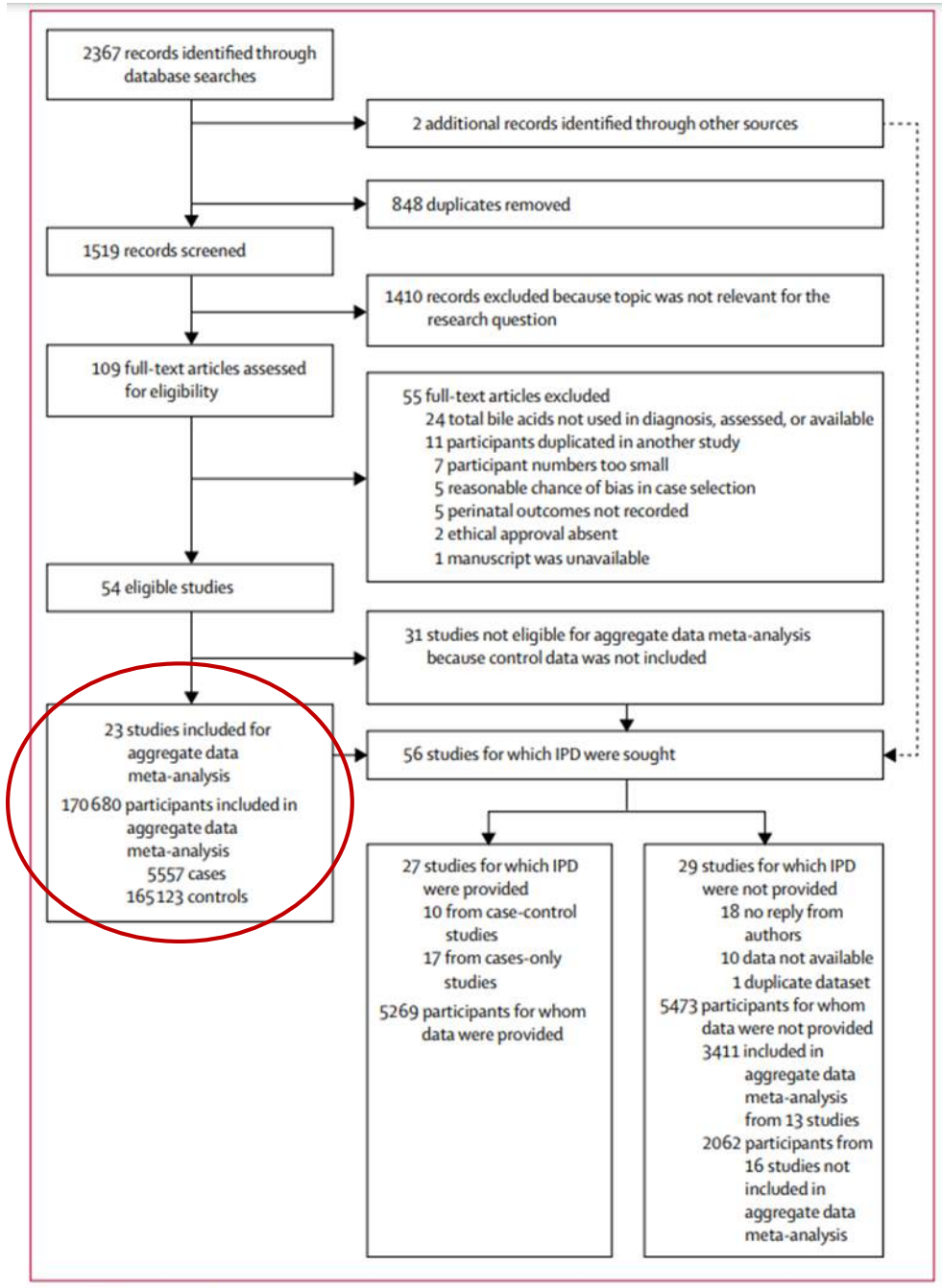



***Figure 1:*** **Flow chart of search results**
IPD=individual patient data.

# Cochrane 2020

Cochrane Library

Cochrane Database of Systematic Reviews

Cochrane 2020

## Pharmacological interventions for treating intrahepatic cholestasis of pregnancy (Review)

Walker KF, Chappell LC, Hague WM, Middleton P, Thornton JG.
Pharmacological interventions for treating intrahepatic cholestasis of pregnancy.
*Cochrane Database of Systematic Reviews* 2020, Issue 7. Art. No.: CD000493.
DOI: 10.1002/14651858.CD000493.pub3.

réseau sécurité naissance NAÎTRE ENSEMBLE 26e Journées Scientifiques

## Included studies

The original review (2001) included nine randomised controlled trials (Diaferia 1996; Floreani 1996; Frezza 1984; Frezza 1990; Kaaja 1994; Nicastri 1998; Palma 1997; Ribalta 1991; Riikonen 2000). The 2013 update included 11 new studies (Binder 2006; Fang 2009; Glantz 2005; Huang 2004; Kondrackiene 2005; Liu 2006; Luo 2008; Chappell 2012; Roncaglia 2004; Shi 2002; Zhang 2012). In addition, one study (Leino 1998) was a conference abstract and excluded from the original review (Burrows 2001). This was included in the update.

The updated search identified six new studies, five of which we judged to be eligible for inclusion (Chappell 2019; Joutsiniemi 2014; Sun 2014; Zhang 2015; Wang 2003).

Thus we now include 26 trials involving 2007 women in this review. See table of Characteristics of included studies for a full description.

***Interventions***

Nine different pharmacological interventions were compared with placebo, with no treatment or with another intervention. However combination treatments were also evaluated, so we ended up with 14 comparisons (with some trials appearing in more than one comparison):

- UDCA versus placebo or no treatment - 10 studies (Chappell 2012; Chappell 2019; Diaferia 1996; Glantz 2005; Joutsiniemi 2014; Leino 1998; Liu 2006; Nicastri 1998; Palma 1997; Wang 2003);
- SAMe versus placebo - four studies (Frezza 1984; Frezza 1990; Nicastri 1998; Ribalta 1991);
- Guar gum versus placebo - one study (Riikonen 2000);
- Activated charcoal versus no treatment - one study (Kaaja 1994);
- Dexamethasone versus placebo - one study (Glantz 2005);
- UDCA versus SAMe - six studies (Binder 2006; Floreani 1996; Nicastri 1998; Roncaglia 2004; Zhang 2012; Zhang 2015);
- UDCA versus dexamethasone - one study (Glantz 2005);
- UDCA versus cholestyramine - one study (Kondrackiene 2005);
- UDCA+SAMe versus placebo - one study (Nicastri 1998);
- UDCA+SAMe versus SAMe - four studies (Binder 2006; Nicastri 1998; Zhang 2012; Zhang 2015);
- UDCA+SAMe versus UDCA - six studies (Binder 2006; Luo 2008; Nicastri 1998; Sun 2014; Zhang 2012; Zhang 2015);
- UDCA+Salvia versus UDCA - one study (Fang 2009);
- Yinchenghao decoction (YCHD) versus SAMe - one study (Huang 2004);
- Danxioling Pill (DXLP) versus Yiganling - one stud

# Définition

Survenue d'un prurit évocateur (Sensibilité 91%, Spécificité 93%)

- Isolé
- Palmoplantaire
- Nocturne

# Définition

Survenue d'un prurit évocateur (Sensibilité 91%, Spécificité 93%)

- Isolé
- Palmoplantaire
- Nocturne

Associé à

élévations des acides biliaires >10µmol/L à jeûn

**OU**

augmentation des ALAT >2N

# Définition

Survenue d'un prurit évocateur (Sensibilité 91%, Spécificité 93%)

- Isolé
- Palmoplantaire
- Nocturne

Associé à

élévations des acides biliaires >10µmol/L à jeûn

**OU**

augmentation des ALAT >2N

Après élimination des autres orientations étiologiques à l'examen clinique (interrogatoire et examen physique)

# Définition

Survenue d'un prurit évocateur (Sensibilité 91%, Spécificité 93%)

- Isolé
- Palmoplantaire
- Nocturne

Associé à

élévations des acides biliaires >10µmol/L à jeûn

**OU**

augmentation des ALAT >2N

Après élimination des autres orientations étiologiques à l'examen clinique (interrogatoire et examen physique)

En l'absence de symptômes évocateurs d'un diagnostic différentiel : pas de bilan complémentaire biologique (sauf ASAT/ALAT et sels biliaires) ou échographique

**Tableau 2**

Récapitulatif des recommandations des principales sociétés savantes concernant le diagnostic de cholestase gravidique. Ce tableau reprend celui issu de la revue de Bicocca et al. avec la recommandation allemande supplémentaire et la mise à jour de la *Society for Maternal-Fetal Medicine* [12] et du *Royal College of Obstetricians and Gynaecologists*.

| Société savante | EASL [13] | SAMNCP [14] | GWADOH [15] | ACG [16] | Allemagne [17] | SMFM [18] | RCOG [19] | CNGOF |
|---|---|---|---|---|---|---|---|---|
| Année | 2009 | 2016 | 2016 | 2017 | 2021 | 2021 | 2022 | 2023 |
| Prurit | Nécessaire | Nécessaire | Nécessaire | Nécessaire | Nécessaire | Nécessaire | Nécessaire | Nécessaire |
| Acides biliaires | > 10 µmol/L | Nécessaire<br>> 10 IU/L : suspicion ;<br>> 15 IU/L : diagnostic ;<br>> 40 IU/L : sévère | Diagnostic si augmenté ; non nécessaire | > 10 µmol/L | Diagnostic si > 10 µmol/L à jeûn ou > 14 µmol/L en postprandial | Diagnostic si augmenté ; seuil de 10 µmol/L habituellement retenu même si discutable | Diagnostic si supérieur à 19 µmol/L quel que soit le moment du dosage | Diagnostic si > 10 µmol/L |
| GammaGT | Pas pour le diagnostic | Pas pour le diagnostic | Diagnostic si augmentées | – | – | – | – | Pas pour le diagnostic |
| Transaminases | Peuvent être augmentées | Peuvent être augmentées | Diagnostic si augmentées | Peuvent être augmentées | Diagnostic si augmentées et présence d'un prurit mais avec acides bilaires normaux | Peuvent être augmentées | – | Diagnostic si augmentation des ALAT > 2N |
| Résolution après la naissance | – | Prurit : 1–2 jours<br>Ictère : 1 semaine<br>Acides biliaires : 1 semaine<br>Fonction hépatique : 6 semaines | Prurit : 1–2 jours<br>Fonction hépatique : 1 mois | Oui | Spontanément résolutive<br>Normalisation des transaminases à 6 semaines | – | Normalisation du prurit et du bilan biologique à 4 semaines | Correction des anomalies dans les deux mois suivant l'accouchement |

ACG : American College of Gastroenterologists ; CNGOF : Collège national des gynécologues obstétriciens français ; EASL : *European Association for the Study of the Liver* ; GWADOH : *Government of Western Australia Department of Health* ; RCOG : *Royal College of Obstetricians and Gynaecologists* ; SAMNCP : *South Australia Maternal and Neonatal Community of Practice* ; SMFM : *Society for Maternal-Fetal Medicine*.

**Tableau 2**

Récapitulatif des recommandations des principales sociétés savantes concernant le diagnostic de cholestase gravidique. Ce tableau reprend celui issu de la revue de Bicocca et al. avec la recommandation allemande supplémentaire et la mise à jour de la *Society for Maternal-Fetal Medicine* [12] et du *Royal College of Obstetricians and Gynaecologists*.

| Société savante | EASL [13] | SAMNCP [14] | GWADOH [15] | ACG [16] | Allemagne [17] | SMFM [18] | RCOG [19] | CNGOF |
|---|---|---|---|---|---|---|---|---|
| Année | 2009 | 2016 | 2016 | 2017 | 2021 | 2021 | 2022 | 2023 |
| Prurit | Nécessaire | Nécessaire | Nécessaire | Nécessaire | Nécessaire | Nécessaire | Nécessaire | Nécessaire |
| Acides biliaires | > 10 µmol/L | Nécessaire<br>> 10 IU/L : suspicion ;<br>> 15 IU/L : diagnostic ;<br>> 40 IU/L : sévère | Diagnostic si augmenté ; non nécessaire | > 10 µmol/L | Diagnostic si > 10 µmol/L à jeûn ou > 14 µmol/L en postprandial | Diagnostic si augmenté ; seuil de 10 µmol/L habituellement retenu même si discutable | Diagnostic si supérieur à 19 µmol/L quel que soit le moment du dosage | Diagnostic si > 10 µmol/L |
| GammaGT | Pas pour le diagnostic | Pas pour le diagnostic | Diagnostic si augmentées | – | – | – | – | Pas pour le diagnostic |
| Transaminases | Peuvent être augmentées | Peuvent être augmentées | Diagnostic si augmentées | Peuvent être augmentées | Diagnostic si augmentées et présence d'un prurit mais avec acides bilaires normaux | Peuvent être augmentées | – | Diagnostic si augmentation des ALAT > 2N |
| Résolution après la naissance | – | Prurit : 1–2 jours<br>Ictère : 1 semaine<br>Acides biliaires : 1 semaine<br>Fonction hépatique : 6 semaines | Prurit : 1–2 jours<br>Fonction hépatique : 1 mois | Oui | Spontanément résolutive<br>Normalisation des transaminases à 6 semaines | – | Normalisation du prurit et du bilan biologique à 4 semaines | Correction des anomalies dans les deux mois suivant l'accouchement |

ACG : American College of Gastroenterologists ; CNGOF : Collège national des gynécologues obstétriciens français ; EASL : *European Association for the Study of the Liver* ; GWADOH : *Government of Western Australia Department of Health* ; RCOG : *Royal College of Obstetricians and Gynaecologists* ; SAMNCP : *South Australia Maternal and Neonatal Community of Practice* ; SMFM : *Society for Maternal-Fetal Medicine*.

**Tableau 2**

Récapitulatif des recommandations des principales sociétés savantes concernant le diagnostic de cholestase gravidique. Ce tableau reprend celui issu de la revue de Bicocca et al. avec la recommandation allemande supplémentaire et la mise à jour de la *Society for Maternal-Fetal Medicine* [12] et du *Royal College of Obstetricians and Gynaecologists*.

| Société savante | EASL [13] | SAMNCP [14] | GWADOH [15] | ACG [16] | Allemagne [17] | SMFM [18] | RCOG [19] | CNGOF |
|---|---|---|---|---|---|---|---|---|
| Année | 2009 | 2016 | 2016 | 2017 | 2021 | 2021 | 2022 | 2023 |
| Prurit | Nécessaire | Nécessaire | Nécessaire | Nécessaire | Nécessaire | Nécessaire | Nécessaire | Nécessaire |
| Acides biliaires | > 10 µmol/L | Nécessaire<br>> 10 IU/L : suspicion ;<br>> 15 IU/L : diagnostic ;<br>> 40 IU/L : sévère | Diagnostic si augmenté ; non nécessaire | > 10 µmol/L | Diagnostic si > 10 µmol/L à jeûn ou > 14 µmol/L en postprandial | Diagnostic si augmenté ; seuil de 10 µmol/L habituellement retenu même si discutable | Diagnostic si supérieur à 19 µmol/L quel que soit le moment du dosage | Diagnostic si > 10 µmol/L |
| GammaGT | Pas pour le diagnostic | Pas pour le diagnostic | Diagnostic si augmentées | – | – | – | – | Pas pour le diagnostic |
| Transaminases | Peuvent être augmentées | Peuvent être augmentées | Diagnostic si augmentées | Peuvent être augmentées | Diagnostic si augmentées et présence d'un prurit mais avec acides bilaires normaux | Peuvent être augmentées | – | Diagnostic si augmentation des ALAT > 2N |
| Résolution après la naissance | – | Prurit : 1–2 jours<br>Ictère : 1 semaine<br>Acides biliaires : 1 semaine<br>Fonction hépatique : 6 semaines | Prurit : 1–2 jours<br>Fonction hépatique : 1 mois | Oui | Spontanément résolutive<br>Normalisation des transaminases à 6 semaines | – | Normalisation du prurit et du bilan biologique à 4 semaines | Correction des anomalies dans les deux mois suivant l'accouchement |

ACG : American College of Gastroenterologists ; CNGOF : Collège national des gynécologues obstétriciens français ; EASL : *European Association for the Study of the Liver* ; GWADOH : *Government of Western Australia Department of Health* ; RCOG : *Royal College of Obstetricians and Gynaecologists* ; SAMNCP : *South Australia Maternal and Neonatal Community of Practice* ; SMFM : *Society for Maternal-Fetal Medicine*.

**Tableau 2**

Récapitulatif des recommandations des principales sociétés savantes concernant le diagnostic de cholestase gravidique. Ce tableau reprend celui issu de la revue de Bicocca et al. avec la recommandation allemande supplémentaire et la mise à jour de la *Society for Maternal-Fetal Medicine* [12] et du *Royal College of Obstetricians and Gynaecologists*.

| Société savante | EASL [13] | SAMNCP [14] | GWADOH [15] | ACG [16] | Allemagne [17] | SMFM [18] | RCOG [19] | CNGOF |
|---|---|---|---|---|---|---|---|---|
| Année | 2009 | 2016 | 2016 | 2017 | 2021 | 2021 | 2022 | 2023 |
| Prurit | Nécessaire | Nécessaire | Nécessaire | Nécessaire | Nécessaire | Nécessaire | Nécessaire | Nécessaire |
| Acides biliaires | > 10 µmol/L | Nécessaire<br>> 10 IU/L : suspicion ;<br>> 15 IU/L : diagnostic ;<br>> 40 IU/L : sévère | Diagnostic si augmenté ; non nécessaire | > 10 µmol/L | Diagnostic si > 10 µmol/L à jeûn ou > 14 µmol/L en postprandial | Diagnostic si augmenté ; seuil de 10 µmol/L habituellement retenu même si discutable | Diagnostic si supérieur à 19 µmol/L quel que soit le moment du dosage | Diagnostic si > 10 µmol/L |
| GammaGT | Pas pour le diagnostic | Pas pour le diagnostic | Diagnostic si augmentées | – | – | – | – | Pas pour le diagnostic |
| Transaminases | Peuvent être augmentées | Peuvent être augmentées | Diagnostic si augmentées | Peuvent être augmentées | Diagnostic si augmentées et présence d'un prurit mais avec acides bilaires normaux | Peuvent être augmentées | – | Diagnostic si augmentation des ALAT > 2N |
| Résolution après la naissance | – | Prurit : 1–2 jours<br>Ictère : 1 semaine<br>Acides biliaires : 1 semaine<br>Fonction hépatique : 6 semaines | Prurit : 1–2 jours<br>Fonction hépatique : 1 mois | Oui | Spontanément résolutive<br>Normalisation des transaminases à 6 semaines | – | Normalisation du prurit et du bilan biologique à 4 semaines | Correction des anomalies dans les deux mois suivant l'accouchement |

ACG : American College of Gastroenterologists ; CNGOF : Collège national des gynécologues obstétriciens français ; EASL : *European Association for the Study of the Liver* ; GWADOH : *Government of Western Australia Department of Health* ; RCOG : *Royal College of Obstetricians and Gynaecologists* ; SAMNCP : *South Australia Maternal and Neonatal Community of Practice* ; SMFM : *Society for Maternal-Fetal Medicine*.

**Tableau 2**

Récapitulatif des recommandations des principales sociétés savantes concernant le diagnostic de cholestase gravidique. Ce tableau reprend celui issu de la revue de Bicocca et al. avec la recommandation allemande supplémentaire et la mise à jour de la *Society for Maternal-Fetal Medicine* [12] et du *Royal College of Obstetricians and Gynaecologists*.

| Société savante | EASL [13] | SAMNCP [14] | GWADOH [15] | ACG [16] | Allemagne [17] | SMFM [18] | RCOG [19] | CNGOF |
|---|---|---|---|---|---|---|---|---|
| Année | 2009 | 2016 | 2016 | 2017 | 2021 | 2021 | 2022 | 2023 |
| Prurit | Nécessaire | Nécessaire | Nécessaire | Nécessaire | Nécessaire | Nécessaire | Nécessaire | Nécessaire |
| Acides biliaires | > 10 µmol/L | Nécessaire<br>> 10 IU/L : suspicion ;<br>> 15 IU/L : diagnostic ;<br>> 40 IU/L : sévère | Diagnostic si augmenté ; non nécessaire | > 10 µmol/L | Diagnostic si > 10 µmol/L à jeûn ou > 14 µmol/L en postprandial | Diagnostic si augmenté ; seuil de 10 µmol/L habituellement retenu même si discutable | Diagnostic si supérieur à 19 µmol/L quel que soit le moment du dosage | Diagnostic si > 10 µmol/L |
| GammaGT | Pas pour le diagnostic | Pas pour le diagnostic | Diagnostic si augmentées | – | – | – | – | Pas pour le diagnostic |
| Transaminases | Peuvent être augmentées | Peuvent être augmentées | Diagnostic si augmentées | Peuvent être augmentées | Diagnostic si augmentées et présence d'un prurit mais avec acides bilaires normaux | Peuvent être augmentées | – | Diagnostic si augmentation des ALAT > 2N |
| Résolution après la naissance | – | Prurit : 1–2 jours<br>Ictère : 1 semaine<br>Acides biliaires : 1 semaine<br>Fonction hépatique : 6 semaines | Prurit : 1–2 jours<br>Fonction hépatique : 1 mois | Oui | Spontanément résolutive<br>Normalisation des transaminases à 6 semaines | – | Normalisation du prurit et du bilan biologique à 4 semaines | Correction des anomalies dans les deux mois suivant l'accouchement |

ACG : American College of Gastroenterologists ; CNGOF : Collège national des gynécologues obstétriciens français ; EASL : *European Association for the Study of the Liver* ; GWADOH : *Government of Western Australia Department of Health* ; RCOG : *Royal College of Obstetricians and Gynaecologists* ; SAMNCP : *South Australia Maternal and Neonatal Community of Practice* ; SMFM : *Society for Maternal-Fetal Medicine*.

# Examens complémentaires

Certaines sociétés savantes proposent:

## Bilan biologique:

- NFS, plaquettes
- TP
- Créatininémie
- Protéinurie
- Sérologies hépatites A,B,C,E
- Sérologies EBV, HSV et CMV

## Bilan imagerie:

- Echographie du foie et voies biliaires

# Examens complémentaires

Certaines sociétés savantes proposent:

## Bilan biologique:

- NFS, plaquettes
- TP
- Créatininémie
- Protéinurie
- Sérologies hépatites A,B,C,E
- Sérologies EBV, HSV et CMV

## Bilan imagerie:

- Echographie du foie et voies biliaires

Série française de Donet et al. 2020

## 254 cas de cholestase gravidique (2012-2018)

- Seulement la moitié avait eu un bilan pour recherche d'un diagnostic différentiel
- 1 seul cas d'obstruction biliaire
- Aucune autre anomalie retrouvée si bilan réalisé

# Examens complémentaires

Certaines sociétés savantes proposent:

## Bilan biologique:

- NFS, plaquettes
- TP
- Créatininémie
- Protéinurie
- Sérologies hépatites A,B,C,E
- Sérologies EBV, HSV et CMV

## Bilan imagerie:

- Echographie du foie et voies biliaires

Série française de Donet et al. 2020

## 254 cas de cholestase gravidique (2012-2018)

- Seulement la moitié avait eu un bilan pour recherche d'un diagnostic différentiel
- 1 seul cas d'obstruction biliaire
- Aucune autre anomalie retrouvée si bilan réalisé

En l'absence de signes évocateurs d'un diagnostic différentiel:
pas de bilan complémentaire autre que transaminases et acides biliaires

# Acide ursodésoxycholique

= AUDC

| | Ursodeoxycholic acid (n=304) | Placebo (n=300) | Adjusted effect estimate (95% CI) | p value |
|---|---|---|---|---|
| Itch score*, N | 241 | 227 | .. | .. |
| Itch score†, mm | 49·5 (12·9) | 56·9 (13·3) | Mean difference −5·7 (−9·7 to −1·7) | 0·0054 |
| Maternal serum bile acid concentration*, N | 256 | 247 | .. | .. |
| Maternal serum bile acid concentration† (μmol/L), geometric mean (95% CI) | 22·4 (21·4 to 23·5) | 18·5 (17·7 to 19·4) | Geometric mean ratio 1·18 (1·02 to 1·36) | 0·030 |
| Maternal serum alanine transaminase*, N | 242 | 240 | .. | .. |
| Maternal serum alanine transaminase† (U/L), geometric mean (95% CI) | 49·5 (43·8 to 55·8) | 58·0 (51·0 to 65·9) | Geometric mean ratio 0·74 (0·66 to 0·83) | <0·0001 |
| Gestational diabetes | 3 (1%) | 9 (3%) | RR 0·33 (0·10 to 1·10) | 0·071 |
| Additional therapy for cholestasis†, n/N (%) | 134/261 (51%) | 125/245 (51%) | .. | .. |
| Antihistamine, n/N (%) | 102/134 (76%) | 105/125 (84%) | .. | .. |
| Topical emollient, n/N (%) | 101/134 (75%) | 93/125 (74%) | .. | .. |
| Rifampicin, n/N (%) | 1/134 (1%) | 2/125 (2%) | .. | .. |
| Open-label ursodeoxycholic acid (tablets stopped), n/N (%) | 17/134 (13%) | 21/125 (17%) | .. | .. |
| Delivered before first follow-up visit, n | 33 | 42 | .. | .. |
| Missing, n | 10 | 13 | .. | .. |
| Maximum dose of trial medication | | | | |
| One tablet once a day | 4 (1%) | 5 (2%) | .. | .. |
| One tablet twice a day | 203 (67%) | 198 (66%) | .. | .. |
| One tablet three times a day | 62 (20%) | 65 (22%) | .. | .. |
| Two tablets twice a day | 35 (12%) | 32 (11%) | .. | .. |
| Mode of onset of labour | | | | |
| Spontaneous | 33 (11%) | 55 (18%) | RR 0·59 (0·42 to 0·83) | 0·0025 |
| Induced or pre-labour rupture of membranes and stimulation | 215 (71%) | 200 (67%) | RR 1·06 (0·95 to 1·17) | 0·30 |
| Pre-labour caesarean | 56 (18%) | 44 (15%) | .. | .. |
| Initiation of delivery‡ | | | | |
| Severe maternal symptoms, n/N (%) | 17/271 (6%) | 28/244 (11%) | .. | .. |
| Maternal serum bile acid, n/N (%) | 53/271 (20%) | 32/244 (13%) | .. | .. |
| Fetal compromise, n/N (%) | 24/271 (9%) | 24/244 (10%) | .. | .. |
| Gestational age, n/N (%) | 161/271 (59%) | 150/244 (61%) | .. | .. |
| Maternal request, n/N (%) | 32/271 (12%) | 29/244 (12%) | .. | .. |
| Other§, n/N (%) | 37/271 (14%) | 33/244 (14%) | .. | .. |
| Estimated blood loss at delivery, mL | 350 (250 to 600) | 400 (250 to 600) | Median difference −50 (−95 to −5) | 0·029 |
| <500 | 195 (64%) | 185 (62%) | .. | .. |
| ≥500 and <1000 | 79 (26%) | 80 (27%) | .. | .. |
| ≥1000 | 30 (10%) | 34 (11%) | .. | .. |

| | Ursodeoxycholic acid (n=304) | Placebo (n=300) | Adjusted effect estimate (95% CI) | p value |
|---|---|---|---|---|
| Itch score*, N | 241 | 227 | .. | .. |
| Itch score†, mm | 49·5 (12·9) | 56·9 (13·3) | Mean difference −5·7 (−9·7 to −1·7) | 0·0054 |
| Maternal serum bile acid concentration*, N | 256 | 247 | .. | .. |
| Maternal serum bile acid concentration† (μmol/L), geometric mean (95% CI) | 22·4 (21·4 to 23·5) | 18·5 (17·7 to 19·4) | Geometric mean ratio 1·18 (1·02 to 1·36) | 0·030 |
| Maternal serum alanine transaminase*, N | 242 | 240 | .. | .. |
| Maternal serum alanine transaminase† (U/L), geometric mean (95% CI) | 49·5 (43·8 to 55·8) | 58·0 (51·0 to 65·9) | Geometric mean ratio 0·74 (0·66 to 0·83) | <0·0001 |
| Gestational diabetes | 3 (1%) | 9 (3%) | RR 0·33 (0·10 to 1·10) | 0·071 |
| Additional therapy for cholestasis†, n/N (%) | 134/261 (51%) | 125/245 (51%) | .. | .. |
| Antihistamine, n/N (%) | 102/134 (76%) | 105/125 (84%) | .. | .. |
| Topical emollient, n/N (%) | 101/134 (75%) | 93/125 (74%) | .. | .. |
| Rifampicin, n/N (%) | 1/134 (1%) | 2/125 (2%) | .. | .. |
| Open-label ursodeoxycholic acid (tablets stopped), n/N (%) | 17/134 (13%) | 21/125 (17%) | .. | .. |
| Delivered before first follow-up visit, n | 33 | 42 | .. | .. |
| Missing, n | 10 | 13 | .. | .. |
| Maximum dose of trial medication | | | | |
| One tablet once a day | 4 (1%) | 5 (2%) | .. | .. |
| One tablet twice a day | 203 (67%) | 198 (66%) | .. | .. |
| One tablet three times a day | 62 (20%) | 65 (22%) | .. | .. |
| Two tablets twice a day | 35 (12%) | 32 (11%) | .. | .. |
| Mode of onset of labour | | | | |
| Spontaneous | 33 (11%) | 55 (18%) | RR 0·59 (0·42 to 0·83) | 0·0025 |
| Induced or pre-labour rupture of membranes and stimulation | 215 (71%) | 200 (67%) | RR 1·06 (0·95 to 1·17) | 0·30 |
| Pre-labour caesarean | 56 (18%) | 44 (15%) | .. | .. |
| Initiation of delivery‡ | | | | |
| Severe maternal symptoms, n/N (%) | 17/271 (6%) | 28/244 (11%) | .. | .. |
| Maternal serum bile acid, n/N (%) | 53/271 (20%) | 32/244 (13%) | .. | .. |
| Fetal compromise, n/N (%) | 24/271 (9%) | 24/244 (10%) | .. | .. |
| Gestational age, n/N (%) | 161/271 (59%) | 150/244 (61%) | .. | .. |
| Maternal request, n/N (%) | 32/271 (12%) | 29/244 (12%) | .. | .. |
| Other§, n/N (%) | 37/271 (14%) | 33/244 (14%) | .. | .. |
| Estimated blood loss at delivery, mL | 350 (250 to 600) | 400 (250 to 600) | Median difference −50 (−95 to −5) | 0·029 |
| <500 | 195 (64%) | 185 (62%) | .. | .. |
| ≥500 and <1000 | 79 (26%) | 80 (27%) | .. | .. |
| ≥1000 | 30 (10%) | 34 (11%) | .. | .. |

# Cochrane 2020

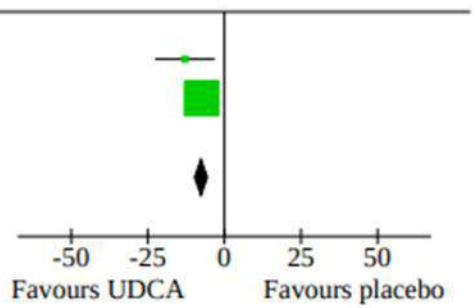
**Analysis 1.1. Comparison 1: UDCA versus placebo, Outcome 1: Mean of worst itching scores over preceding 24 hours between randomisation and delivery**

| Study or Subgroup | UDCA Mean | UDCA SD | UDCA Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Chappell 2012 (1) | 49 | 24.8 | 56 | 61.9 | 27.2 | 55 | 4.4% | -12.90 [-22.59 , -3.21] |
| Chappell 2019 | 49.5 | 12.9 | 304 | 56.9 | 13.3 | 300 | 95.6% | -7.40 [-9.49 , -5.31] |
| **Total (95% CI)** | | | **360** | | | **355** | **100.0%** | **-7.64 [-9.69 , -5.60]** |

Heterogeneity: $Chi^2 = 1.18$, $df = 1$ ($P = 0.28$); $I^2 = 15\%$

Test for overall effect: $Z = 7.33$ ($P < 0.00001$)

Test for subgroup differences: Not applicable



# Cochrane 2020

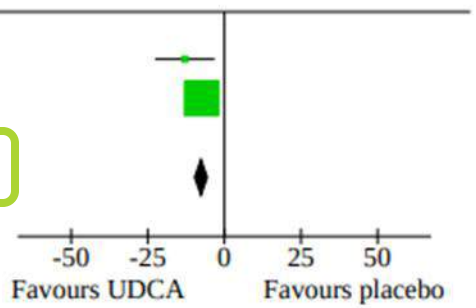
**Analysis 1.1. Comparison 1: UDCA versus placebo, Outcome 1: Mean of worst itching scores over preceding 24 hours between randomisation and delivery**

| Study or Subgroup | UDCA Mean | UDCA SD | UDCA Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| Chappell 2012 (1) | 49 | 24.8 | 56 | 61.9 | 27.2 | 55 | 4.4% | -12.90 [-22.59 , -3.21] |
| Chappell 2019 | 49.5 | 12.9 | 304 | 56.9 | 13.3 | 300 | 95.6% | -7.40 [-9.49 , -5.31] |
| **Total (95% CI)** | | | **360** | | | **355** | **100.0%** | **-7.64 [-9.69 , -5.60]** |

Heterogeneity: Chi² = 1.18, df = 1 (P = 0.28); I² = 15%

Test for overall effect: Z = 7.33 (P < 0.00001)

Test for subgroup differences: Not applicable



# AUDC

**Chez des femmes présentant une cholestase gravidique, il est recommandé d'administrer de l'acide ursodésoxycholique afin de réduire l'intensité du prurit maternel.**

RECOMMANDATION FORTE – QUALITÉ DE LA PREUVE MODEREE

| | Ursodeoxycholic acid (n=304) | Placebo (n=300) | Adjusted effect estimate (95% CI) | p value |
|---|---|---|---|---|
| Itch score*, N | 241 | 227 | .. | .. |
| Itch score†, mm | 49·5 (12·9) | 56·9 (13·3) | Mean difference −5·7 (−9·7 to −1·7) | 0·0054 |
| Maternal serum bile acid concentration*, N | 256 | 247 | .. | .. |
| Maternal serum bile acid concentration† (μmol/L), geometric mean (95% CI) | 22·4 (21·4 to 23·5) | 18·5 (17·7 to 19·4) | Geometric mean ratio 1·18 (1·02 to 1·36) | 0·030 |
| Maternal serum alanine transaminase*, N | 242 | 240 | .. | .. |
| Maternal serum alanine transaminase† (U/L), geometric mean (95% CI) | 49·5 (43·8 to 55·8) | 58·0 (51·0 to 65·9) | Geometric mean ratio 0·74 (0·66 to 0·83) | <0·0001 |
| Gestational diabetes | 3 (1%) | 9 (3%) | RR 0·33 (0·10 to 1·10) | 0·071 |
| Additional therapy for cholestasis†, n/N (%) | 134/261 (51%) | 125/245 (51%) | .. | .. |
| Antihistamine, n/N (%) | 102/134 (76%) | 105/125 (84%) | .. | .. |
| Topical emollient, n/N (%) | 101/134 (75%) | 93/125 (74%) | .. | .. |
| Rifampicin, n/N (%) | 1/134 (1%) | 2/125 (2%) | .. | .. |
| Open-label ursodeoxycholic acid (tablets stopped), n/N (%) | 17/134 (13%) | 21/125 (17%) | .. | .. |
| Delivered before first follow-up visit, n | 33 | 42 | .. | .. |
| Missing, n | 10 | 13 | .. | .. |
| Maximum dose of trial medication | | | | |
| One tablet once a day | 4 (1%) | 5 (2%) | .. | .. |
| One tablet twice a day | 203 (67%) | 198 (66%) | .. | .. |
| One tablet three times a day | 62 (20%) | 65 (22%) | .. | .. |
| Two tablets twice a day | 35 (12%) | 32 (11%) | .. | .. |
| Mode of onset of labour | | | | |
| Spontaneous | 33 (11%) | 55 (18%) | RR 0·59 (0·42 to 0·83) | 0·0025 |
| Induced or pre-labour rupture of membranes and stimulation | 215 (71%) | 200 (67%) | RR 1·06 (0·95 to 1·17) | 0·30 |
| Pre-labour caesarean | 56 (18%) | 44 (15%) | .. | .. |
| Initiation of delivery‡ | | | | |
| Severe maternal symptoms, n/N (%) | 17/271 (6%) | 28/244 (11%) | .. | .. |
| Maternal serum bile acid, n/N (%) | 53/271 (20%) | 32/244 (13%) | .. | .. |
| Fetal compromise, n/N (%) | 24/271 (9%) | 24/244 (10%) | .. | .. |
| Gestational age, n/N (%) | 161/271 (59%) | 150/244 (61%) | .. | .. |
| Maternal request, n/N (%) | 32/271 (12%) | 29/244 (12%) | .. | .. |
| Other§, n/N (%) | 37/271 (14%) | 33/244 (14%) | .. | .. |
| Estimated blood loss at delivery, mL | 350 (250 to 600) | 400 (250 to 600) | Median difference −50 (−95 to −5) | 0·029 |
| <500 | 195 (64%) | 185 (62%) | .. | .. |
| ≥500 and <1000 | 79 (26%) | 80 (27%) | .. | .. |
| ≥1000 | 30 (10%) | 34 (11%) | .. | .. |

| | Ursodeoxycholic acid (n=304) | Placebo (n=300) | Adjusted effect estimate (95% CI) | p value |
|---|---|---|---|---|
| Itch score*, N | 241 | 227 | .. | .. |
| Itch score†, mm | 49·5 (12·9) | 56·9 (13·3) | Mean difference −5·7 (−9·7 to −1·7) | 0·0054 |
| Maternal serum bile acid concentration*, N | 256 | 247 | .. | .. |
| Maternal serum bile acid concentration† (μmol/L), geometric mean (95% CI) | 22·4 (21·4 to 23·5) | 18·5 (17·7 to 19·4) | Geometric mean ratio 1·18 (1·02 to 1·36) | 0·030 |
| Maternal serum alanine transaminase*, N | 242 | 240 | .. | .. |
| Maternal serum alanine transaminase† (U/L), geometric mean (95% CI) | 49·5 (43·8 to 55·8) | 58·0 (51·0 to 65·9) | Geometric mean ratio 0·74 (0·66 to 0·83) | <0·0001 |
| Gestational diabetes | 3 (1%) | 9 (3%) | RR 0·33 (0·10 to 1·10) | 0·071 |
| Additional therapy for cholestasis†, n/N (%) | 134/261 (51%) | 125/245 (51%) | .. | .. |
| Antihistamine, n/N (%) | 102/134 (76%) | 105/125 (84%) | .. | .. |
| Topical emollient, n/N (%) | 101/134 (75%) | 93/125 (74%) | .. | .. |
| Rifampicin, n/N (%) | 1/134 (1%) | 2/125 (2%) | .. | .. |
| Open-label ursodeoxycholic acid (tablets stopped), n/N (%) | 17/134 (13%) | 21/125 (17%) | .. | .. |
| Delivered before first follow-up visit, n | 33 | 42 | .. | .. |
| Missing, n | 10 | 13 | .. | .. |
| Maximum dose of trial medication | | | | |
| One tablet once a day | 4 (1%) | 5 (2%) | .. | .. |
| One tablet twice a day | 203 (67%) | 198 (66%) | .. | .. |
| One tablet three times a day | 62 (20%) | 65 (22%) | .. | .. |
| Two tablets twice a day | 35 (12%) | 32 (11%) | .. | .. |
| Mode of onset of labour | | | | |
| Spontaneous | 33 (11%) | 55 (18%) | RR 0·59 (0·42 to 0·83) | 0·0025 |
| Induced or pre-labour rupture of membranes and stimulation | 215 (71%) | 200 (67%) | RR 1·06 (0·95 to 1·17) | 0·30 |
| Pre-labour caesarean | 56 (18%) | 44 (15%) | .. | .. |
| Initiation of delivery‡ | | | | |
| Severe maternal symptoms, n/N (%) | 17/271 (6%) | 28/244 (11%) | .. | .. |
| Maternal serum bile acid, n/N (%) | 53/271 (20%) | 32/244 (13%) | .. | .. |
| Fetal compromise, n/N (%) | 24/271 (9%) | 24/244 (10%) | .. | .. |
| Gestational age, n/N (%) | 161/271 (59%) | 150/244 (61%) | .. | .. |
| Maternal request, n/N (%) | 32/271 (12%) | 29/244 (12%) | .. | .. |
| Other§, n/N (%) | 37/271 (14%) | 33/244 (14%) | .. | .. |
| Estimated blood loss at delivery, mL | 350 (250 to 600) | 400 (250 to 600) | Median difference −50 (−95 to −5) | 0·029 |
| <500 | 195 (64%) | 185 (62%) | .. | .. |
| ≥500 and <1000 | 79 (26%) | 80 (27%) | .. | .. |
| ≥1000 | 30 (10%) | 34 (11%) | .. | .. |

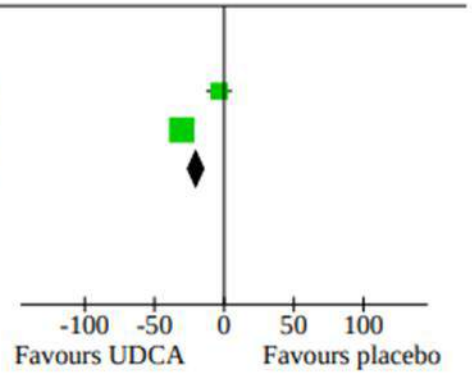
| | Ursodeoxycholic acid (n=304) | Placebo (n=300) | Adjusted effect estimate (95% CI) | p value |
|---|---|---|---|---|
| Itch score*, N | 241 | 227 | .. | .. |
| Itch score†, mm | 49·5 (12·9) | 56·9 (13·3) | Mean difference −5·7 (−9·7 to −1·7) | 0·0054 |
| Maternal serum bile acid concentration*, N | 256 | 247 | .. | .. |
| Maternal serum bile acid concentration† (μmol/L), geometric mean (95% CI) | 22·4 (21·4 to 23·5) | 18·5 (17·7 to 19·4) | Geometric mean ratio 1·18 (1·02 to 1·36) | 0·030 |
| Maternal serum alanine transaminase*, N | 242 | 240 | .. | .. |
| Maternal serum alanine transaminase† (U/L), geometric mean (95% CI) | 49·5 (43·8 to 55·8) | 58·0 (51·0 to 65·9) | Geometric mean ratio 0·74 (0·66 to 0·83) | <0·0001 |
| Gestational diabetes | 3 (1%) | 9 (3%) | RR 0·33 (0·10 to 1·10) | 0·071 |
| Additional therapy for cholestasis†, n/N (%) | 134/261 (51%) | 125/245 (51%) | .. | .. |
| Antihistamine, n/N (%) | 102/134 (76%) | 105/125 (84%) | .. | .. |
| Topical emollient, n/N (%) | 101/134 (75%) | 93/125 (74%) | .. | .. |
| Rifampicin, n/N (%) | 1/134 (1%) | 2/125 (2%) | .. | .. |
| Open-label ursodeoxycholic acid (tablets stopped), n/N (%) | 17/134 (13%) | 21/125 (17%) | .. | .. |
| Delivered before first follow-up visit, n | 33 | 42 | .. | .. |
| Missing, n | 10 | 13 | .. | .. |
| Maximum dose of trial medication | | | | |
| One tablet once a day | 4 (1%) | 5 (2%) | .. | .. |
| One tablet twice a day | 203 (67%) | 198 (66%) | .. | .. |
| One tablet three times a day | 62 (20%) | 65 (22%) | .. | .. |
| Two tablets twice a day | 35 (12%) | 32 (11%) | .. | .. |
| Mode of onset of labour | | | | |
| Spontaneous | 33 (11%) | 55 (18%) | RR 0·59 (0·42 to 0·83) | 0·0025 |
| Induced or pre-labour rupture of membranes and stimulation | 215 (71%) | 200 (67%) | RR 1·06 (0·95 to 1·17) | 0·30 |
| Pre-labour caesarean | 56 (18%) | 44 (15%) | .. | .. |
| Initiation of delivery‡ | | | | |
| Severe maternal symptoms, n/N (%) | 17/271 (6%) | 28/244 (11%) | .. | .. |
| Maternal serum bile acid, n/N (%) | 53/271 (20%) | 32/244 (13%) | .. | .. |
| Fetal compromise, n/N (%) | 24/271 (9%) | 24/244 (10%) | .. | .. |
| Gestational age, n/N (%) | 161/271 (59%) | 150/244 (61%) | .. | .. |
| Maternal request, n/N (%) | 32/271 (12%) | 29/244 (12%) | .. | .. |
| Other§, n/N (%) | 37/271 (14%) | 33/244 (14%) | .. | .. |
| Estimated blood loss at delivery, mL | 350 (250 to 600) | 400 (250 to 600) | Median difference −50 (−95 to −5) | 0·029 |
| <500 | 195 (64%) | 185 (62%) | .. | .. |
| ≥500 and <1000 | 79 (26%) | 80 (27%) | .. | .. |
| ≥1000 | 30 (10%) | 34 (11%) | .. | .. |

## Analysis 1.7. Comparison 1: UDCA versus placebo, Outcome 7: Change in bile acid concentration, µmol/L

| Study or Subgroup | UDCA Mean | UDCA SD | UDCA Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.7.1 At 20 days** | | | | | | | | |
| Chappell 2019 | -0.6 | 45.3 | 256 | 3 | 59 | 247 | 37.1% | -3.60 [-12.82 , 5.62] |
| Nicastri 1998 | -33 | 10 | 8 | -2.6 | 2.1 | 8 | 62.9% | -30.40 [-37.48 , -23.32] |
| **Subtotal (95% CI)** | | | **264** | | | **255** | **100.0%** | **-20.45 [-26.07 , -14.84]** |

Heterogeneity: Chi² = 20.43, df = 1 (P < 0.00001); I² = 95%

Test for overall effect: Z = 7.14 (P < 0.00001)




**Cochrane 2020**

## Analysis 1.9. Comparison 1: UDCA versus placebo, Outcome 9: ALT reduction, IU/L

| Study or Subgroup | UDCA Mean | UDCA SD | UDCA Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.9.1 At 20 days** | | | | | | | | |
| Chappell 2019 (1) | 40.4 | 110.6 | 242 | -8 | 115 | 240 | 49.8% | 48.40 [28.25 , 68.55] |
| Nicastri 1998 | 131.1 | 19.3 | 8 | 10.1 | 21.6 | 8 | 50.2% | 121.00 [100.93 , 141.07] |
| **Subtotal (95% CI)** | | | **250** | | | **248** | **100.0%** | **84.83 [70.61 , 99.05]** |

Heterogeneity: Chi² = 25.04, df = 1 (P < 0.00001); I² = 96%

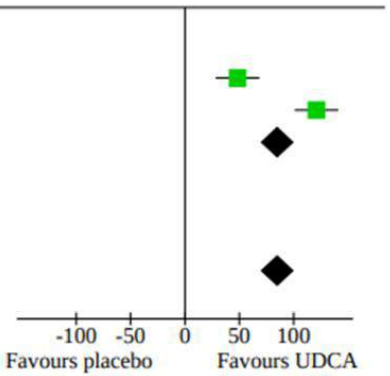
Test for overall effect: Z = 11.69 (P < 0.00001)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Total (95% CI)** | | | **250** | | | **248** | **100.0%** | **84.83 [70.61 , 99.05]** |

Heterogeneity: Chi² = 25.04, df = 1 (P < 0.00001); I² = 96%

Test for overall effect: Z = 11.69 (P < 0.00001)

Test for subgroup differences: Not applicable

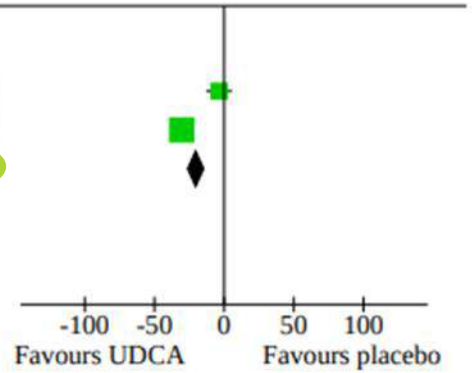


## Analysis 1.7. Comparison 1: UDCA versus placebo, Outcome 7: Change in bile acid concentration, µmol/L

| Study or Subgroup | UDCA Mean | UDCA SD | UDCA Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.7.1 At 20 days** | | | | | | | | |
| Chappell 2019 | -0.6 | 45.3 | 256 | 3 | 59 | 247 | 37.1% | -3.60 [-12.82 , 5.62] |
| Nicastri 1998 | -33 | 10 | 8 | -2.6 | 2.1 | 8 | 62.9% | -30.40 [-37.48 , -23.32] |
| **Subtotal (95% CI)** | | | **264** | | | **255** | **100.0%** | **-20.45 [-26.07 , -14.84]** |

Heterogeneity: Chi² = 20.43, df = 1 (P < 0.00001); I² = 95%

Test for overall effect: Z = 7.14 (P < 0.00001)




**Cochrane 2020**

## Analysis 1.9. Comparison 1: UDCA versus placebo, Outcome 9: ALT reduction, IU/L

| Study or Subgroup | UDCA Mean | UDCA SD | UDCA Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.9.1 At 20 days** | | | | | | | | |
| Chappell 2019 (1) | 40.4 | 110.6 | 242 | -8 | 115 | 240 | 49.8% | 48.40 [28.25 , 68.55] |
| Nicastri 1998 | 131.1 | 19.3 | 8 | 10.1 | 21.6 | 8 | 50.2% | 121.00 [100.93 , 141.07] |
| **Subtotal (95% CI)** | | | **250** | | | **248** | **100.0%** | **84.83 [70.61 , 99.05]** |

Heterogeneity: Chi² = 25.04, df = 1 (P < 0.00001); I² = 96%

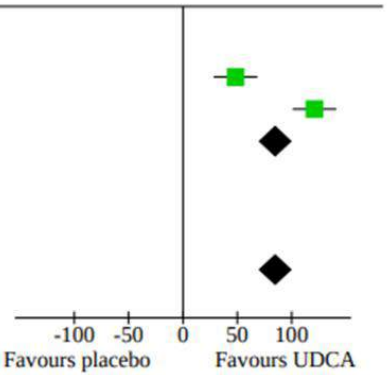
Test for overall effect: Z = 11.69 (P < 0.00001)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Total (95% CI)** | | | **250** | | | **248** | **100.0%** | **84.83 [70.61 , 99.05]** |

Heterogeneity: Chi² = 25.04, df = 1 (P < 0.00001); I² = 96%

Test for overall effect: Z = 11.69 (P < 0.00001)

Test for subgroup differences: Not applicable

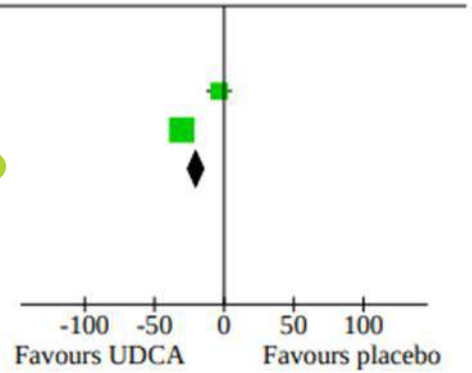


## Analysis 1.7. Comparison 1: UDCA versus placebo, Outcome 7: Change in bile acid concentration, µmol/L

| Study or Subgroup | UDCA Mean | UDCA SD | UDCA Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.7.1 At 20 days** | | | | | | | | |
| Chappell 2019 | -0.6 | 45.3 | 256 | 3 | 59 | 247 | 37.1% | -3.60 [-12.82 , 5.62] |
| Nicastri 1998 | -33 | 10 | 8 | -2.6 | 2.1 | 8 | 62.9% | -30.40 [-37.48 , -23.32] |
| **Subtotal (95% CI)** | | | **264** | | | **255** | **100.0%** | **-20.45 [-26.07 , -14.84]** |

Heterogeneity: Chi² = 20.43, df = 1 (P < 0.00001); I² = 95%

Test for overall effect: Z = 7.14 (P < 0.00001)




**Cochrane 2020**

## Analysis 1.9. Comparison 1: UDCA versus placebo, Outcome 9: ALT reduction, IU/L

| Study or Subgroup | UDCA Mean | UDCA SD | UDCA Total | Placebo Mean | Placebo SD | Placebo Total | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|---|---|
| **1.9.1 At 20 days** | | | | | | | | |
| Chappell 2019 (1) | 40.4 | 110.6 | 242 | -8 | 115 | 240 | 49.8% | 48.40 [28.25 , 68.55] |
| Nicastri 1998 | 131.1 | 19.3 | 8 | 10.1 | 21.6 | 8 | 50.2% | 121.00 [100.93 , 141.07] |
| **Subtotal (95% CI)** | | | **250** | | | **248** | **100.0%** | **84.83 [70.61 , 99.05]** |

Heterogeneity: Chi² = 25.04, df = 1 (P < 0.00001); I² = 96%

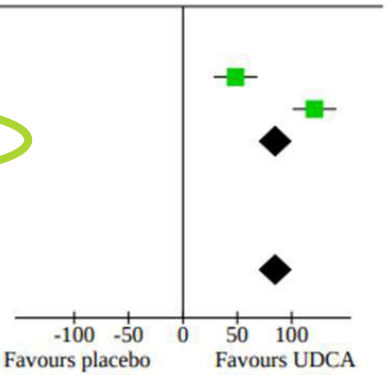
Test for overall effect: Z = 11.69 (P < 0.00001)

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Total (95% CI)** | | | **250** | | | **248** | **100.0%** | **84.83 [70.61 , 99.05]** |

Heterogeneity: Chi² = 25.04, df = 1 (P < 0.00001); I² = 96%

Test for overall effect: Z = 11.69 (P < 0.00001)

Test for subgroup differences: Not applicable



# AUDC

**Chez des femmes présentant une cholestase gravidique, il est recommandé d'administrer l'acide ursodésoxycholique afin d'améliorer le bilan biologique (acides biliaires totaux et ALAT).**

RECOMMANDATION FORTE – QUALITÉ DE LA PREUVE MODEREE

| | Ursodeoxycholic acid (n=322) | Placebo (n=318) | Adjusted effect estimate (95% CI) | p value |
|---|---|---|---|---|
| Perinatal death, preterm delivery,* or neonatal unit admission | 74 (23%) | 85 (27%) | RR 0·85 (0·62 to 1·15) | 0·28 |
| In-utero fetal death | 1 (<1%) | 2 (1%) | RR 0·51 (0·04 to 6·25) | 0·60 |
| Preterm delivery* | 54 (17%) | 65 (20%) | RR 0·79 (0·57 to 1·10) | 0·17 |
| Known neonatal death up to 7 days after birth | 0 | 0 | .. | .. |
| Neonatal unit admission for ≥4 h | 45 (14%) | 54 (17%) | RR 0·81 (0·58 to 1·13) | 0·21 |
| Livebirth | 321 (>99%) | 316 (99%) | .. | .. |
| Gestational age at delivery, weeks | 37·6 (37·1–38·1) | 37·4 (37·0–38·1) | Median difference 0·1 (0·0 to 0·3) | 0·065 |
| Birthweight, g | 3105 (2775–3390) | 3040 (2660–3320) | Median difference 94·0 (18·7 to 169·3) | 0·014 |
| Birthweight percentile† | 59·3 (28·4) | 56·3 (27·8) | .. | .. |
| <10th percentile | 16 (5%) | 18 (6%) | RR 0·89 (0·47 to 1·69) | 0·73 |
| <3rd percentile | 7 (2%) | 7 (2%) | RR 1·09 (0·38 to 3·12) | 0·88 |
| Mode of delivery | | | | |
| Spontaneous vaginal (cephalic) | 193 (60%) | 182 (57%) | RR 1·04 (0·91 to 1·20) | 0·56 |
| Vaginal (breech) | 1 (<1%) | 3 (1%) | .. | .. |
| Assisted vaginal (cephalic) | 21 (7%) | 35 (11%) | .. | .. |
| Pre-labour caesarean | 71 (22%) | 62 (19%) | .. | .. |
| Caesarean | 36 (11%) | 36 (11%) | RR 1·00 (0·68 to 1·46) | 1·0 |
| Presence of meconium-stained amniotic fluid | 34 (11%) | 52 (16%) | RR 0·65 (0·43 to 0·98) | 0·040 |
| Apgar score at 5 min after birth‡ | 9·0 (9·0–10·0) | 9·0 (9·0–10·0) | Median difference 0 (–0·4 to 0·4) | 1·0 |
| Apgar score of <7 at 5 min after birth‡, n/N (%) | 8/321 (2%) | 7/316 (2%) | .. | .. |
| Umbilical cord blood sampling, N | 112 | 102 | .. | .. |
| Umbilical arterial pH | 7·2 (0·1) | 7·2 (0·1) | Mean difference –0·02 (–0·04 to 0·01) | 0·18 |
| Nights in the neonatal unit§ | 5·5 (3·0–13·0) | 6·0 (2·0–16·0) | Median difference 0 (–3·2 to 3·2) | 1·0 |
| Main diagnosis for first neonatal unit admission | | | | |
| Prematurity, n/N (%) | 14/45 (31%) | 17/54 (31%) | .. | .. |
| Respiratory disease, n/N (%) | 16/45 (36%) | 15/54 (28%) | .. | .. |
| Infection suspected or confirmed, n/N (%) | 5/45 (11%) | 7/54 (13%) | .. | .. |
| Other¶, n/N (%) | 10/45 (22%) | 15/54 (28%) | .. | .. |

| | Ursodeoxycholic acid (n=322) | Placebo (n=318) | Adjusted effect estimate (95% CI) | p value |
|---|---|---|---|---|
| Perinatal death, preterm delivery,* or neonatal unit admission | 74 (23%) | 85 (27%) | RR 0·85 (0·62 to 1·15) | 0·28 |
| In-utero fetal death | 1 (<1%) | 2 (1%) | RR 0·51 (0·04 to 6·25) | 0·60 |
| Preterm delivery* | 54 (17%) | 65 (20%) | RR 0·79 (0·57 to 1·10) | 0·17 |
| Known neonatal death up to 7 days after birth | 0 | 0 | .. | .. |
| Neonatal unit admission for ≥4 h | 45 (14%) | 54 (17%) | RR 0·81 (0·58 to 1·13) | 0·21 |
| Livebirth | 321 (>99%) | 316 (99%) | .. | .. |
| Gestational age at delivery, weeks | 37·6 (37·1–38·1) | 37·4 (37·0–38·1) | Median difference 0·1 (0·0 to 0·3) | 0·065 |
| Birthweight, g | 3105 (2775–3390) | 3040 (2660–3320) | Median difference 94·0 (18·7 to 169·3) | 0·014 |
| Birthweight percentile† | 59·3 (28·4) | 56·3 (27·8) | .. | .. |
| <10th percentile | 16 (5%) | 18 (6%) | RR 0·89 (0·47 to 1·69) | 0·73 |
| <3rd percentile | 7 (2%) | 7 (2%) | RR 1·09 (0·38 to 3·12) | 0·88 |
| Mode of delivery | | | | |
| Spontaneous vaginal (cephalic) | 193 (60%) | 182 (57%) | RR 1·04 (0·91 to 1·20) | 0·56 |
| Vaginal (breech) | 1 (<1%) | 3 (1%) | .. | .. |
| Assisted vaginal (cephalic) | 21 (7%) | 35 (11%) | .. | .. |
| Pre-labour caesarean | 71 (22%) | 62 (19%) | .. | .. |
| Caesarean | 36 (11%) | 36 (11%) | RR 1·00 (0·68 to 1·46) | 1·0 |
| Presence of meconium-stained amniotic fluid | 34 (11%) | 52 (16%) | RR 0·65 (0·43 to 0·98) | 0·040 |
| Apgar score at 5 min after birth‡ | 9·0 (9·0–10·0) | 9·0 (9·0–10·0) | Median difference 0 (–0·4 to 0·4) | 1·0 |
| Apgar score of <7 at 5 min after birth‡, n/N (%) | 8/321 (2%) | 7/316 (2%) | .. | .. |
| Umbilical cord blood sampling, N | 112 | 102 | .. | .. |
| Umbilical arterial pH | 7·2 (0·1) | 7·2 (0·1) | Mean difference –0·02 (–0·04 to 0·01) | 0·18 |
| Nights in the neonatal unit§ | 5·5 (3·0–13·0) | 6·0 (2·0–16·0) | Median difference 0 (–3·2 to 3·2) | 1·0 |
| Main diagnosis for first neonatal unit admission | | | | |
| Prematurity, n/N (%) | 14/45 (31%) | 17/54 (31%) | .. | .. |
| Respiratory disease, n/N (%) | 16/45 (36%) | 15/54 (28%) | .. | .. |
| Infection suspected or confirmed, n/N (%) | 5/45 (11%) | 7/54 (13%) | .. | .. |
| Other¶, n/N (%) | 10/45 (22%) | 15/54 (28%) | .. | .. |

| | All studies (n=34) | | | | Randomised controlled trials (n=4) | | | |
|---|---|---|---|---|---|---|---|---|
| | Treated with ursodeoxycholic acid | Not treated with ursodeoxycholic acid | aOR (95% CI) | p value | Treated with ursodeoxycholic acid | Not treated with ursodeoxycholic acid | aOR (95% CI) | p value |
| **Perinatal outcomes** | | | | | | | | |
| Stillbirth | 35/5097 (0·7%) | 12/2038 (0·6%) | 1·04 (0·35–3·07) | p=0·95 | 1/439 (0·2%) | 3/429 (0·7%) | 0·29 (0·04–2·42) | p=0·25 |
| Composite outcome | 2480/5314 (46·7%) | 514/2213 (23·2%) | 1·28 (0·86–1·91) | p=0·22 | 75/439 (17·1%) | 107/429 (24·9%) | 0·60 (0·39–0·91) | p=0·016 |
| Total preterm birth (<37 weeks' gestation) | 2476/5287 (46·8%) | 508/2208 (23·0%) | 1·30 (0·87–1·94) | p=0·20 | 75/438 (17·1%) | 106/428 (24·8%) | 0·61 (0·40–0·92) | p=0·019 |
| Spontaneous preterm birth (<37 weeks' gestation) | 767/4871 (15·7%) | 169/2175 (7·8%) | 0·55 (0·35–0·88) | p=0·012 | 30/438 (6·8%) | 52/428 (12·1%) | 0·56 (0·31–1·01) | p=0·052 |
| Iatrogenic preterm birth (<37 weeks' gestation) | 1293/4871 (26·5%) | 306/2175 (14·1%) | 1·13 (0·75–1·70) | p=0·55 | 45/438 (10·3%) | 54/428 (12·6%) | 0·80 (0·48–1·33) | p=0·39 |
| Meconium-stained amniotic fluid | 703/4694 (15·0%) | 304/1987 (15·3%) | 0·69 (0·50–0·95) | p=0·022 | 55/436 (12·6%) | 85/425 (20·0%) | 0·51 (0·34–0·77) | p=0·001 |
| Apgar score less than 7 at 5 min | 156/5008 (3·1%) | 37/2150 (1·7%) | 1·09 (0·57–2·07) | p=0·80 | 10/437 (2·3%) | 11/419 (2·6%) | 0·85 (0·37–1·94) | p=0·70 |
| Umbilical cord arterial pH less than 7·0 | 6/1649 (0·4%) | 8/871 (0·9%) | 0·86 (0·15–4·82) | p=0·86 | 3/164 (1·8%) | 3/161 (1·9%) | 0·71 (0·12–4·10) | p=0·70 |
| Large for gestational age | 492/4116 (12·0%) | 220/1432 (15·4%) | 1·57 (1·09–2·25) | p=0·014 | 65/402 (16·2%) | 45/395 (11·4%) | 1·51 (1·00–2·29) | p=0·052 |
| Small for gestational age | 351/4116 (8·5%) | 83/1432 (5·8%) | 0·98 (0·60–1·59) | p=0·92 | 23/402 (5·7%) | 20/395 (5·1%) | 1·25 (0·62–2·50) | p=0·53 |
| Neonatal unit admission | 1298/4787 (27·1%) | 457/2081 (22·0%) | 0·96 (0·70–1·32) | p=0·79 | 58/438 (13·2%) | 78/427 (18·3%) | 0·67 (0·43–1·03) | p=0·067 |
| Perinatal death | 34/3403 (1·0%) | 9/1606 (0·6%) | 1·37 (0·32–5·87) | p=0·67 | 1/378 (0·3%) | 2/363 (0·6%) | 0·40 (0·04–3·63) | p=0·41 |
| **Maternal outcomes** | | | | | | | | |
| Pre-eclampsia | 206/3618 (5·7%) | 121/1574 (7·7%) | 1·14 (0·53–2·47) | p=0·74 | 1/51 (2·0%) | 0/43 (0·0%) | NA | NA |
| Unassisted vaginal birth | 1926/3842 (50·1%) | 1146/1853 (61·8%) | 1·08 (0·83–1·41) | p=0·58 | 261/412 (63·3%) | 253/397 (63·7%) | 0·94 (0·70–1·27) | p=0·70 |

Data are n/N (%), unless otherwise specified. ORs were calculated using logistic regression with Huber–White correction, with study level as a fixed effect and clustering by fetuses for those with multifetal pregnancies. For stillbirth, the composite outcome (stillbirth or preterm birth), preterm birth, and other perinatal outcomes, analyses were done by number of fetuses; for maternal outcomes, analyses were done by number of pregnancies. Data were adjusted by baseline bile acid concentration and maternal parity. aOR=adjusted odds ratio. NA=not applicable.

***Table 1:*** **Perinatal and maternal outcomes according to ursodeoxycholic acid treatment using individual participant data from all studies**

Ovadia et al. 2021

| | All studies (n=34) | | | | Randomised controlled trials (n=4) | | | |
|---|---|---|---|---|---|---|---|---|
| | Treated with ursodeoxycholic acid | Not treated with ursodeoxycholic acid | aOR (95% CI) | p value | Treated with ursodeoxycholic acid | Not treated with ursodeoxycholic acid | aOR (95% CI) | p value |
| **Perinatal outcomes** | | | | | | | | |
| Stillbirth | 35/5097 (0·7%) | 12/2038 (0·6%) | 1·04 (0·35–3·07) | p=0·95 | 1/439 (0·2%) | 3/429 (0·7%) | 0·29 (0·04–2·42) | p=0·25 |
| Composite outcome | 2480/5314 (46·7%) | 514/2213 (23·2%) | 1·28 (0·86–1·91) | p=0·22 | 75/439 (17·1%) | 107/429 (24·9%) | 0·60 (0·39–0·91) | p=0·016 |
| Total preterm birth (<37 weeks' gestation) | 2476/5287 (46·8%) | 508/2208 (23·0%) | 1·30 (0·87–1·94) | p=0·20 | 75/438 (17·1%) | 106/428 (24·8%) | 0·61 (0·40–0·92) | p=0·019 |
| Spontaneous preterm birth (<37 weeks' gestation) | 767/4871 (15·7%) | 169/2175 (7·8%) | 0·55 (0·35–0·88) | p=0·012 | 30/438 (6·8%) | 52/428 (12·1%) | 0·56 (0·31–1·01) | p=0·052 |
| Iatrogenic preterm birth (<37 weeks' gestation) | 1293/4871 (26·5%) | 306/2175 (14·1%) | 1·13 (0·75–1·70) | p=0·55 | 45/438 (10·3%) | 54/428 (12·6%) | 0·80 (0·48–1·33) | p=0·39 |
| Meconium-stained amniotic fluid | 703/4694 (15·0%) | 304/1987 (15·3%) | 0·69 (0·50–0·95) | p=0·022 | 55/436 (12·6%) | 85/425 (20·0%) | 0·51 (0·34–0·77) | p=0·001 |
| Apgar score less than 7 at 5 min | 156/5008 (3·1%) | 37/2150 (1·7%) | 1·09 (0·57–2·07) | p=0·80 | 10/437 (2·3%) | 11/419 (2·6%) | 0·85 (0·37–1·94) | p=0·70 |
| Umbilical cord arterial pH less than 7·0 | 6/1649 (0·4%) | 8/871 (0·9%) | 0·86 (0·15–4·82) | p=0·86 | 3/164 (1·8%) | 3/161 (1·9%) | 0·71 (0·12–4·10) | p=0·70 |
| Large for gestational age | 492/4116 (12·0%) | 220/1432 (15·4%) | 1·57 (1·09–2·25) | p=0·014 | 65/402 (16·2%) | 45/395 (11·4%) | 1·51 (1·00–2·29) | p=0·052 |
| Small for gestational age | 351/4116 (8·5%) | 83/1432 (5·8%) | 0·98 (0·60–1·59) | p=0·92 | 23/402 (5·7%) | 20/395 (5·1%) | 1·25 (0·62–2·50) | p=0·53 |
| Neonatal unit admission | 1298/4787 (27·1%) | 457/2081 (22·0%) | 0·96 (0·70–1·32) | p=0·79 | 58/438 (13·2%) | 78/427 (18·3%) | 0·67 (0·43–1·03) | p=0·067 |
| Perinatal death | 34/3403 (1·0%) | 9/1606 (0·6%) | 1·37 (0·32–5·87) | p=0·67 | 1/378 (0·3%) | 2/363 (0·6%) | 0·40 (0·04–3·63) | p=0·41 |
| **Maternal outcomes** | | | | | | | | |
| Pre-eclampsia | 206/3618 (5·7%) | 121/1574 (7·7%) | 1·14 (0·53–2·47) | p=0·74 | 1/51 (2·0%) | 0/43 (0·0%) | NA | NA |
| Unassisted vaginal birth | 1926/3842 (50·1%) | 1146/1853 (61·8%) | 1·08 (0·83–1·41) | p=0·58 | 261/412 (63·3%) | 253/397 (63·7%) | 0·94 (0·70–1·27) | p=0·70 |

Data are n/N (%), unless otherwise specified. ORs were calculated using logistic regression with Huber–White correction, with study level as a fixed effect and clustering by fetuses for those with multifetal pregnancies. For stillbirth, the composite outcome (stillbirth or preterm birth), preterm birth, and other perinatal outcomes, analyses were done by number of fetuses; for maternal outcomes, analyses were done by number of pregnancies. Data were adjusted by baseline bile acid concentration and maternal parity. aOR=adjusted odds ratio. NA=not applicable.

***Table 1:*** **Perinatal and maternal outcomes according to ursodeoxycholic acid treatment using individual participant data from all studies**

Ovadia et al. 2021

# AUDC

**Chez les femmes présentant une cholestase gravidique,**

**il est recommandé de prescrire de l'acide ursodésoxycholique pour réduire la prématurité totale.**

RECOMMANDATION FORTE – QUALITÉ DE LA PREUVE MODÉRÉE

| | Ursodeoxycholic acid (n=322) | Placebo (n=318) | Adjusted effect estimate (95% CI) | p value |
|---|---|---|---|---|
| Perinatal death, preterm delivery,* or neonatal unit admission | 74 (23%) | 85 (27%) | RR 0·85 (0·62 to 1·15) | 0·28 |
| In-utero fetal death | 1 (<1%) | 2 (1%) | RR 0·51 (0·04 to 6·25) | 0·60 |
| Preterm delivery* | 54 (17%) | 65 (20%) | RR 0·79 (0·57 to 1·10) | 0·17 |
| Known neonatal death up to 7 days after birth | 0 | 0 | .. | .. |
| Neonatal unit admission for ≥4 h | 45 (14%) | 54 (17%) | RR 0·81 (0·58 to 1·13) | 0·21 |
| Livebirth | 321 (>99%) | 316 (99%) | .. | .. |
| Gestational age at delivery, weeks | 37·6 (37·1–38·1) | 37·4 (37·0–38·1) | Median difference 0·1 (0·0 to 0·3) | 0·065 |
| Birthweight, g | 3105 (2775–3390) | 3040 (2660–3320) | Median difference 94·0 (18·7 to 169·3) | 0·014 |
| Birthweight percentile† | 59·3 (28·4) | 56·3 (27·8) | .. | .. |
| <10th percentile | 16 (5%) | 18 (6%) | RR 0·89 (0·47 to 1·69) | 0·73 |
| <3rd percentile | 7 (2%) | 7 (2%) | RR 1·09 (0·38 to 3·12) | 0·88 |
| Mode of delivery | | | | |
| Spontaneous vaginal (cephalic) | 193 (60%) | 182 (57%) | RR 1·04 (0·91 to 1·20) | 0·56 |
| Vaginal (breech) | 1 (<1%) | 3 (1%) | .. | .. |
| Assisted vaginal (cephalic) | 21 (7%) | 35 (11%) | .. | .. |
| Pre-labour caesarean | 71 (22%) | 62 (19%) | .. | .. |
| Caesarean | 36 (11%) | 36 (11%) | RR 1·00 (0·68 to 1·46) | 1·0 |
| Presence of meconium-stained amniotic fluid | 34 (11%) | 52 (16%) | RR 0·65 (0·43 to 0·98) | 0·040 |
| Apgar score at 5 min after birth‡ | 9·0 (9·0–10·0) | 9·0 (9·0–10·0) | Median difference 0 (–0·4 to 0·4) | 1·0 |
| Apgar score of <7 at 5 min after birth‡, n/N (%) | 8/321 (2%) | 7/316 (2%) | .. | .. |
| Umbilical cord blood sampling, N | 112 | 102 | .. | .. |
| Umbilical arterial pH | 7·2 (0·1) | 7·2 (0·1) | Mean difference –0·02 (–0·04 to 0·01) | 0·18 |
| Nights in the neonatal unit§ | 5·5 (3·0–13·0) | 6·0 (2·0–16·0) | Median difference 0 (–3·2 to 3·2) | 1·0 |
| Main diagnosis for first neonatal unit admission | | | | |
| Prematurity, n/N (%) | 14/45 (31%) | 17/54 (31%) | .. | .. |
| Respiratory disease, n/N (%) | 16/45 (36%) | 15/54 (28%) | .. | .. |
| Infection suspected or confirmed, n/N (%) | 5/45 (11%) | 7/54 (13%) | .. | .. |
| Other¶, n/N (%) | 10/45 (22%) | 15/54 (28%) | .. | .. |

| | Ursodeoxycholic acid (n=322) | Placebo (n=318) | Adjusted effect estimate (95% CI) | p value |
|---|---|---|---|---|
| Perinatal death, preterm delivery,* or neonatal unit admission | 74 (23%) | 85 (27%) | RR 0·85 (0·62 to 1·15) | 0·28 |
| In-utero fetal death | 1 (<1%) | 2 (1%) | RR 0·51 (0·04 to 6·25) | 0·60 |
| Preterm delivery* | 54 (17%) | 65 (20%) | RR 0·79 (0·57 to 1·10) | 0·17 |
| Known neonatal death up to 7 days after birth | 0 | 0 | .. | .. |
| Neonatal unit admission for ≥4 h | 45 (14%) | 54 (17%) | RR 0·81 (0·58 to 1·13) | 0·21 |
| Livebirth | 321 (>99%) | 316 (99%) | .. | .. |
| Gestational age at delivery, weeks | 37·6 (37·1–38·1) | 37·4 (37·0–38·1) | Median difference 0·1 (0·0 to 0·3) | 0·065 |
| Birthweight, g | 3105 (2775–3390) | 3040 (2660–3320) | Median difference 94·0 (18·7 to 169·3) | 0·014 |
| Birthweight percentile† | 59·3 (28·4) | 56·3 (27·8) | .. | .. |
| <10th percentile | 16 (5%) | 18 (6%) | RR 0·89 (0·47 to 1·69) | 0·73 |
| <3rd percentile | 7 (2%) | 7 (2%) | RR 1·09 (0·38 to 3·12) | 0·88 |
| Mode of delivery | | | | |
| Spontaneous vaginal (cephalic) | 193 (60%) | 182 (57%) | RR 1·04 (0·91 to 1·20) | 0·56 |
| Vaginal (breech) | 1 (<1%) | 3 (1%) | .. | .. |
| Assisted vaginal (cephalic) | 21 (7%) | 35 (11%) | .. | .. |
| Pre-labour caesarean | 71 (22%) | 62 (19%) | .. | .. |
| Caesarean | 36 (11%) | 36 (11%) | RR 1·00 (0·68 to 1·46) | 1·0 |
| Presence of meconium-stained amniotic fluid | 34 (11%) | 52 (16%) | RR 0·65 (0·43 to 0·98) | 0·040 |
| Apgar score at 5 min after birth‡ | 9·0 (9·0–10·0) | 9·0 (9·0–10·0) | Median difference 0 (–0·4 to 0·4) | 1·0 |
| Apgar score of <7 at 5 min after birth‡, n/N (%) | 8/321 (2%) | 7/316 (2%) | .. | .. |
| Umbilical cord blood sampling, N | 112 | 102 | .. | .. |
| Umbilical arterial pH | 7·2 (0·1) | 7·2 (0·1) | Mean difference –0·02 (–0·04 to 0·01) | 0·18 |
| Nights in the neonatal unit§ | 5·5 (3·0–13·0) | 6·0 (2·0–16·0) | Median difference 0 (–3·2 to 3·2) | 1·0 |
| Main diagnosis for first neonatal unit admission | | | | |
| Prematurity, n/N (%) | 14/45 (31%) | 17/54 (31%) | .. | .. |
| Respiratory disease, n/N (%) | 16/45 (36%) | 15/54 (28%) | .. | .. |
| Infection suspected or confirmed, n/N (%) | 5/45 (11%) | 7/54 (13%) | .. | .. |
| Other¶, n/N (%) | 10/45 (22%) | 15/54 (28%) | .. | .. |

| | Ursodeoxycholic acid (n=322) | Placebo (n=318) | Adjusted effect estimate (95% CI) | p value |
|---|---|---|---|---|
| Perinatal death, preterm delivery,* or neonatal unit admission | 74 (23%) | 85 (27%) | RR 0·85 (0·62 to 1·15) | 0·28 |
| In-utero fetal death | 1 (<1%) | 2 (1%) | RR 0·51 (0·04 to 6·25) | 0·60 |
| Preterm delivery* | 54 (17%) | 65 (20%) | RR 0·79 (0·57 to 1·10) | 0·17 |
| Known neonatal death up to 7 days after birth | 0 | 0 | .. | .. |
| Neonatal unit admission for ≥4 h | 45 (14%) | 54 (17%) | RR 0·81 (0·58 to 1·13) | 0·21 |
| Livebirth | 321 (>99%) | 316 (99%) | .. | .. |
| Gestational age at delivery, weeks | 37·6 (37·1–38·1) | 37·4 (37·0–38·1) | Median difference 0·1 (0·0 to 0·3) | 0·065 |
| Birthweight, g | 3105 (2775–3390) | 3040 (2660–3320) | Median difference 94·0 (18·7 to 169·3) | 0·014 |
| Birthweight percentile† | 59·3 (28·4) | 56·3 (27·8) | .. | .. |
| <10th percentile | 16 (5%) | 18 (6%) | RR 0·89 (0·47 to 1·69) | 0·73 |
| <3rd percentile | 7 (2%) | 7 (2%) | RR 1·09 (0·38 to 3·12) | 0·88 |
| Mode of delivery | | | | |
| Spontaneous vaginal (cephalic) | 193 (60%) | 182 (57%) | RR 1·04 (0·91 to 1·20) | 0·56 |
| Vaginal (breech) | 1 (<1%) | 3 (1%) | .. | .. |
| Assisted vaginal (cephalic) | 21 (7%) | 35 (11%) | .. | .. |
| Pre-labour caesarean | 71 (22%) | 62 (19%) | .. | .. |
| Caesarean | 36 (11%) | 36 (11%) | RR 1·00 (0·68 to 1·46) | 1·0 |
| Presence of meconium-stained amniotic fluid | 34 (11%) | 52 (16%) | RR 0·65 (0·43 to 0·98) | 0·040 |
| Apgar score at 5 min after birth‡ | 9·0 (9·0–10·0) | 9·0 (9·0–10·0) | Median difference 0 (–0·4 to 0·4) | 1·0 |
| Apgar score of <7 at 5 min after birth‡, n/N (%) | 8/321 (2%) | 7/316 (2%) | .. | .. |
| Umbilical cord blood sampling, N | 112 | 102 | .. | .. |
| Umbilical arterial pH | 7·2 (0·1) | 7·2 (0·1) | Mean difference –0·02 (–0·04 to 0·01) | 0·18 |
| Nights in the neonatal unit§ | 5·5 (3·0–13·0) | 6·0 (2·0–16·0) | Median difference 0 (–3·2 to 3·2) | 1·0 |
| Main diagnosis for first neonatal unit admission | | | | |
| Prematurity, n/N (%) | 14/45 (31%) | 17/54 (31%) | .. | .. |
| Respiratory disease, n/N (%) | 16/45 (36%) | 15/54 (28%) | .. | .. |
| Infection suspected or confirmed, n/N (%) | 5/45 (11%) | 7/54 (13%) | .. | .. |
| Other¶, n/N (%) | 10/45 (22%) | 15/54 (28%) | .. | .. |

| | Ursodeoxycholic acid (n=322) | Placebo (n=318) | Adjusted effect estimate (95% CI) | p value |
|---|---|---|---|---|
| Perinatal death, preterm delivery,* or neonatal unit admission | 74 (23%) | 85 (27%) | RR 0·85 (0·62 to 1·15) | 0·28 |
| In-utero fetal death | 1 (<1%) | 2 (1%) | RR 0·51 (0·04 to 6·25) | 0·60 |
| Preterm delivery* | 54 (17%) | 65 (20%) | RR 0·79 (0·57 to 1·10) | 0·17 |
| Known neonatal death up to 7 days after birth | 0 | 0 | .. | .. |
| Neonatal unit admission for ≥4 h | 45 (14%) | 54 (17%) | RR 0·81 (0·58 to 1·13) | 0·21 |
| Livebirth | 321 (>99%) | 316 (99%) | .. | .. |
| Gestational age at delivery, weeks | 37·6 (37·1–38·1) | 37·4 (37·0–38·1) | Median difference 0·1 (0·0 to 0·3) | 0·065 |
| Birthweight, g | 3105 (2775–3390) | 3040 (2660–3320) | Median difference 94·0 (18·7 to 169·3) | 0·014 |
| Birthweight percentile† | 59·3 (28·4) | 56·3 (27·8) | .. | .. |
| <10th percentile | 16 (5%) | 18 (6%) | RR 0·89 (0·47 to 1·69) | 0·73 |
| <3rd percentile | 7 (2%) | 7 (2%) | RR 1·09 (0·38 to 3·12) | 0·88 |
| Mode of delivery | | | | |
| Spontaneous vaginal (cephalic) | 193 (60%) | 182 (57%) | RR 1·04 (0·91 to 1·20) | 0·56 |
| Vaginal (breech) | 1 (<1%) | 3 (1%) | .. | .. |
| Assisted vaginal (cephalic) | 21 (7%) | 35 (11%) | .. | .. |
| Pre-labour caesarean | 71 (22%) | 62 (19%) | .. | .. |
| Caesarean | 36 (11%) | 36 (11%) | RR 1·00 (0·68 to 1·46) | 1·0 |
| Presence of meconium-stained amniotic fluid | 34 (11%) | 52 (16%) | RR 0·65 (0·43 to 0·98) | 0·040 |
| Apgar score at 5 min after birth‡ | 9·0 (9·0–10·0) | 9·0 (9·0–10·0) | Median difference 0 (–0·4 to 0·4) | 1·0 |
| Apgar score of <7 at 5 min after birth‡, n/N (%) | 8/321 (2%) | 7/316 (2%) | .. | .. |
| Umbilical cord blood sampling, N | 112 | 102 | .. | .. |
| Umbilical arterial pH | 7·2 (0·1) | 7·2 (0·1) | Mean difference –0·02 (–0·04 to 0·01) | 0·18 |
| Nights in the neonatal unit§ | 5·5 (3·0–13·0) | 6·0 (2·0–16·0) | Median difference 0 (–3·2 to 3·2) | 1·0 |
| Main diagnosis for first neonatal unit admission | | | | |
| Prematurity, n/N (%) | 14/45 (31%) | 17/54 (31%) | .. | .. |
| Respiratory disease, n/N (%) | 16/45 (36%) | 15/54 (28%) | .. | .. |
| Infection suspected or confirmed, n/N (%) | 5/45 (11%) | 7/54 (13%) | .. | .. |
| Other¶, n/N (%) | 10/45 (22%) | 15/54 (28%) | .. | .. |

# Cochrane 2020

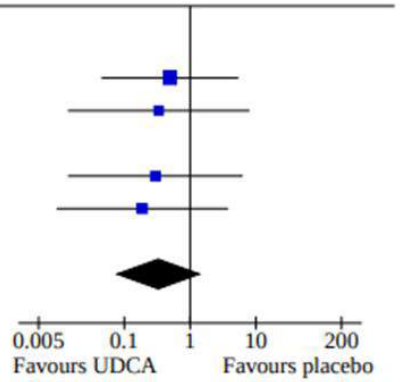
**Analysis 1.4. Comparison 1: UDCA versus placebo, Outcome 4: Stillbirth**

| Study or Subgroup | UDCA Events | UDCA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Chappell 2012 | 0 | 60 | 0 | 64 | | Not estimable |
| Chappell 2019 | 1 | 322 | 2 | 318 | 35.4% | 0.49 [0.04 , 5.42] |
| Glantz 2005 | 0 | 47 | 1 | 47 | 20.2% | 0.33 [0.01 , 7.98] |
| Joutsiniemi 2014 | 0 | 10 | 0 | 8 | | Not estimable |
| Palma 1997 | 0 | 8 | 1 | 7 | 21.8% | 0.30 [0.01 , 6.29] |
| Wang 2003 | 0 | 33 | 2 | 31 | 22.6% | 0.19 [0.01 , 3.77] |
| **Total (95% CI)** | | **480** | | **475** | **100.0%** | **0.33 [0.08 , 1.37]** |
| Total events: | 1 | | 6 | | | |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.25$, df = 3 (P = 0.97); $I^2 = 0\%$

Test for overall effect: Z = 1.53 (P = 0.13)

Test for subgroup differences: Not applicable



# Cochrane 2020

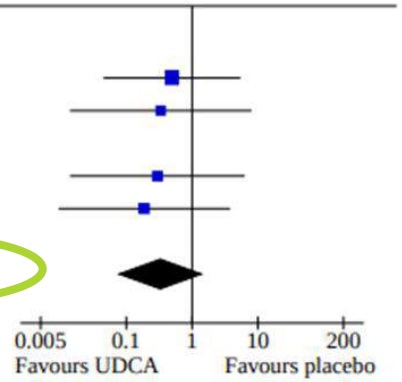
**Analysis 1.4. Comparison 1: UDCA versus placebo, Outcome 4: Stillbirth**

| Study or Subgroup | UDCA Events | UDCA Total | Placebo Events | Placebo Total | Weight | Risk Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Chappell 2012 | 0 | 60 | 0 | 64 | | Not estimable |
| Chappell 2019 | 1 | 322 | 2 | 318 | 35.4% | 0.49 [0.04 , 5.42] |
| Glantz 2005 | 0 | 47 | 1 | 47 | 20.2% | 0.33 [0.01 , 7.98] |
| Joutsiniemi 2014 | 0 | 10 | 0 | 8 | | Not estimable |
| Palma 1997 | 0 | 8 | 1 | 7 | 21.8% | 0.30 [0.01 , 6.29] |
| Wang 2003 | 0 | 33 | 2 | 31 | 22.6% | 0.19 [0.01 , 3.77] |
| **Total (95% CI)** | | **480** | | **475** | **100.0%** | **0.33 [0.08 , 1.37]** |
| Total events: | 1 | | 6 | | | |

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.25$, df = 3 (P = 0.97); $I^2 = 0\%$

Test for overall effect: Z = 1.53 (P = 0.13)

Test for subgroup differences: Not applicable




AUDC
-
Acides biliaires
+
MFIU


AUDC
-
Acides biliaires
+
MFIU
?


**Chez les femmes présentant une cholestase gravidique, il n'est pas recommandé de prescrire de l'acide ursodésoxycholique dans le seul but de réduire le risque de mort foetale *in utero*, de mortalité périnatale, d'hospitalisation en néonatologie, et de score d'Apgar < 7 à 5 minutes.**

RECOMMANDATION FAIBLE – QUALITÉ DE LA PREUVE BASSE

# Conclusion sur l'acide ursodésoxycholique

| |
|---|
| **Chez les femmes présentant une cholestase gravidique, l'administration d'acide ursodésoxycholique est recommandée afin de réduire l'intensité du prurit maternel, pour améliorer le bilan biologique (acides biliaires totaux et ALAT) et pour réduire la prématurité totale.** |
| **Recommandation forte**<br>**Qualité de la preuve modérée** |

# Prurit maternel

**Chez les femmes présentant une cholestase gravidique, il est recommandé de ne pas administrer de la S-adénosyl-methionine, de la dexamethasone, de la gomme de guar ou du charbon activé dans le but de réduire l'intensité du prurit maternel.**

RECOMMANDATION FORTE – QUALITÉ DE LA PREUVE BASSE

# Prurit maternel

**Chez des femmes ayant une cholestase gravidique, Il est recommandé d'administrer de l'acide ursodésoxycholique et non de la cholestyramine ou de la SAMe pour réduire l'intensité du prurit maternel.**

RECOMMANDATION FORTE – QUALITÉ DE LA PREUVE BASSE

# Et si acide ursodesoxycholique insuffisant pour le prurit ?

| | Ursodeoxycholic acid (n=304) | Placebo (n=300) |
|---|---|---|
| (Continued from previous page) | | |
| History of intrahepatic cholestasis of pregnancy, n/N (%) | 92/175 (53%) | 90/190 (47%) |
| Missing, n | 3 | 3 |
| Pre-pregnancy liver disease | 3 (1%) | 6 (2%) |
| Liver ultrasound at randomisation, n/N (%) | 79/293 (27%) | 78/292 (27%) |
| Normal, n/N (%) | 65/77 (84%) | 57/77 (74%) |
| Gallstones, n/N (%) | 9/77 (12%) | 12/77 (16%) |
| Other abnormality, n/N (%) | 3/77 (4%) | 8/77 (10%) |
| Missing result, n | 2 | 1 |
| Previous operation for gallstones | 20 (7%) | 17 (6%) |
| Pre-pregnancy diabetes | 4 (1%) | 4 (1%) |
| Gestational age (weeks), median (IQR)† | 34·4 (32·1–35·9) | 34·4 (31·5–36·0) |
| <34 weeks | 133 (44%) | 131 (44%) |
| 34 to <37 weeks | 141 (46%) | 141 (47%) |
| ≥37 weeks | 30 (10%) | 28 (9%) |
| Twin pregnancy† | 18 (6%) | 19 (6%) |
| Gestational diabetes | 32 (11%) | 25 (8%) |
| Itch score, mean (SD)‡ | 57·1 (25·1) | 59·5 (25·1) |
| Medication for pruritus§, n/N (%) | 146/298 (49%) | 137/297 (46%) |
| Antihistamine, n/N (%) | 121/298 (41%) | 119/297 (40%) |
| Topical emollient, n/N (%) | 102/298 (34%) | 101/297 (34%) |
| Ursodeoxycholic acid, n/N (%) | 15/298 (5%) | 13/297 (4%) |
| Missing, n | 6 | 3 |
| Highest baseline serum concentration before randomisation | | |
| Bile acid (μmol/L), geometric mean (95% CI)† | 28·1 (26·0–30·3) | 26·9 (24·9–29·0) |
| <40 μmol/L | 232 (76%) | 228 (76%) |
| ≥40 μmol/L | 72 (24%) | 72 (24%) |
| Alanine transaminase, N | 286 | 286 |
| Alanine transaminase (U/L), geometric mean (95% CI) | 70·0 (61·5–79·6) | 59·5 (52·0–68·1) |
| Aspartate transaminase, N | 47 | 48 |
| Aspartate transaminase (U/L), geometric mean (95% CI) | 49·0 (38·4–62·5) | 61·6 (46·8–81·0) |

| | Ursodeoxycholic acid (n=304) | Placebo (n=300) |
|---|---|---|
| (Continued from previous page) | | |
| History of intrahepatic cholestasis of pregnancy, n/N (%) | 92/175 (53%) | 90/190 (47%) |
| Missing, n | 3 | 3 |
| Pre-pregnancy liver disease | 3 (1%) | 6 (2%) |
| Liver ultrasound at randomisation, n/N (%) | 79/293 (27%) | 78/292 (27%) |
| Normal, n/N (%) | 65/77 (84%) | 57/77 (74%) |
| Gallstones, n/N (%) | 9/77 (12%) | 12/77 (16%) |
| Other abnormality, n/N (%) | 3/77 (4%) | 8/77 (10%) |
| Missing result, n | 2 | 1 |
| Previous operation for gallstones | 20 (7%) | 17 (6%) |
| Pre-pregnancy diabetes | 4 (1%) | 4 (1%) |
| Gestational age (weeks), median (IQR)† | 34·4 (32·1–35·9) | 34·4 (31·5–36·0) |
| <34 weeks | 133 (44%) | 131 (44%) |
| 34 to <37 weeks | 141 (46%) | 141 (47%) |
| ≥37 weeks | 30 (10%) | 28 (9%) |
| Twin pregnancy† | 18 (6%) | 19 (6%) |
| Gestational diabetes | 32 (11%) | 25 (8%) |
| Itch score, mean (SD)‡ | 57·1 (25·1) | 59·5 (25·1) |
| Medication for pruritus§, n/N (%) | 146/298 (49%) | 137/297 (46%) |
| Antihistamine, n/N (%) | 121/298 (41%) | 119/297 (40%) |
| Topical emollient, n/N (%) | 102/298 (34%) | 101/297 (34%) |
| Ursodeoxycholic acid, n/N (%) | 15/298 (5%) | 13/297 (4%) |
| Missing, n | 6 | 3 |
| Highest baseline serum concentration before randomisation | | |
| Bile acid (μmol/L), geometric mean (95% CI)† | 28·1 (26·0–30·3) | 26·9 (24·9–29·0) |
| <40 μmol/L | 232 (76%) | 228 (76%) |
| ≥40 μmol/L | 72 (24%) | 72 (24%) |
| Alanine transaminase, N | 286 | 286 |
| Alanine transaminase (U/L), geometric mean (95% CI) | 70·0 (61·5–79·6) | 59·5 (52·0–68·1) |
| Aspartate transaminase, N | 47 | 48 |
| Aspartate transaminase (U/L), geometric mean (95% CI) | 49·0 (38·4–62·5) | 61·6 (46·8–81·0) |

| | Ursodeoxycholic acid (n=304) | Placebo (n=300) | Adjusted effect estimate (95% CI) | p value |
|---|---|---|---|---|
| Itch score*, N | 241 | 227 | .. | .. |
| Itch score†, mm | 49·5 (12·9) | 56·9 (13·3) | Mean difference −5·7 (−9·7 to −1·7) | 0·0054 |
| Maternal serum bile acid concentration*, N | 256 | 247 | .. | .. |
| Maternal serum bile acid concentration† (μmol/L), geometric mean (95% CI) | 22·4 (21·4 to 23·5) | 18·5 (17·7 to 19·4) | Geometric mean ratio 1·18 (1·02 to 1·36) | 0·030 |
| Maternal serum alanine transaminase*, N | 242 | 240 | .. | .. |
| Maternal serum alanine transaminase† (U/L), geometric mean (95% CI) | 49·5 (43·8 to 55·8) | 58·0 (51·0 to 65·9) | Geometric mean ratio 0·74 (0·66 to 0·83) | <0·0001 |
| Gestational diabetes | 3 (1%) | 9 (3%) | RR 0·33 (0·10 to 1·10) | 0·071 |
| Additional therapy for cholestasis†, n/N (%) | 134/261 (51%) | 125/245 (51%) | .. | .. |
| Antihistamine, n/N (%) | 102/134 (76%) | 105/125 (84%) | .. | .. |
| Topical emollient, n/N (%) | 101/134 (75%) | 93/125 (74%) | .. | .. |
| Rifampicin, n/N (%) | 1/134 (1%) | 2/125 (2%) | .. | .. |
| Open-label ursodeoxycholic acid (tablets stopped), n/N (%) | 17/134 (13%) | 21/125 (17%) | .. | .. |
| Delivered before first follow-up visit, n | 33 | 42 | .. | .. |
| Missing, n | 10 | 13 | .. | .. |
| Maximum dose of trial medication | | | | |
| One tablet once a day | 4 (1%) | 5 (2%) | .. | .. |
| One tablet twice a day | 203 (67%) | 198 (66%) | .. | .. |
| One tablet three times a day | 62 (20%) | 65 (22%) | .. | .. |
| Two tablets twice a day | 35 (12%) | 32 (11%) | .. | .. |
| Mode of onset of labour | | | | |
| Spontaneous | 33 (11%) | 55 (18%) | RR 0·59 (0·42 to 0·83) | 0·0025 |
| Induced or pre-labour rupture of membranes and stimulation | 215 (71%) | 200 (67%) | RR 1·06 (0·95 to 1·17) | 0·30 |
| Pre-labour caesarean | 56 (18%) | 44 (15%) | .. | .. |
| Initiation of delivery‡ | | | | |
| Severe maternal symptoms, n/N (%) | 17/271 (6%) | 28/244 (11%) | .. | .. |
| Maternal serum bile acid, n/N (%) | 53/271 (20%) | 32/244 (13%) | .. | .. |
| Fetal compromise, n/N (%) | 24/271 (9%) | 24/244 (10%) | .. | .. |
| Gestational age, n/N (%) | 161/271 (59%) | 150/244 (61%) | .. | .. |
| Maternal request, n/N (%) | 32/271 (12%) | 29/244 (12%) | .. | .. |
| Other§, n/N (%) | 37/271 (14%) | 33/244 (14%) | .. | .. |
| Estimated blood loss at delivery, mL | 350 (250 to 600) | 400 (250 to 600) | Median difference −50 (−95 to −5) | 0·029 |
| <500 | 195 (64%) | 185 (62%) | .. | .. |
| ≥500 and <1000 | 79 (26%) | 80 (27%) | .. | .. |
| ≥1000 | 30 (10%) | 34 (11%) | .. | .. |

# Et si acide ursodesoxycholique insuffisant pour le prurit ?

**Chez les femmes présentant une cholestase gravidique, les données de la littérature sont insuffisantes en nombre et en qualité pour émettre une recommandation quant à l'administration d'anti-histaminiques pour réduire l'intensité du prurit maternel.**

ABSENCE DE RECOMMANDATION – QUALITÉ DE LA PREUVE BASSE

# Autres thérapeutiques

**Chez des femmes présentant une cholestase gravidique, il est recommandé de ne pas utiliser la rifampicine pour réduire le prurit maternel et la morbidité périnatale.**

RECOMMANDATION FAIBLE – QUALITÉ DE LA PREUVE TRES BASSE

# Autres thérapeutiques

**Chez des femmes présentant une cholestase gravidique, il est recommandé de ne pas utiliser la rifampicine pour réduire le prurit maternel et la morbidité périnatale.**

RECOMMANDATION FAIBLE – QUALITÉ DE LA PREUVE TRES BASSE

**Chez des femmes ayant une cholestase gravidique il est recommandé de ne pas avoir recours à des échanges plasmatiques pour réduire le prurit maternel ou la morbidité périnatale.**

RECOMMANDATION FORTE – QUALITÉ DE LA PREUVE TRES BASSE

# Surveillance clinique et biologique

**Il est recommandé une surveillance biologique des acides biliaires et des transaminases, sans qu'une fréquence puisse être déterminée, pour réduire la morbi-mortalité périnatale (mort fœtale in utero, prématurité).**

RECOMMANDATION FAIBLE – QUALITÉ DE LA PREUVE BASSE

# Surveillance clinique et biologique

**Il est recommandé une surveillance biologique des acides biliaires et des transaminases, sans qu'une fréquence puisse être déterminée, pour réduire la morbi-mortalité périnatale (mort fœtale in utero, prématurité).**

RECOMMANDATION FAIBLE – QUALITÉ DE LA PREUVE BASSE

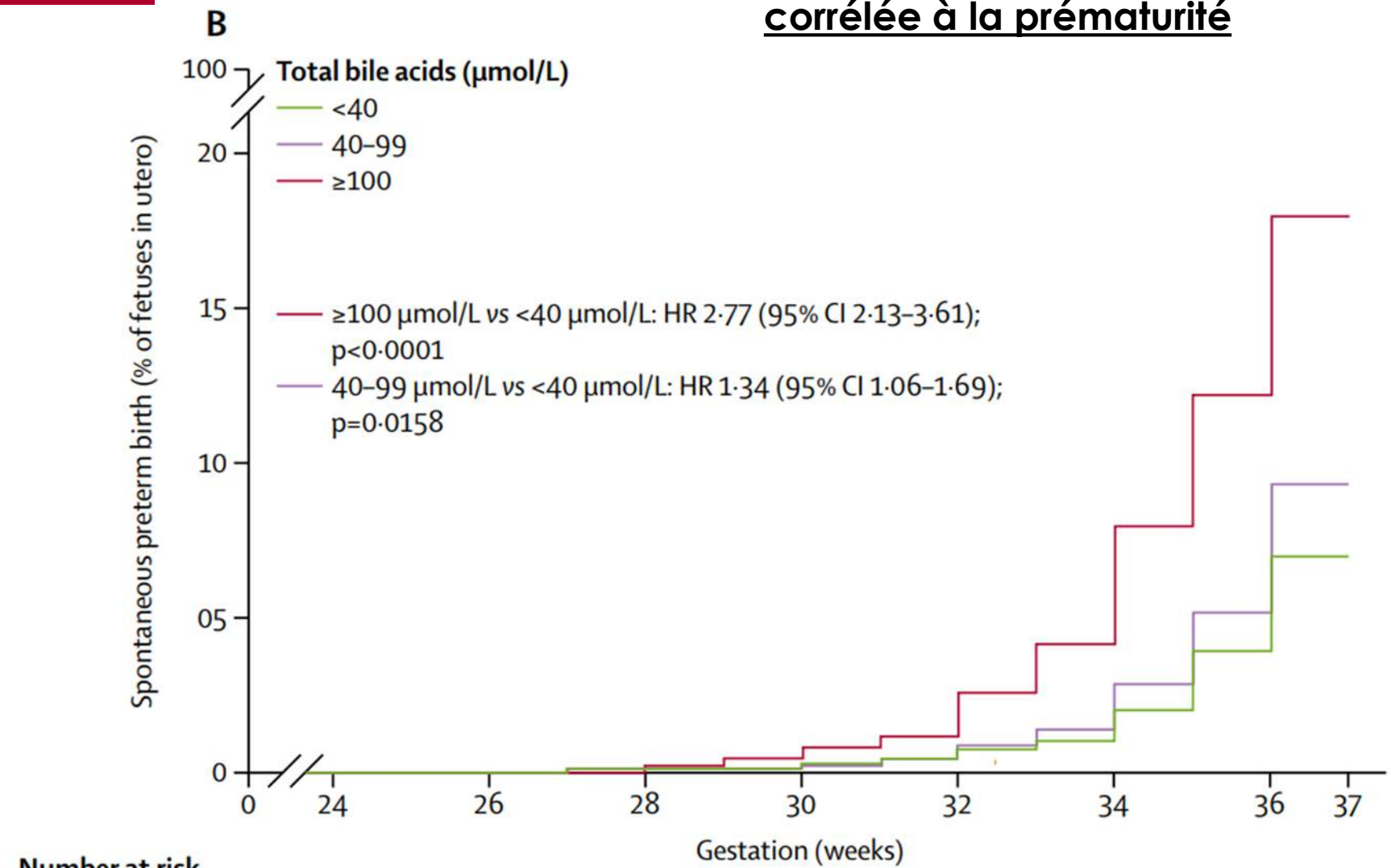
**Les données de la littérature sont insuffisantes en qualité et en nombre pour émettre une recommandation quant à l'intérêt d'une surveillance par analyse du rythme cardiaque fœtal ou par échographie obstétricale pour réduire la morbi-mortalité périnatale.**

ABSENCE DE RECOMMANDATION

# Quel terme de naissance ?

**Ovadia et *al.* 2019**

# Morbidité périnatale corrélée à la prématurité

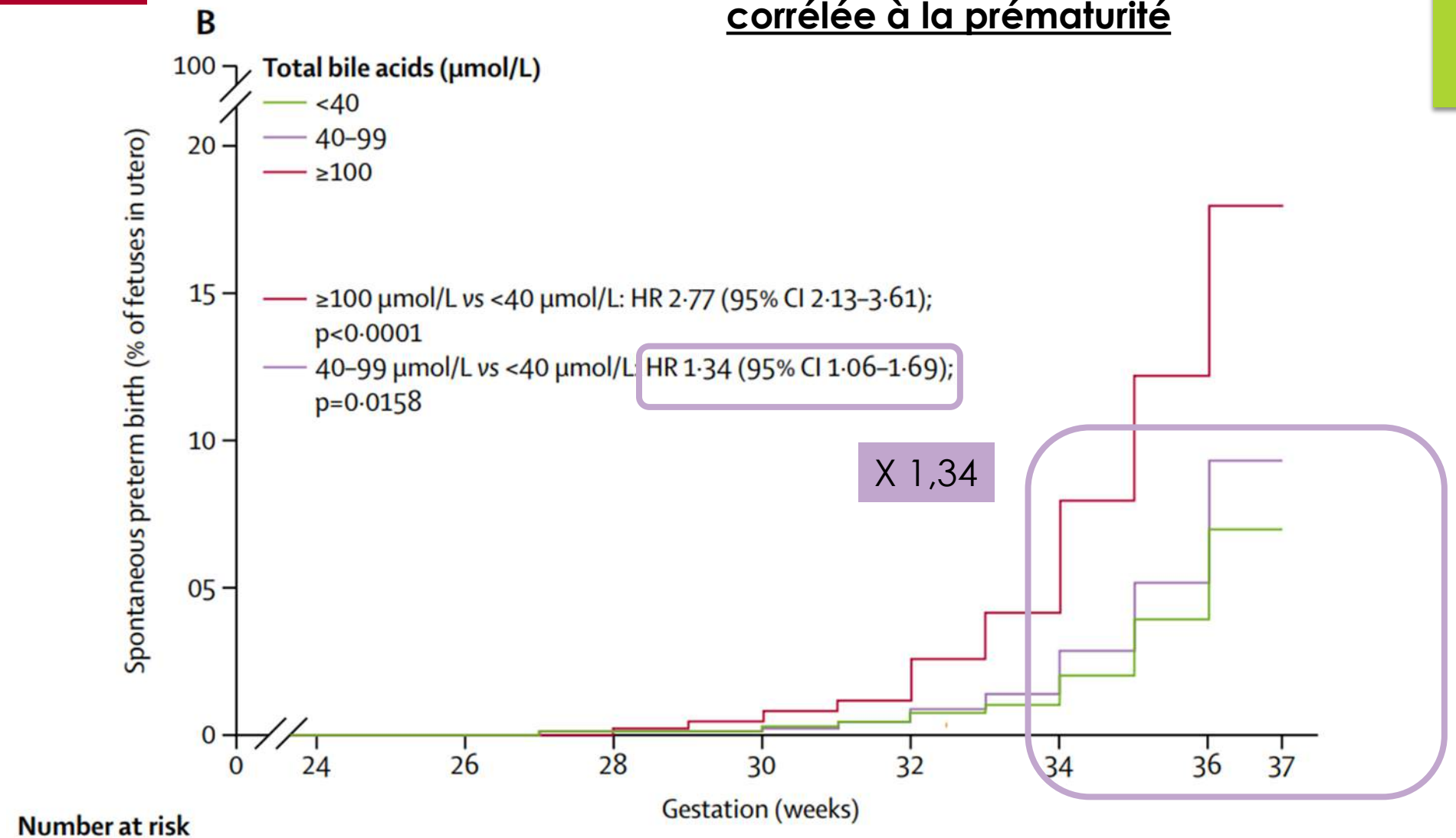



**Number at risk**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| TBA <40 | .. | 2310 | 2310 | 2308 | 2305 | 2291 | 2261 | 2079 | 1782 |
| TBA 40–99 | .. | 1412 | 1412 | 1411 | 1410 | 1398 | 1368 | 1226 | 1013 |
| TBA ≥100 | .. | 524 | 523 | 521 | 515 | 507 | 480 | 378 | 268 |

**Ovadia et *al.* 2019**

# Morbidité périnatale corrélée à la prématurité

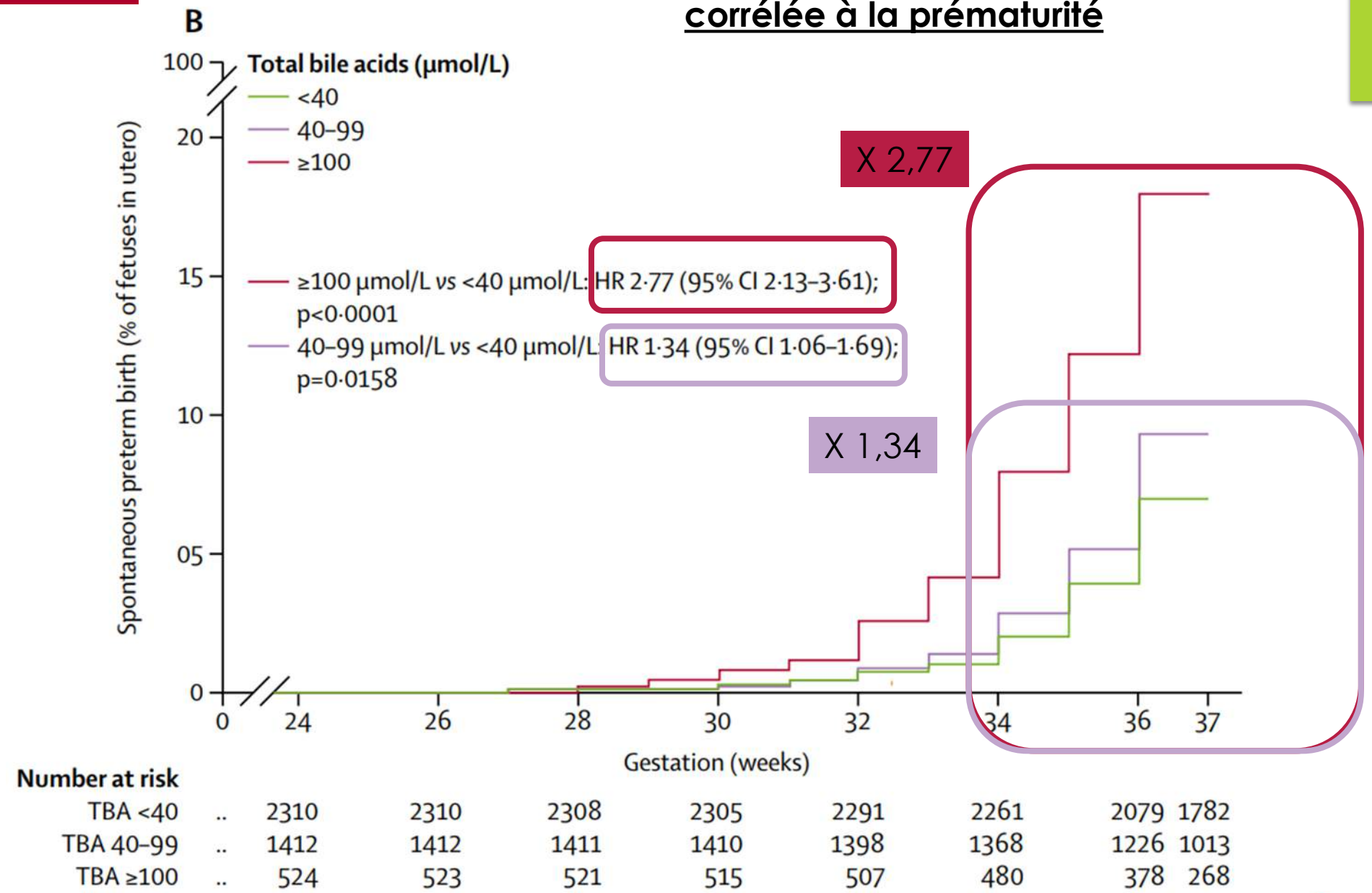



**Number at risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TBA <40 | .. | 2310 | 2310 | 2308 | 2305 | 2291 | 2261 | 2079 | 1782 |
| TBA 40–99 | .. | 1412 | 1412 | 1411 | 1410 | 1398 | 1368 | 1226 | 1013 |
| TBA ≥100 | .. | 524 | 523 | 521 | 515 | 507 | 480 | 378 | 268 |

**Ovadia et *al.* 2019**

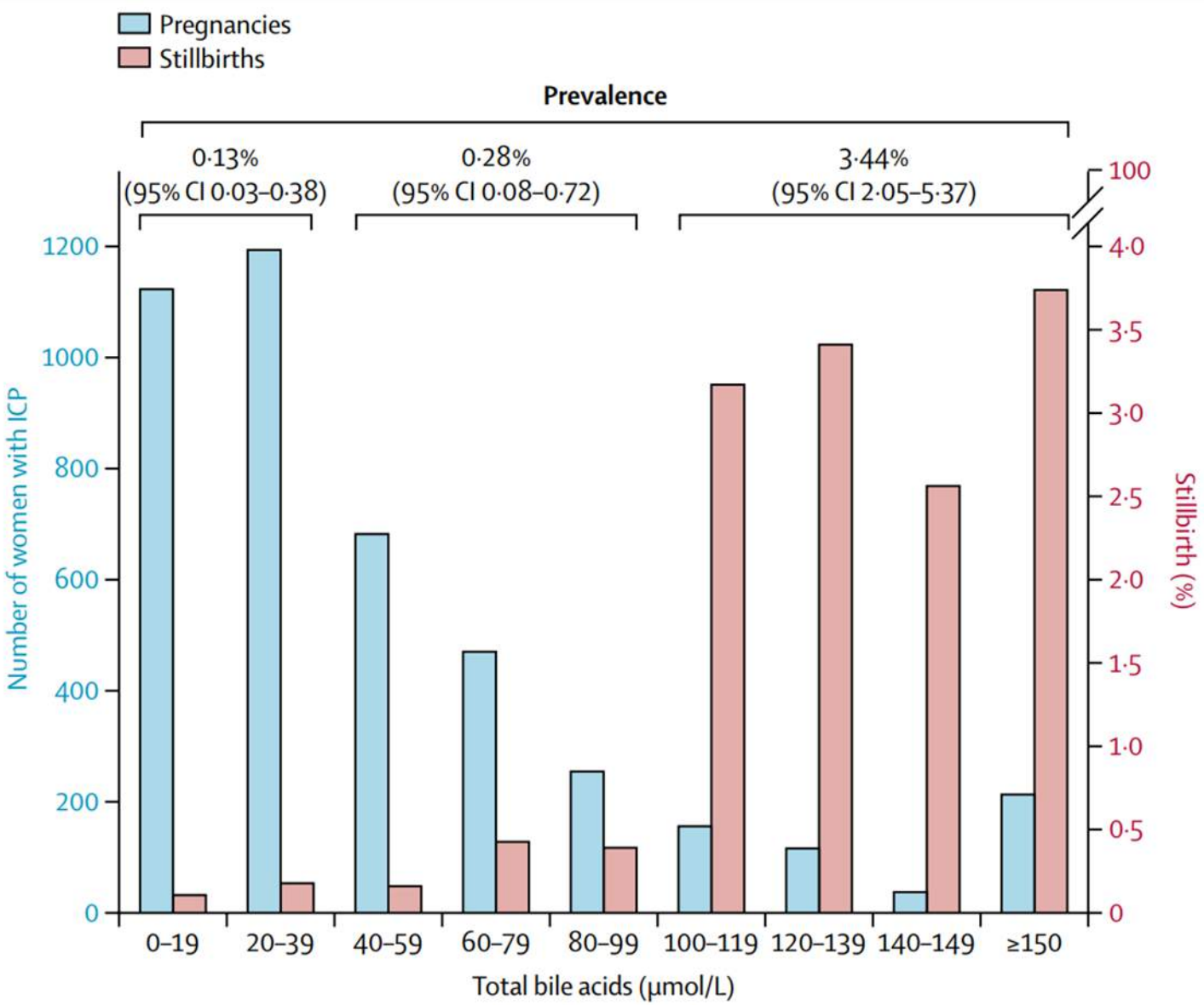
# Morbidité périnatale corrélée à la prématurité



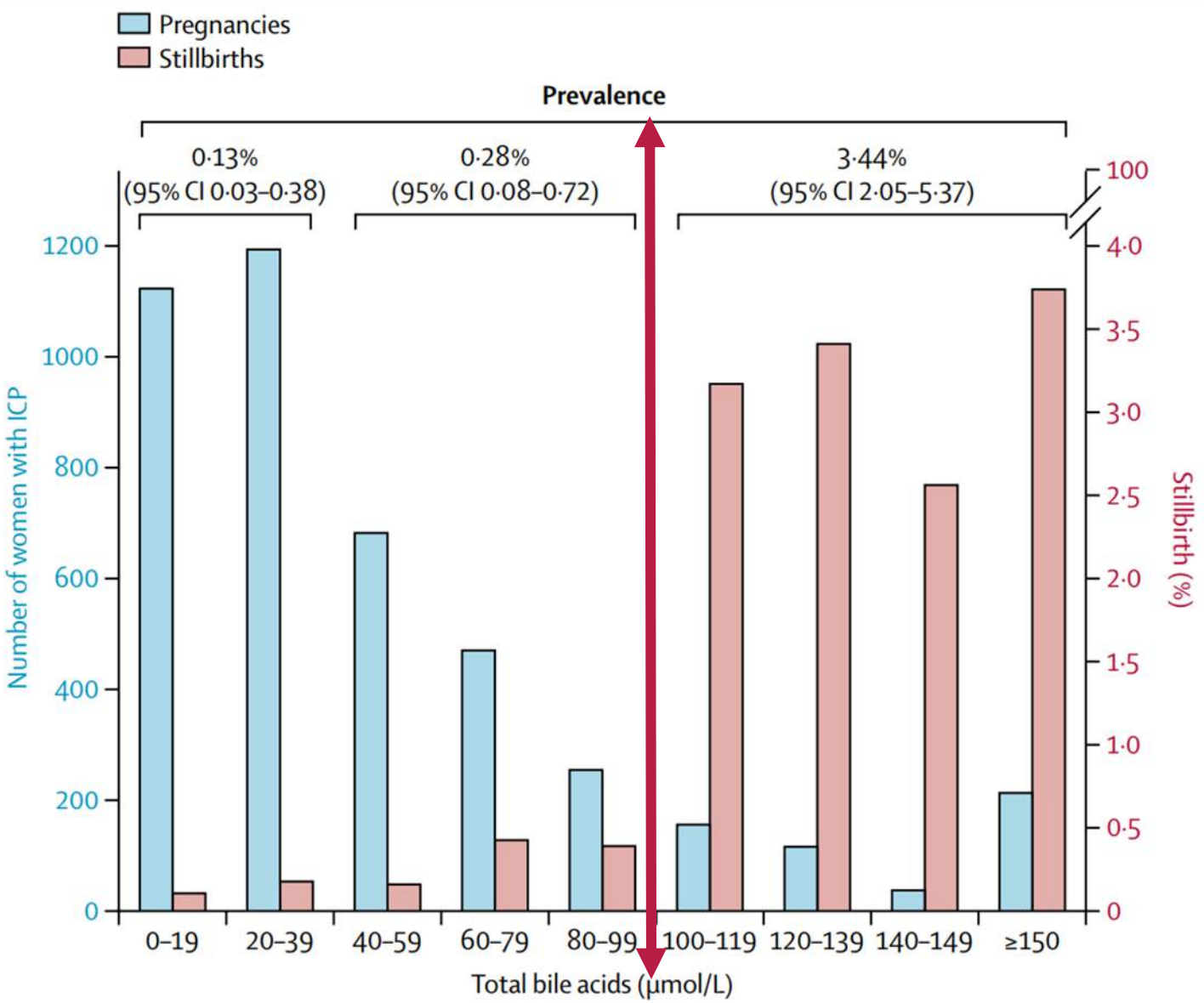

réseau sécurité naissance NAÎTRE ENSEMBLE

26e Journées Scientifiques

# Ovadia et *al.* 2019

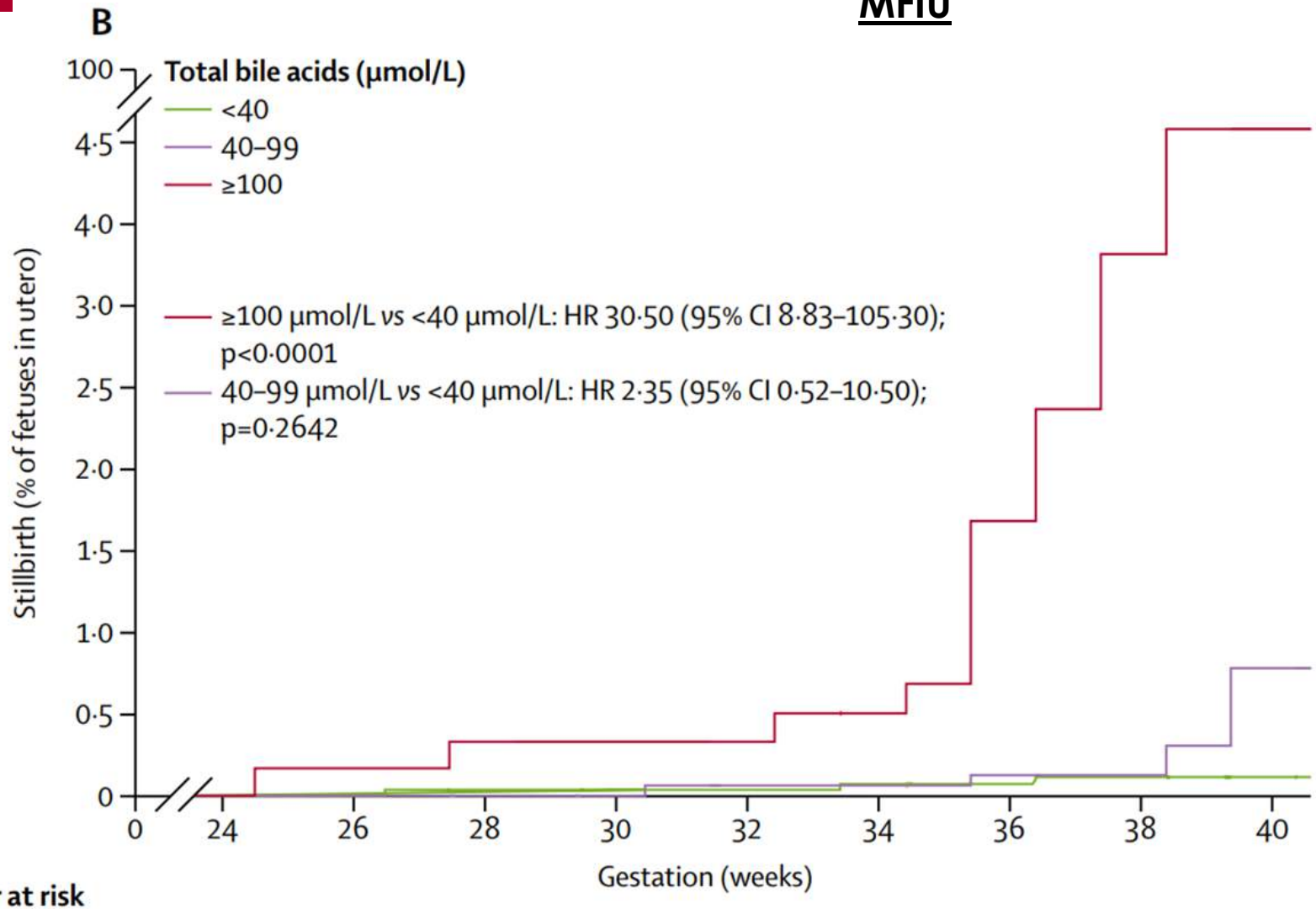


# Ovadia et *al.* 2019



**Ovadia et *al.* 2019**

**MFIU**

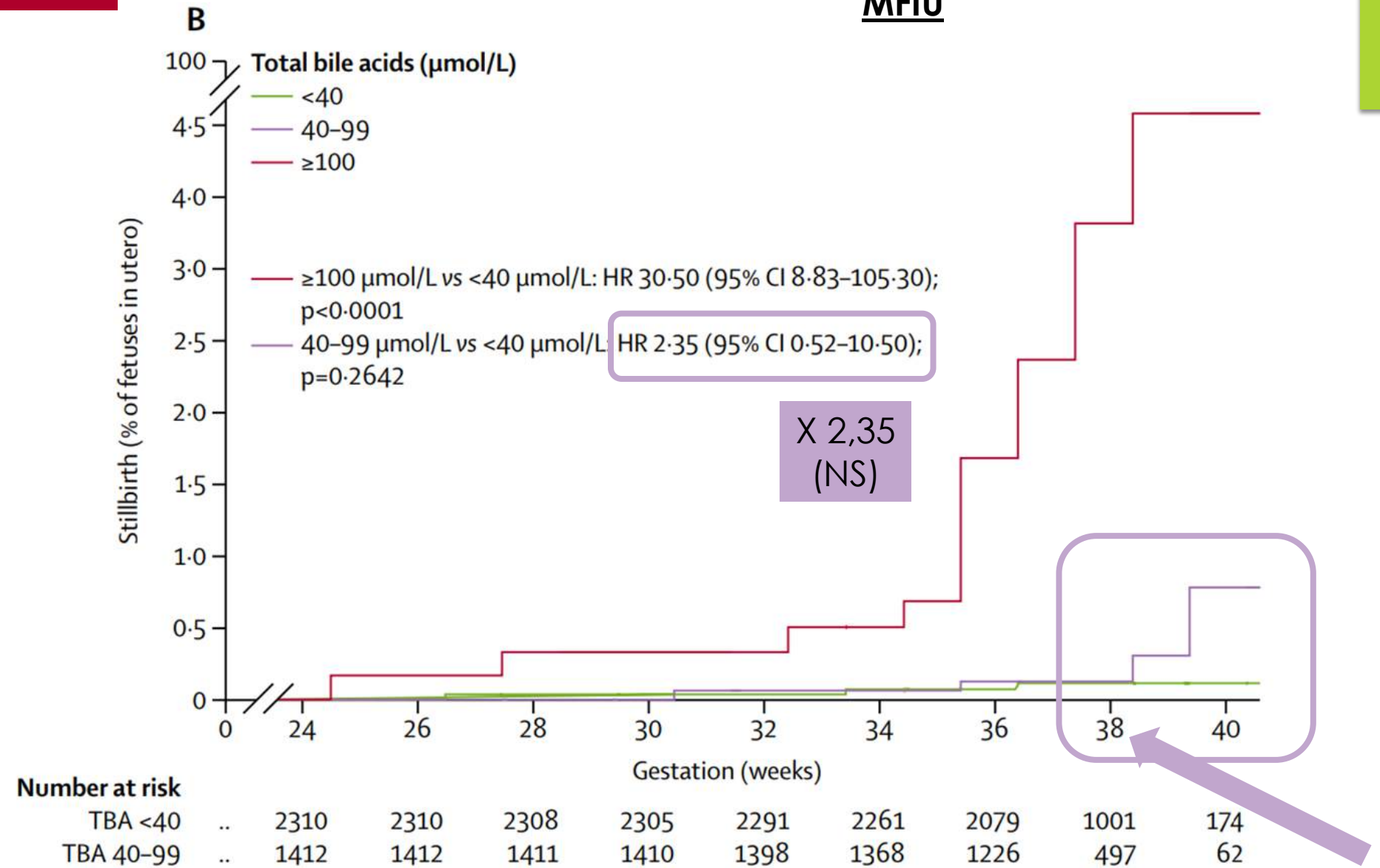



**Number at risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TBA <40 | .. | 2310 | 2310 | 2308 | 2305 | 2291 | 2261 | 2079 | 1001 | 174 |
| TBA 40–99 | .. | 1412 | 1412 | 1411 | 1410 | 1398 | 1368 | 1226 | 497 | 62 |
| TBA ≥100 | .. | 524 | 523 | 521 | 515 | 507 | 480 | 378 | 110 | 13 |

**Ovadia et *al.* 2019**

**MFIU**



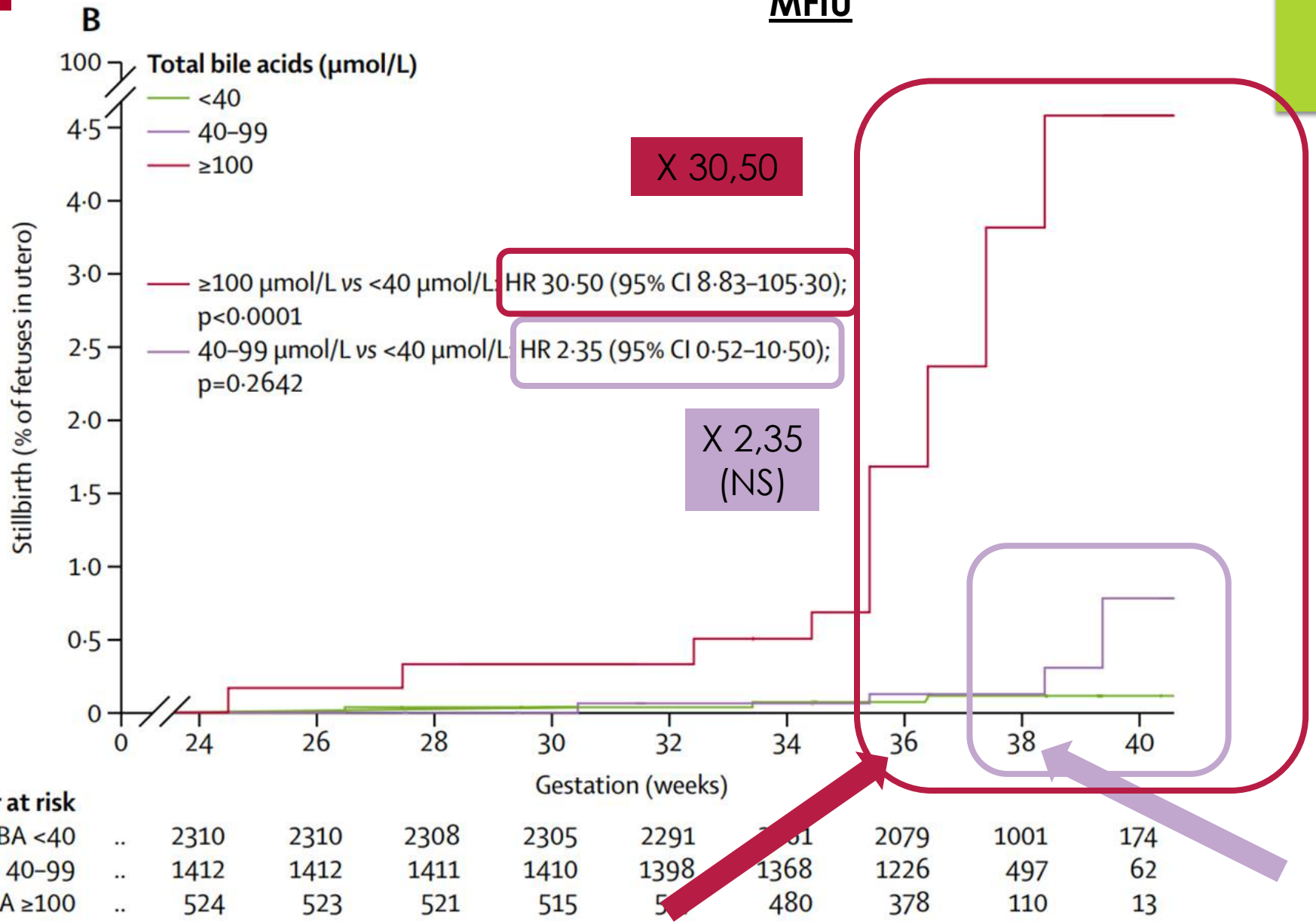

X 2,35 (NS)

**Number at risk**

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| TBA <40 | .. | 2310 | 2310 | 2308 | 2305 | 2291 | 2261 | 2079 | 1001 | 174 |
| TBA 40–99 | .. | 1412 | 1412 | 1411 | 1410 | 1398 | 1368 | 1226 | 497 | 62 |
| TBA ≥100 | .. | 524 | 523 | 521 | 515 | 507 | 480 | 378 | 110 | 13 |

# Ovadia et *al.* 2019

**MFIU**




réseau sécurité naissance NAÎTRE ENSEMBLE

26e Journées Scientifiques

# Terme de naissance

**Chez les femmes présentant une cholestase gravidique, il est recommandé d'induire la naissance en cas de concentration d'acides biliaires ≥ 100 µmol/L à partir de 36 SA pour réduire la morbidité périnatale, en particulier la MFIU.**

RECOMMANDATION FORTE – QUALITÉ DE LA PREUVE BASSE

# Terme de naissance

**Chez les femmes présentant une cholestase gravidique, il est recommandé d'induire la naissance en cas de concentration d'acides biliaires ≥ 100 µmol/L à partir de 36 SA pour réduire la morbidité périnatale, en particulier la MFIU.**

**En cas de concentration d'acides biliaires < 100 µmol/L, il est recommandé d'informer de la possibilité d'induire la naissance entre $37^{+0}$-$39^{+6}$ SA pour réduire la morbidité périnatale.**

RECOMMANDATION FORTE – QUALITÉ DE LA PREUVE BASSE

# Contraception

# Contraception après cholestase gravidique

**Chez les femmes ayant présenté une cholestase gravidique, il est recommandé de contrôler la normalisation du bilan hépatique après l'accouchement avant de prescrire une contraception oestroprogestative idéalement faiblement dosée en oestrogènes (risque de récidive du prurit et de la cytolyse).**

**Un dosage des transaminases sous contraception oestroprogestative pourra être réalisé.**

RECOMMANDATION FAIBLE – QUALITÉ DE LA PREUVE TRES BASSE

**Tableau 1**
Synthèse de la définition et des recommandations pour la prise en charge des femmes présentant une cholestase gravidique.

**Définition**

- Survenue d'un prurit évocateur (palmoplantaire, nocturne)
- Associé à une anomalie biologique : élévation des acides biliaires > 10 µmol/L ou augmentation des ALAT supérieur à 2N
- Après élimination d'autres orientations étiologiques à l'examen clinique (interrogatoire et examen physique)
- En l'absence de symptômes évocateurs d'un diagnostic différentiel, il est proposé de ne pas réaliser de bilan complémentaire biologique ou échographique

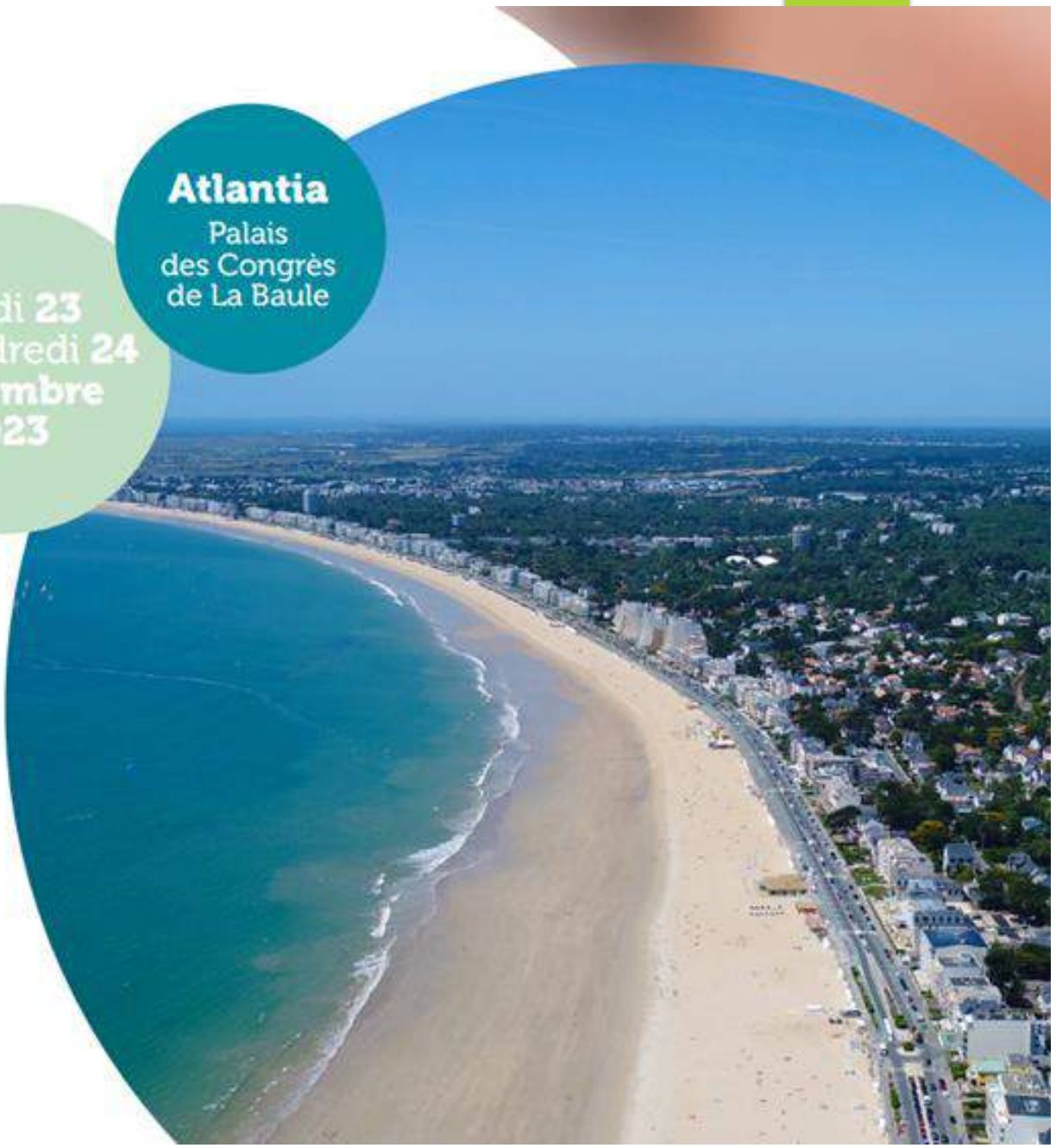
| Recommandation | Grade de la recommandation |
|---|---|
| Il est recommandé d'administrer de l'acide ursodésoxycholique afin de réduire l'intensité du prurit maternel, d'améliorer le bilan biologique (acides biliaires totaux et ALAT) et réduire la prématurité totale | **Recommandation forte**<br>**Qualité de la preuve modérée** |
| Il est recommandé de ne pas administrer de la S-adénosyl-L-méthionine, de la cholestyramine, de la dexaméthasone, de la gomme de guar ou du charbon activé dans le but de réduire l'intensité du prurit maternel | **Recommandation forte**<br>**Qualité de la preuve basse** |
| Les données de la littérature sont insuffisantes en nombre et en qualité pour émettre une recommandation quant à l'administration d'antihistaminiques pour réduire l'intensité du prurit maternel | **Absence de recommandation**<br>**Qualité de la preuve basse** |
| Il est recommandé de ne pas administrer de rifampicine pour réduire le prurit maternel et la morbidité périnatale | **Recommandation faible**<br>**Qualité de la preuve très basse** |
| Il est recommandé de ne pas avoir recours à des échanges plasmatiques chez les femmes ayant une cholestase gravidique pour réduire le prurit maternel ou la morbidité périnatale. | **Recommandation forte**<br>**Qualité de preuve très basse** |
| Une surveillance biologique des acides biliaires et des ALAT est recommandée pour réduire la morbi-mortalité périnatale, sans qu'une fréquence puisse être déterminée | **Recommandation faible**<br>**Qualité de la preuve basse** |
| Les données sont insuffisantes pour émettre une recommandation quant à l'intérêt d'une surveillance par rythme cardiaque fœtal ou par échographie obstétricale pour réduire la morbidité périnatale | **Absence de recommandation** |
| L'induction de la naissance est recommandée en cas de concentration d'acides biliaires ≥ 100 µmol/L à partir de 36 SA pour réduire la morbidité périnatale, en particulier la MFIU. En cas de concentration d'acides biliaires < 100 µmol/L, il est recommandé d'informer de la possibilité d'induire la naissance entre $37^{+0}$ et $39^{+6}$ SA pour réduire la morbidité périnatale | **Recommandation forte**<br>**Qualité de la preuve basse** |
| La normalisation du bilan hépatique après l'accouchement doit être contrôlée avant de prescrire une contraception œstroprogestative idéalement faiblement dosée en œstrogènes. Un dosage des ALAT sous contraception œstroprogestative pourra être réalisé | **Recommandation faible**<br>**Qualité de la preuve très basse** |

réseau sécurité naissance
NAÎTRE ENSEMBLE

# Merci

Jeudi **23**
et vendredi **24**
**novembre**
**2023**

**Atlantia**
Palais
des Congrès
de La Baule



# 26e Journées Scientifiques