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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Ovadia C, Sajous J, Seed PT, et al. Ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: a systematic review and individual participant data meta-analysis. *Lancet Gastroenterol Hepatol* 2021; published online April 26. https://doi.org/10.1016/S2468-1253(21)00074-1.

Appendix

Modifications to PROSPERO incorporated into the Data Analysis Plan

The Data Analysis Plan was written following completion of the systematic review, based upon the numbers of participants anticipated to be eligible for analysis and an informal summary of data points available from early study responders, but prior to data review or analysis.

1. Addition of the composite outcome of stillbirth and preterm birth as a secondary outcome. During data collection, it became apparent that sufficient data on stillbirth would not be available to provide power to determine whether UDCA had an effect on its rate. We therefore added analysis of preterm birth (including overall and spontaneous preterm birth, with rates <37/40 gestation and <34/40 gestation) to include a new composite (stillbirth and overall preterm birth).
2. Maternal pre-eclampsia and gestational diabetes mellitus. Meta-regression by diagnostic criteria. Information on the diagnostic criteria for both conditions were rarely reported in eligible studies, therefore meta-regression by diagnostic criteria was not attempted.
3. Subgroup analysis of the composite and main secondary outcomes was planned by important confounders (baseline bile acid concentration, gestation of disease onset, and UDCA dose).
4. Additional secondary outcomes were included, such as labour onset, post-partum haemorrhage rate and perinatal death. Results for unassisted vaginal birth were presented instead of caesarean section rate and large for gestational age/ small for gestational age rates rather than birthweight centile as we believed that these were more clinically-relevant outcomes.

Data Analysis Plan

The impact of ursodeoxycholic acid on perinatal outcomes in cholestatic pregnancies – an Individual Participant Data Meta-analysis

Study name

Individual participant data meta-analysis to determine the effects of ursodeoxycholic acid treatment for intrahepatic cholestasis of pregnancy

Study registration (Prospero)

PROSPERO 2019 CRD42019131495
https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=131495

Funders

NIHR Senior Investigator Award

Sign off

Professor Catherine Williamson Date 10/3/2020

Contents

Abbreviations:

ICP	intrahepatic cholestasis of pregnancy (obstetric cholestasis)
IPD	individual participant data
TBA	total bile acids
UDCA	ursodeoxycholic acid
NNU	neonatal unit
MSAF	meconium-stained amniotic fluid
SVD	spontaneous (unassisted) vaginal delivery
AVD	assisted vaginal delivery
ELCS	elective caesarean section
EMCS	emergency caesarean section
SGA	small for gestational age
LGA	large for gestational age
PPH	postpartum haemorrhage
PP	postpartum

Definitions:
Intrahepatic cholestasis of pregnancy (ICP): defined according to local diagnostic criteria.

Severe intrahepatic cholestasis of pregnancy: Bile acid concentration ≥40μmol/L in pregnancy with associated pruritus, with all signs and symptoms resolving postnatally.

Small for gestational age (SGA): birthweight ≤10^{th} centile.

Large for gestational age (LGA): birthweight ≥90^{th} centile.

Postpartum haemorrhage (PPH): post-delivery maternal blood loss >500ml.

Gestational diabetes mellitus (GDM): diagnosed according to local diagnostic criteria.

Version history
First draft (rough notes written by CO) 7 Feb 2020

Version 0·1 (7 Feb 2020) Written by PTS in collaboration with CO, using the first draft as a guideline

Version 0·2 (26 Feb 2020) Minor amendments by CW

Version 0·3 (26 Feb 2020) Extended and clarified by PTS, CO & JS

Sections and tables given consistent numbering, secondary analysis of primary outcome clarified, time to SPTB added, references added. Extension & clarification of bile acid data to be collected.

Version 0·4 (5 March 2020) Further work by PTS, CO & CW

New section 6 added on management of women with ICP. New subgroup analysis by total exposure.

Version 0·5 (9 March 2020) Changes approved by JS, current study progress updated. Author list and proof-reading completed by CO

Version 1·0 (10 March 2020) Version sign-off by CW

Version 1·1 (5 October 2020) Formatting for publication by CO

1. Hypothesis, Aims and objectives

Hypothesis

That UDCA treatment in severe intrahepatic cholestasis of pregnancy is associated with reduced rates of adverse fetal outcomes.

Aims

To improve the management of women with severe and non-severe ICP by a better understanding of the effects of UDCA on maternal and neonatal outcomes. Our main interest is in stillbirth, but, as this is rare, we will also investigate a composite outcome that is more likely to be adequately powered.

Objectives

Primary objective: To determine whether women with ICP taking UDCA have lower rates of stillbirth than untreated women with ICP.

Secondary objectives:

1. To determine whether women with ICP taking UDCA have lower rates of preterm birth (iatrogenic and spontaneous), meconium-stained amniotic fluid, neonatal unit admission, low Apgar score, low umbilical artery pH, birthweight centile and perinatal death.
2. To determine whether women with ICP taking UDCA have lower rates of a composite adverse perinatal outcome (stillbirth and preterm birth) than untreated women with ICP.
3. To determine whether women treated with UDCA have altered rates of adverse maternal outcomes (pre-eclampsia, gestational diabetes mellitus, postpartum haemorrhage).

2. Inclusion and exclusion criteria

Study inclusion criteria

- Prospective case-control studies, prospective cohort studies, retrospective cohort studies, population-based studies, and randomised controlled trials that reported bile acid levels and neonatal outcomes were included. Personal communication of unpublished cohorts
- ICP diagnosis based upon pruritus and elevated serum bile acid levels
- Reporting of bile acid concentrations, UDCA usage and perinatal outcomes
- Ethical approval to share the data

Study exclusion criteria

- Case reports, studies not comprising cohorts or successive cases seen in a unit
- <30 study participants
- Diagnosis of ICP not using serum bile acid levels
- Studies that did not report the serum bile acid level or any perinatal outcomes

Participant inclusion criteria

- Women with ICP diagnosed by pruritus in pregnancy and raised serum bile acids, not attributed to an alternative underlying cause of liver pathology
- Study participants with data recorded for ***either*** peak TBA pre-treatment/pre-randomisation/at diagnosis and peak TBA post-treatment/post placebo, ***or*** peak TBA during pregnancy if pre-treatment is not available or treatment not administered
- Study participant with one or more of the following antenatal predictors and perinatal details recorded: parity; number of fetuses; UDCA treatment; live birth/stillbirth; gestation at delivery; neonatal death; meconium presence/absence

Participant exclusion criteria

- Studies investigating only mild disease (bile acids <40μmol/L)

3. Data to be collected

Study-level data

Numbers of treated and untreated, ICP diagnostic criteria, country, outcomes, study quality, dates.

Essential information needed from all studies

Maternal demographic and antenatal predictors:

- Parity
- Number of fetuses
- UDCA treatment (yes/no)
- *Either*:
    - Peak TBA pre-treatment/pre-randomisation/at diagnosis
    - Peak TBA post-treatment/post placebo/post diagnosis
- *Or*:
    - Peak TBA during pregnancy if pre-treatment is not available

Neonatal and perinatal details (Where relevant, information collected for each neonate):

- Gestation at delivery, stillbirth

Additional information to be collected where available

Maternal demographic and antenatal predictors:

- Age, BMI, gestation at ICP diagnosis, pre-eclampsia, gestational diabetes, pre-existing diabetes, other liver conditions, chronic hypertension, metformin treatment, insulin treatment
- UDCA treatment (timing and dosage), cholestyramine treatment, rifampicin treatment, S-adenosyl methionine treatment, vitamin K treatment
- Maximum total bile acids after treatment with UDCA/placebo/other disease modifying drugs

Neonatal and perinatal details (Where relevant, information collected for each neonate):

- Mode of delivery, induction of labour status, blood loss, birthweight, birthweight centile, sex, umbilical cord artery pH, Apgar at 5 minutes, meconium-stained amniotic fluid, neonatal unit admission, neonatal death
- Preterm birth before 37 weeks, operative delivery, blood loss ≥ 500 mL, SGA (< 10^{th} Intergrow birthweight centile), umbilical artery pH < 7, Apgar ≤ 7 (5 minutes, meconium-stained amniotic fluid, neonatal unit admission, neonatal death

4. Analysis and presentation of results

The meta-analysis of results will investigate three things: the size and direction of effect, consistency between studies, strength of evidence. We are most interested in whether the efficacy of UDCA varies with bile acid levels pre-treatment in 3 groups: <40 µmol/L, 40-99 µmol/L, 100+ µmol/L.

Because we have individual participant data, we are not restricted to standard meta-analysis techniques, but can use multi-level modelling, with participants nested within studies, and (for multiple pregnancy) infants within mothers (Rabe-Hesketh & Skrondal, 2012)[1]. Our main results will be for all studies together, with adjustment for possible confounding by parity and number of fetuses.

Sensitivity analyses (if there are sufficient data) will

1. Consider RCTs separately
2. Exclude low-quality studies (as defined by NHLBI study scoring system, 2020)[2]
3. Adjust for maximum bile acids pre-treatment/diagnosis (where available)
4. Adjust for maximum bile acid measurement

Data analysis will be in the statistical package Stata version 16·0 or later (StataCorp, College Station, Texas).

Data search procedure and results
Standard PRISMA flow diagram with numbers of studies and participants included and excluded with reasons

5. Primary outcome
Stillbirth rates by UDCA (any vs none). The analysis will be adjusted for bile acid level at diagnosis, prior to the start of UDCA, parity and number of fetuses.

Odds ratios are calculated using multilevel models, with fetus, mother and study considered as separate levels. The analysis will be adjusted for bile acid level at diagnosis, prior to the start of UDCA, parity, and number of fetuses.

The composite outcome is defined as any of stillbirth, iatrogenic or spontaneous preterm birth. It is recorded once for each fetus.

Secondary analyses of primary outcome:
(1) By study quality
Look at randomised studies only; check for heterogeneity between studies.

(2) By bile acid level at diagnosis (>100, over 100)
A subgroup analysis to work out the treatment effect in each subgroup. We will carry out an interaction test for moderation of effect.

(3) By gestation at diagnosis (<32weeks vs 32+)
A subgroup analysis to work out the treatment effect in each subgroup. We will carry out an interaction test for moderation of effect. Other groupings may be considered depending on the data.

(4) By maximum prescribed UDCA dosing
A dose-response analysis. This will include tests for differences in effect between the two dosage groups. Other groupings may be considered depending on the data.

The main comparison will be between <1 g vs ≥1 g maximum dose/day. Other major doses will be considered depending on the data.

(5) By total exposure to UDCA (in women whose pregnancy continued for at least 1 week after start of UDCA)
This analysis is designed to show the cumulative effect of UDCA treatment. There are technical problems: UDCA treatment duration and total exposure are closely linked to length of pregnancy and hence to stillbirth and exact UDCA treatment schedule is not generally collected. To some extent they are addressed by limiting the analysis to women who were on UDCA long enough for there to be an effect. Groups will be defined when the data is available.

Odds ratios are calculated using multilevel models, with fetus, mother and study considered as separate levels. Adjustment is made for bile acid level at diagnosis, parity and number of fetuses.

The composite outcome is defined as any of stillbirth, iatrogenic or spontaneous preterm birth.

6. Management of women with ICP
This analysis will attempt to identify the level of TBA corresponding to an unacceptable risk separately according to UDCA treatment; as in our previous paper (Ovadia 2019).[3] UDCA groups may be changed depending on numbers available.

Risk of stillbirth by maximum level of TBA (separately for women ever or never prescribed UDCA during the pregnancy) and ROC curves of UDCA as a predictor of stillbirth will be presented.

7. Maternal (safety) outcomes

Maternal outcomes: onset of labour as spontaneous, induced, or elective caesarean; mode of delivery as spontaneous vaginal, assisted vaginal, elective caesarean, emergency caesarean; pre-eclampsia; gestational diabetes mellitus; postpartum haemorrhage; postpartum blood loss.

Pruritus specifically not included, as no standardisable scale exists.

Odds ratios are calculated using multilevel models, with fetus, mother and study considered as separate levels. Adjustment is made for parity and number of fetuses.

Stillborn babies are not included in onset of labour or mode of delivery analyses.

8. Secondary outcomes

To be analysed according the same methods as the primary outcome

Composite outcome (stillbirth and preterm birth)

All components of composite (including data from studies without the full composite outcome)

Spontaneous Preterm delivery

This will be based on multilevel parametric survival analysis of all women using time from diagnosis to spontaneous preterm delivery, with censoring of non-cases at 37 weeks, or (for iatrogenic delivery) at delivery. As with the QUiPP app (Watson 2017),[4] we will develop a suitable parametric model, using Akaike and Bayesian Information Criteria (AIC & BIC) to determine the best model. Predictors to be considered will include study (random effect), UDCA (yes/no), bile acid level at diagnosis, parity, and gestation at diagnosis.

Other individual outcomes

Secondary outcomes to analyse: NNU admission; MSAF; umbilical arterial pH <7·0; Apgar <7 at 5 minutes of life; neonatal death; perinatal death; SGA; LGA.

9. Additional analyses

S1 Sensitivity analysis 1: excluding unpublished data

Restricted to primary outcome, composite and most important safety features: pre-eclampsia, GDM

S2 Sensitivity analysis 2: per-protocol analysis excluding women on treatments other than UDCA

Exclude women prescribed rifampicin, cholestyramine, S-adenosyl methionine (SAMe); data on dexamethasone prescription not available.

Other possible subgroup analyses (depending on availability of data):

S3 Include as a confounder the background stillbirth rate for each country of study, maternal age, BMI

S4 Subgroup of women with pre-pregnancy liver conditions

S5 Subgroup of women with other pre-pregnancy conditions

For example, diabetes Type 1 or 2, CHT, CKD

S6 Subgroup of women with other pregnancy-induced conditions

For example, gestational diabetes, preeclampsia. Ideally, pre-diagnosis only, but we probably will not know when they were diagnosed

Deviations from the Data Analysis Plan

1. Use of multilevel modelling. Particularly for perinatal outcomes, multilevel modelling failed to converge. We therefore used logistic regression with Huber-White correction for clustering by mother/fetus, and study level as a fixed effect in the majority of analyses (method used indicated in the relevant table footnote).
2. Analysis for singleton pregnancies only. *Post hoc*, we elected to further investigate the main study outcomes for singleton pregnancies only, results for which are presented in the supplementary material.
3. Section 4. Sensitivity analysis excluding low quality studies. We did not specifically perform this sensitivity analysis as considerations to study quality were included within the analysis: using IPD enabled us to adjust for the main confounders, and the analysis of aggregate data from RCTs was divided by masking, and the comparator treatment used, as a reflection of study quality; heterogeneity between studies was studied. The effect of adjustment on primary outcomes for the observational cohorts was so marked that we elected to limit the subanalyses by major disease factors (bile acids/ gestation of disease onset / UDCA dosing) to the RCTs only.
4. Section 5. Analysis by total exposure to UDCA – as anticipated in the Data Analysis Plan, availability of this was limited, therefore this analysis was not performed.
5. Section 6. Given that previous studies demonstrated the association between bile acid concentrations and stillbirth occurred for women with singleton pregnancies, we elected, *post hoc*, to perform this analysis restricted to singleton pregnancies.
6. Section 7. Maternal outcomes. Rates of gestational diabetes mellitus (GDM) were collected and analysed, however the gestation of onset of GDM occurred prior to the onset of ICP for the majority of women. Assuming that the majority of women were diagnosed with GDM at around 28/40, from the whole cohort there were only 44 women diagnosed with ICP before this gestation and then GDM, of whom 39/251 (15·5%) were taking UDCA and 5/20 (25%) not taking UDCA. We felt these numbers were not sufficient to reliably perform this comparison. Similarly, there was not enough data on rates of pre-eclampsia from participants within RCTs to perform a reliable comparison of the effect of UDCA.
7. Section 8. Secondary outcomes – Spontaneous preterm birth. Given the proportion of iatrogenic preterm births within the cohort, we elected to perform this analysis with different methodology, presenting hazard ratios of preterm birth by disease category according to baseline bile acid concentration. Additionally, rates of neonatal death reported were too low to be reliable in analysis, thus results for this comparison are not presented.
8. Section 9. Sensitivity analyses. Due to very small numbers of affected women, sensitivity analyses are not presented for the exclusion of unpublished cohorts, women given additional disease-modifying treatments and pre-pregnancy conditions. As numbers of stillbirths were relatively low and confidence intervals wide, analysis by background stillbirth rates of the countries was not performed.

Table S1. Search terms used for identification of relevant literature

Search terms
cholestasis, intrahepatic, of pregnancy; pregnancy-related cholestasis; recurrent intrahepatic cholestasis of pregnancy; obstetric cholestasis; cholestasis, intrahepatic of pregnancy; cholestasis, pregnancy-related; familial intrahepatic cholestasis of pregnancy; intrahepatic cholestasis of pregnancy
pregnancy outcome; fetal outcome; fetal distress; obstetric labour complication*; obstetric labor complication*; pregnancy, high*risk; delivery, obstetric; labour, obstetric; labor, obstetric; live birth; obstetric labour, premature; obstetric labor, premature; premature birth; cesarean section; caesarean section; abortion, spontaneous; stillbirth; fetal death; infant mortality; maternal mortality; perinatal mortality; gestational age; infant, low birth weight; Apgar score; pregnancy outcome*; pregnancy complication; obstetric outcome*; obstetric complication*; normal birth*; live birth*; premature birth*; preterm birth*; preterm deliver*; born preterm; cesarean*; c-section; LSCS; caesarean*; miscarriage*; stillbirth*; intrauterine death*; neonatal death*; postpartum haemorrhage*; postpartum hemorrhage*; postpartum complication*; special care baby unit admission*; SCBU admission*; neonatal intensive care unit admission*; NICU admission*; neonatal unit*; NNU admission*; small for gestational age; SGA; intra-uterine growth restriction; IUGR; Apgar; foetal distress; foetal outcome; foetal death; pregnancy loss; fetal demise; foetal demise

Table S2. Inclusion and exclusion criteria for selection of studies

Inclusion criteria	Prospective case-control studies, prospective cohort studies, retrospective cohort studies, population-based studies and randomised controlled trials. ICP was defined as pruritus in pregnancy with elevated serum bile acid concentration, with or without elevated aminotransferase concentration. Severe ICP was diagnosed as above, but with bile acid concentration ≥40 μmol at any point in pregnancy. Where possible, participants were also offered an abdominal ultrasound scan to exclude the presence of gallstones, sludge, or other hepatic pathologies, and serum screening to confirm postpartum resolution. The minimum study sample size was 30 participants. Publications had to report at least one of stillbirth, preterm birth, neonatal unit admission, meconium-stained amniotic fluid, or neonatal death.
Exclusion criteria	Studies with fewer than 30 participants, case reports, studies without cohorts or successive cases seen in a unit, or studies with a high risk of bias were excluded. Studies with no cases of severe disease (bile acids ≥ 40μmol/L) were excluded. Systematic reviews, meta-analyses and non-clinical studies were excluded although reference lists were checked for studies suitable for inclusion

Table S3. Data requested from authors

Maternal details	Parity, number of fetuses, gestation of delivery, induction of delivery, mode of delivery, estimated blood loss
ICP details	Gestation of diagnosis, bile acids at baseline, gestation of baseline, peak bile acids post baseline, gestation of peak bile acids post baseline
UDCA treatment	Gestation of commencement, treatment duration, maximum dose, maximum frequency
Other ICP treatments	SAMe, rifampicin, cholestyramine, vitamin K – use and gestations of use
Other conditions	Liver conditions, chronic hypertension, pre-eclampsia, pre-existing diabetes mellitus, gestational diabetes mellitus, metformin treatment, insulin treatment
Neonatal details	Birthweight, sex, abnormal cardiotocography, umbilical arterial pH, Apgar score at 5 minutes, meconium-staining of the amniotic fluid, neonatal unit admission, stillbirth, neonatal death

Table S4. Description of studies used for individual participant data meta-analysis

Author and year	Country	Data collection period	Number of participants (UDCA / no UDCA)	Design	ICP definition	Bile acid measurement	Data quality[2]	Major predictors	Outcome measures
Alessandrelli et al., 2009[5]	Italy	2001-2007	84/70	Retrospective cohort	Pruritus, ↑TBA	Fasting	9	Pruritus severity, TBA, individual BA	Apgar score, IUFD, PTB
Bacq et al., 2017[6]	France	1999-2013	98/0	Retrospective cohort	Gestational pruritus, ↑TBA or ALT on two occasions, no other liver disorder, or dermatoses of pregnancy	Fasting	11	Pruritus severity, TBA, ALT, AST, bilirubin, GGT, ALP, ABCB4 mutations, PT	GA delivery, IOL, MOD
Batsry et al., 2019[7]	Israel	2011-2016	159/83	Retrospective cohort	Pruritus, ↑TBA and/or ↑ALT or AST, absence of other diseases that may cause similar symptoms and laboratory abnormalities	Fasting	11	TBA, AST, ALT	Apgar score, BW, GA delivery, GDM, IOL, ICH, LGA, MOD, MSAF, NNU, PET, PND, RDS, SGA, UC arterial pH
Broom and Kane, 2016[8]	Australia	2012-2014	116/39	Retrospective cohort	Pruritus, ↑TBA and/or ↑ALT or AST with no other cause	Fasting and non-fasting	8	TBA	GA delivery, IOL, MSAF, NRHRM, PPH
Brouwers et al., 2015[9]	Netherlands	2005-2012	151/63	Retrospective cohort	Gestational pruritus, ↑TBA	Non-fasting	12	TBA, ALT, AST, bilirubin, GGT, ALP, LDH	Apgar score, BW, EBL, GA delivery, IOL, MOD, MSAF, NNU, PND, SGA
Brun-Furrer et al., 2016[10]	Switzerland	2004-2014	345/0	Retrospective case-control	Database coding, no other liver dysfunction	Non-fasting	11	TBA	Apgar score, BW, EBL, GA delivery, Hb, IOL, IUFD, MOD, MSAF, NNU, PND, UC arterial pH
Casagrandi et al., 2017[11]	UK	2015-2016	56/27	Retrospective cohort	↑TBA	Non-fasting	9	TBA	IOL, MOD, MSAF, NNU
Castaño et al., 2006[12]	Argentina	2004-2005	42/0	Prospective case-control	Pruritus, ↑TBA, and ↑ALT/AST after 20/40, no other autoimmune disease, moderate-severe alcohol intake, HIV infection, Hepatitis A, B, or C infection, skin disease, or biliary obstruction, post-partum normalisation	Fasting	8	Pruritus severity, TBA, individual BA, ALT, AST, bilirubin, GGT, ALP	Apgar score, BW, GA delivery, IOL, MOD, MSAF, PND, SGA
Chappell et al., 2012[13]	UK	2008-2011	56/55	Randomised controlled trial	Gestational pruritus, ↑TBA or ALT, no other cause of pruritus or liver dysfunction (except concurrent hepatitis C or cholelithiasis)	Non-fasting	12	Pruritus severity, TBA, ALT, AST, bilirubin, GGT	Apgar score, BW, EBL, GA delivery, IOL, MOD, NNU, UC arterial pH
Chappell et al., 2019[14]	UK	2015-2018	305/300	Randomised controlled trial	Pruritus of no other cause, ↑TBA	Non-fasting	13	Pruritus severity, TBA, ALT, AST, bilirubin, GGT	Apgar score, BW, EBL, GA delivery, GDM, IOL, MOD, MSAF, NNU, PND, PTB, UC arterial pH

Author and year	Country	Data collection period	Number of participants (UDCA / no UDCA)	Design	ICP definition	Bile acid measurement	Data quality[2]	Major predictors	Outcome measures
Cui et al., 2018[15]	China	2012-2015	37/0	Prospective case-control	As per RCOG Guideline 2nd edition: i.e. gestational pruritus, ↑TBA and/or ↑ALT/AST, postpartum resolution, no other cause of itching or liver dysfunction	Fasting	10	TBA, individual BA, ALT, AST, bilirubin, GGT, ALP	BW, EBL, GA delivery, MOD, MSAF, PROM
Estiú et al., 2017[16]	Argentina	2009-2013	298/84	Prospective cohort	Pruritus, ↑TBA, no other cause for pruritus or hepatic disease	Fasting	12	TBA	Apgar score, GA delivery, IUFD, MSAF, NNU, PND, SGA, UC arterial pH
Gardiner et al., 2019[17]	Australia	2014-2016	192/158	Retrospective cohort	Pruritus with no other explanation, ↑TBA or ALT/AST,	Fasting	8	TBA, ALT, AST, bilirubin	GA delivery, IUFD, MOD, NNU
Geenes et al., 2014[18]	UK	2010-2011	510/192	Prospective population cohort	Pruritus without a rash, severe ICP: TBA≥ 40μmol/L	Non-fasting	11	TBA, ALT, AST, bilirubin, GGT	Apgar score, BW, GA delivery, IUFD, MOD, MSAF, NNU
Grymowicz et al., 2016[19]	Poland	2005-2006	129/28	Prospective case-control	Pruritus onset after 20/40, ↑TBA or ALT/AST, no other cause of pruritus, liver disease, or dermatological disease	Fasting	10	Pruritus severity, TBA, ALT, AST, bilirubin	GA delivery, MOD, UC arterial pH, Apgar score, MSAF, BW, NNU, ICH, RDS, IUFD
Günaydin et al., 2017[20]	Turkey	2015	27/11	Retrospective cohort	ICD codes, ↑TBA	Fasting	9	↑TBA, ALT, AST, bilirubin, GGT, LDH, coagulation profile	MOD, GA delivery, IUFD, BW, Apgar score
Juusela et al., 2019[21]	USA	2013-2017	49/18	Retrospective cohort	↑TBA, no other cause for liver disease	Fasting and non-fasting	10	TBA, AST	IUFD, MSAF NND, NNU, SPTB
Kebapcilar et al., 2010[22]	Turkey	2008-2009	40/0	Prospective case-control	Pruritus onset after 20/40, ↑TBA, no other liver disease or skin disease	Fasting	9	TBA, ALT, AST, ALP, lipid, and coagulation profiles	GA delivery, Apgar score
Kenyon et al., 2001[23]	UK	1999-2001	29/44	Prospective cohort	Pruritus, ↑TBA or ↑ALT/AST/GGT, no other liver disease, postnatal resolution	Non-fasting	9	Pruritus	MOD, APH, PPH, BW, NNU, IOL, IUFD, PND
Kohari et al., 2017[24]	USA	2005-2014	355/516	Retrospective cohort	Pruritus, ↑TBA	Non-fasting	9	TBA, ALT, AST	MSAF, IUFD, SGA, MOD, GA delivery, BW, Apgar score, UC arterial pH, NNU, RDS
Kondrackiene et al., 2005[25]	Lithuania	1999-2002	33/27	Randomised controlled trial	Pruritus starting in the 2nd/3rd trimesters, ↑ TBA, ALT, and/or AST in the absence of chronic liver disease, hepatic viral infections, skin disease, allergic disease, and symptomatic cholelithiasis	Fasting	9	Pruritus severity, TBA, and individual BA, ALT, AST	GA delivery, Apgar score, MOD, BW, IUFD
Lee et al., 2007[26]	USA	2000-2007	37/80	Retrospective cohort	ICP notes coding, pruritus, ↑TBA, no rash	Non-fasting	12	TBA, ALT, AST, bilirubin	MSAF, NRHRM, PPH, NNU, IUFD

Author and year	Country	Data collection period	Number of participants (UDCA / no UDCA)	Design	ICP definition	Bile acid measurement	Data quality[2]	Major predictors	Outcome measures
Liu et al., 2016[27]	China	2006-2014	113/16	Retrospective population cohort	Pruritus, ↑TBA	Fasting	9	TBA	MSAF, GA delivery, PET, GDM, IOL, Apgar score, NND, BW, LGA, SGA, RDS, NNU, IUFD
Madazli et al., 2015[28]	Turkey	2003-2013	89/0	Retrospective cohort	Pruritus, ↑TBA in the absence of any other liver or skin pathology	Fasting	12	TBA, ALT, AST, bilirubin, ALP	Apgar score, NRHRM, BW, GA delivery, MSAF, RDS, MOD, IUFD, NND, SGA
Majewska et al., 2019[29]	Poland	2015-2017	57/0	Retrospective cohort	Pruritus, ↑TBA, ↑LFTs	Fasting	9	TBA, ALT, AST, bilirubin	GA delivery, MOD, BW, SGA, LGA, Apgar score
Marathe et al., 2017[30]	Australia	2001-2010	210/149	Retrospective cohort	Pruritus, ↑TBA	Non-fasting	11	TBA	GDM, PET, GA delivery, Apgar score, UC arterial pH, BW, MSAF, RDS, NNU
Öztekin et al., 2009[31]	Turkey	2004-2008	187/0	Retrospective cohort	Pruritus, ↑TBA in the absence of other liver diseases, skin diseases, allergic disorders, symptomatic cholelithiasis, and ongoing viral infections affecting the liver	Fasting	8	TBA, ALT, AST, ALP, HDL, LDL, total cholesterol, triacylglycerol	Apgar score, GA delivery, IUFD, NND
Roncaglia et al., 2004[32]	Italy	1996-2001	24/22	Randomised controlled trial	Pruritus starting in the 2nd/3rd trimester in the absence of other pruritic medical conditions, ↑TBA, ALT and/or AST	Fasting	11	TBA, ALT, AST, bilirubin	MSAF, SGA, GA delivery, NNU, RDS, EBL, MOD, Apgar score, BW, UC arterial pH
Rook et al., 2012[33]	USA	2005-2009	29/71	Retrospective cohort	ICD9 coding, pruritus, onset in 2nd /3rd trimesters, no other cause for pruritus, chronic liver disease, acute fatty liver of pregnancy, or HELLP syndrome	Non-fasting	9	TBA, individual BA, ALT, AST, bilirubin, ALP, alb	MOD, IOL, GA delivery, BW, Apgar score, RDS, MSAF, NRHRM
Shan et al., 2016[34]	China	2013-2015	310/12	Retrospective cohort	ICD 10 coding, pruritus, ↑TBA, ALT, AST, no other cause of liver dysfunction, pruritus, gallstones, cholecystitis, or cirrhosis	Fasting	12	TBA, ALT, AST, LDH	PPH, MOD, MSAF, IUFD, GA delivery, BW, Apgar score, NNU, RDS, SGA
Turro et al., 2020[35]	Australia, Argentina, Sweden, UK	2012-2017	217/36	Retrospective cohort	Gestational pruritus, ↑TBA, no other cause for pruritus or hepatic dysfunction	Non-fasting	n/a*	Pruritus severity, TBA, ALT, AST, bilirubin	Apgar score, BW, EBL, GA delivery, GDM, IOL, IUFD, MOD, MSAF, NND, NNU, NRHRM, PTB, SPTB, UC arterial pH
Wong et al., 2009[36]	Ireland	2004-2006	87/63	Retrospective case-control	Pruritus, ↑TBA ± LFTs, no other cause for raised TBA	Fasting	9	TBA	MOD, IOL, Apgar score, NNU, NRHRM, PPH, BW, GA delivery

Author and year	Country	Data collection period	Number of participants (UDCA / no UDCA)	Design	ICP definition	Bile acid measurement	Data quality[2]	Major predictors	Outcome measures
Unpublished cohorts at the time of analysis									
Indraccolo et al.	Italy	2016-2019	73/12	Retrospective cohort	Pruritus, ↑TBA, no other liver disease	Fasting	n/a	TBA	Apgar score, BW, EBL, GA delivery, IOL, IPTB, MOD, MSAF, NND, NNU, NRHRM, IUFD, SPTB, UC arterial pH
Williamson et al.	UK	2001-2019	182/72	Prospective cohort	Gestational pruritus, ↑TBA, no other cause for pruritus or hepatic dysfunction	Non-fasting	n/a	Pruritus severity, TBA, ALT, AST, bilirubin	Apgar score, BW, EBL, GA delivery, GDM, IOL, IUFD, MOD, MSAF, NND, NNU, NRHRM, PTB, SPTB, UC arterial pH

*Manuscript published after data inclusion, description in manuscript insufficient for quality assessment according to NHLBI cohort tool. Only women with ICP were included where case-control studies included women with uncomplicated pregnancies as the comparator group. alb: albumin, ALP: alkaline phosphatase, ALT: alanine aminotransferase, APH: antepartum haemorrhage, AST: aspartate aminotransferase, BW: birthweight, EBL: estimated blood loss, GA delivery: gestational age of delivery, GDM: gestational diabetes mellitus, GGT: Gamma-glutamyl transferase, Hb: haemoglobin, ICD: International Classification of Disease, ICH: intra-cerebral haemorrhage, IOL: induction of labour, IPTB: iatrogenic preterm birth, IUFD: intrauterine fetal death, LDH: lactate dehydrogenase, LFTs: liver function tests, LGA: large for gestational age, MOD: mode of delivery, MSAF: meconium-staining of the amniotic fluid, n/a: not applicable, NND: neonatal death, NNU: neonatal unit admission, NRHRM: non-reassuring heart rate monitoring, PET: pre-eclampsia, PPH: post-partum haemorrhage, PTB: preterm birth, RDS: respiratory distress syndrome, SGA: small for gestational age, SPTB: spontaneous preterm birth, TBA: serum total bile acids, UC: umbilical cord

Table S5. Studies selected but not included in the individual participant data meta-analysis

Authors	Date	Country	Number of participants with ICP	Study type	Reason not included
Aksan Desteli et al.[37]	2016	Turkey	113	Retrospective case-control	No reply
Al-Obaidly et al.[38]	2019	Qatar	163*	Population-based cohort	No reply
Al Shobaili et al.[39]	2011	Saudi Arabia	76	Prospective cohort	No reply
Alsulyman et al.[40]	1996	USA	79	Retrospective cohort	No reply
Binder et al.[41]	2006	Czech Republic	78	Randomised controlled trial	Data not available
Bolukbas el al.[42]	2017	Turkey	59	Retrospective cohort	No reply
Carballu-Núñez et al.[43]	2015	Spain	71	Retrospective cohort	No reply
Çelik et al.[44]	2019	Turkey	370	Retrospective cohort	No reply
Chen et al.[45]	2013	China	106	Retrospective cohort	No reply
Demir et al.[46]	2014	Turkey	61	Retrospective cohort	No reply
Erkenekli et al.[47]	2015	Turkey	103	Retrospective cohort	No reply
Feng et al.[48]	2018	China	142	Retrospective cohort	No reply
Frezza et al. [49]	1990	Italy	30	Randomised controlled trial	No reply
Friberg et al.[50]	2016	Denmark	113	Retrospective cohort	Data not available
Garcia-Flores et al.[51]	2015	Spain	47	Prospective cohort	No reply
Ge et al.[52]	2016	China	196	Prospective cohort	No reply
Glantz et al.[53]	2005	Sweden	130	Randomised controlled trial	Data not available
Heinonen et al.[54]	1999	Finland	91	Prospective cohort	Data not available
Herrera et al.[55]	2018	USA	487	Retrospective cohort	No reply
Jain et al.[56]	2013	India	69	Randomised controlled trial	No bile acid measurements
Jin et al.[57]	2015	China	371	Retrospective cohort	No reply
Joutsiniemi et al.[58]	2015	Finland	103	Retrospective cohort	No reply
Kawakita et al.[59]	2015	USA	233	Retrospective cohort	No reply
Koroglu et al.[60]	2017	Turkey	40	Prospective case-control	No reply
Kowalska-Kańka et al.[61]	2013	Poland	41	Prospective case-control	No reply
Labbe et al.[62]	2018	France	138	Retrospective cohort	No reply
Li et al.[63]	2017	China	313	Retrospective cohort	No reply
Lin et al.[64]	2017	China	407	Retrospective cohort	No reply
Liu et al.[65]	2006	China	68	Randomised controlled trial	No reply
Lu et al.[66]	2014	China	88	Retrospective cohort	No reply
Mahey et al.[67]	2009	India	50*	Prospective case-control	No reply
Oztas et al.[68]	2015	Turkey	117	Prospective case-control	No reply
Nicastri et al.[69]	1998	Italy	32	Randomised controlled trial	No reply
Pata et al.[70]	2011	Turkey	32	Retrospective cohort	No reply
Proehl et al.[71]	2017	USA	4329*	Retrospective cohort	No reply
Raddatz et al.[72]	2019	Germany	97*	Retrospective cohort	No reply
Reyihanguli et al.[73]	2017	China	207	Prospective cohort	No contact details
Riikonen et al.[74]	2000	Finland	48	Randomised controlled trial	Data not available
Rioseco et al.[75]	1994	Chile, USA	320	Retrospective case-control	No contact details
Sargin Oruç et al.[76]	2014	Turkey	57	Prospective case-control	No reply
Singla et al.[77]	2016	India	50	Prospective case-control	No reply
Temel Yuksel et al.[78]	2019	Turkey	40	Prospective case-control	No reply
Turkmen et al.[79]	2016	Turkey	37	Retrospective case-control	No reply
Vural Yilmaz et al.[80]	2017	Turkey	90	Prospective case-control	No reply
Yayla Abide et al.[81]	2017	Turkey	84	Retrospective case-control	No reply
Zapata et al.[82]	2005	Chile	48	Retrospective cohort	No reply
Zecca et al.[83]	2006	Italy	77	Retrospective cohort	Data not available
Zhang et al.[84]	2010	China	120	Retrospective case-control	No reply
Zhang et al.[85]	2014	China	40	Retrospective cohort	No reply
Zhang et al.[86]	2015	China	120	Randomised controlled trial	No reply
Zhou et al.[87]	2014	China	30	Prospective case-control	No reply

*denotes conference abstracts, all other studies were published full manuscripts

Table S6. Characteristics of women providing individual participant data, from all studies (Group A)

	UDCA n (%) (Total = 4726)	**No UDCA n (%) (Total = 2248)**
Baseline bile acid concentration (μmol/L)	*N=3377*	*N=522*
<20·0	978 (29·0)	216 (41·4)
20·0-39·9	925 (27·4)	172 (33·0)
40·0-59·9	578 (17·1)	58 (11·1)
60·0-79·9	345 (10·2)	28 (5·4)
80·0-99·9	183 (5·4)	14 (2·7)
100·0-119·9	117 (3·5)	12 (2·3)
≥120	251 (7·4)	22 (4·2)
Peak bile acid concentration (μmol/L)	*N=4576*	*N=2103*
<20·0	1148 (25·1)	690 (32·8)
20·0-39·9	1251 (27·3)	558 (26·5)
40·0-59·9	781 (17·1)	352 (16·7)
60·0-79·9	480 (10·5)	216 (10·3)
80·0-99·9	286 (6·3)	96 (4·6)
100·0-119·9	167 (3·6)	57 (2·7)
≥120	463 (10·1)	134 (6·4)
Nulliparity	*N=4609*	*N=2161*
	1565 (34·0)	879 (40·7)
Multifetal pregnancy	*N=4722*	*N=2246*
	795 (16·8)	152 (6·8)

UDCA: ursodeoxycholic acid

Table S7. Early preterm birth rate according to ursodeoxycholic acid treatment using individual participant data, from all studies (Groups A, B, E, F – Appendix p26)

Outcome	All studies IPD			Randomised Controlled Trials IPD		
	UDCA n/N (%)	No UDCA n/N (%)	aOR (95% CI, p value)	UDCA (n/N) (%)	No UDCA (n/N) (%)	aOR (95% CI, p value)
All pregnancies						
Preterm birth <34 weeks' gestation	436/5287 (8·2)	77/2208 (3·5)	0·89 (0·51-1·55, p=0·68)	10/438 (2·3)	24/428 (5·6)	0·41 (0·16-1·06, p=0·066)
Spontaneous preterm birth <34 weeks' gestation	182/4871 (3·7)	39/2175 (1·8)	0·83 (0·42-1·67, p=0·61)	7/438 (1·6)	18/428 (4·2)	0·40 (0·13-1·22, p=0·11)
Iatrogenic preterm birth <34 weeks' gestation	165/4871 (3·4)	34/2175 (1·6)	0·57 (0·17-1·90, p=0·36)	3/438 (0·7)	6/428 (1·4)	0·49 (0·09-2·74, p=0·42)
Singleton pregnancies						
Preterm birth <34 weeks' gestation	196/3855 (5·1)	41/1952 (2·1)	0·44 (0·18-1·06, p=0·068)	6/387 (1·6)	10/366 (2·7)	0·55 (0·20-1·54, p=0·25)
Spontaneous preterm birth <34 weeks' gestation	65/3701 (1·8)	22/1932 (1·1)	0·69 (0·23-2·11, p=0·52)	5/387 (1·3)	6/366 (1·6)	0·75 (0·23-2·51, p=0·65)
Iatrogenic preterm birth <34 weeks' gestation	85/3702 (2·3)	15/1932 (0·8)	0·27 (0·06-1·23, p=0·090)	1/387 (0·3)	4/366 (1·1)	0·24 (0·03-2·19, p=0·21)

Odds ratios were calculated by logistic regression with Huber-White correction for clustering by fetus where multifetal pregnancies were included, with study level as a fixed effect. Adjustments were performed for bile acid concentration at baseline, parity, and number of fetuses. IPD: individual participant data, UDCA: ursodeoxycholic acid, n/N: number affected/total number, aOR: adjusted odds ratio, CI: confidence interval

Table S8. Perinatal and maternal outcomes according to ursodeoxycholic acid treatment, using individual participant data, excluding single-arm studies (Groups C, D – Appendix p26)

	Singleton and multifetal pregnancies			Singleton pregnancies		
Outcome	**UDCA n/N (%)**	**No UDCA n/N (%)**	**aOR (95% CI, p value)**	**UDCA n/N (%)**	**No UDCA n/N (%)**	**aOR (95% CI, p value)**
Stillbirth	33/4122 (0·8)	12/2038 (0·6)	1·09 (0·51 to 2·33, p=0·82)	19/2832 (0·7)	11/1801 (0·6)	0·71 (0·10 to 4·99, p=0·73)
Composite outcome	2126/4336 (49·0)	514/2213 (23·2)	2·23 (1·92 to 2·59, p<0·001)	996/3013 (33·1)	353/1955 (18·1)	0·68 (0·48 to 0·97, p=0·033)
Preterm birth <37 weeks' gestation	2122/4139 (49·1)	508/2208 (23·0)	2·26 (1·94 to 2·63, p<0·001)	992/2997 (33·1)	347/1952 (17·8)	0·69 (0·48 to 0·98, p=0·038)
Spontaneous preterm birth <37 weeks' gestation	615/3984 (15·4)	169/2175 (7·8)	1·35 (1·06 to 1·71, p=0·015)	245/2921 (8·4)	109/1932 (5·6)	0·54 (0·31 to 0·94, p=0·028)
Iatrogenic preterm birth <37 weeks' gestation	1172/3984 (29·4)	306/2175 (14·1)	2·17 (1·82 to 2·59, p<0·001)	671/2921 (23·0)	218/1932 (11·3)	0·88 (0·56 to 1·37, p=0·56)
Pre-eclampsia	203/3153 (6·4)	121/1574 (7·7)	1·14 (0·53 to 2·47, p=0·74)	119/2512 (4·7)	99/1469 (6·7)	0·75 (0·26 to 2·21, p=0·61)
Unassisted vaginal birth	1553/3001 (51·7)	1146/1853 (61·8)	1·08 (0·83 to 1·40, p=0·59)	1495/2478 (60·3)	1121/1740 (64·4)	1·05 (0·80 to 1·39, p=0·71)
Meconium-stained amniotic fluid	612/3941 (15·5)	304/1987 (15·3)	0·98 (0·83 to 1·17, p=0·84)	419/2964 (15·6)	266/1760 (15·1)	0·59 (0·41 to 0·83, p=0·003)
Apgar score <7 at 5 minutes	108/4170 (2·6)	37/2150 (1·7)	1·33 (8857 to 2·00, p=0·17)	69/2878 (2·4)	32/1902 (1·7)	0·81 (0·33 to 1·98, p=0·65)
Umbilical cord arterial pH <7.0	6/1251 (0·5%)	8/871 (0·9)	0·51 (0·14 to 1·91, p=0·32)	3/1024 (0·3%)	8/779 (1·0)	0·37 (0·04 to 3·30, p=0·37)
Large for gestational age	399/3443 (11·6)	220/1432 (15·4)	0·94 (0·78 to 1·14, p=0·52)	371/2301 (16·1)	213/1217 (17·5)	1·55 (1·07 to 2·26, p=0·021)
Small for gestational age	306/3443 (8·9)	83/1432 (5·8)	1·12 (0·83 to 1·52, p=0·47)	95/2301 (4·1)	39/1217 (3·2)	1·33 (0·61 to 2·93, p=0·48)
Neonatal unit admission	1180/4180 (28·2)	457/2081 (22·0)	1·58 (1·35 to 1·84, p<0·001)	645/2887 (22·3)	371/1842 (20·1)	0·72 (0·49 to 1·06, p=0·097)
Perinatal death	33/2999 (1·1)	9/1606 (0·6)	1·44 (0·63 to 3·27, p=0·39)	18/2369 (0·8)	9/1439 (0·6)	0·54 (0·06 to 4·83, p=0·58)

Odds ratios were calculated using logistic regression with Huber-White correction, with study level as a fixed effect, and clustering by fetuses for those in multifetal pregnancies. Adjustments were performed for bile acid concentration at baseline, parity, and number of fetuses. For stillbirth, composite outcome (stillbirth or preterm birth), preterm birth, and perinatal outcomes, analyses were performed by number of fetuses; for maternal outcomes, analyses were performed by number of pregnancies. IPD: individual participant data, RCTs: randomised controlled trials, UDCA: ursodeoxycholic acid, n/N: number affected/total number, aOR: adjusted odds ratio, CI: confidence interval

Table S9. Impact of bile acid concentration at baseline, gestation at diagnosis, and maximum daily ursodeoxycholic acid dose on the composite outcome using individual participant data, from randomised controlled trials (Group E – Appendix p26)

	UDCA n/N (%)	No UDCA n/N (%)	aOR (95% CI, p value)	Interaction test
Bile acids (µmol/L)	**Composite outcome**			
<40	43/323 (13·3)	64/319 (20·1)	0·63 (0·37-1·06, p=0·079)	p=0·74
≥40	32/116 (27·6)	43/110 (39·1)	0·56 (0·29-1·09, p=0·086)	
<100	66/410 (16·1)	98/403 (24·3)	0·58 (0·38-0·90, p=0·014)	p=0·79
≥100	9/29 (31·0)	9/26 (34·6)	0·75 (0·20-2·81, p=0·67)	
Diagnosis gestation (weeks)				
<32	35/117 (29·9)	38/115 (33·0)	0·76 (0·39-1·48, p=0·42)	p=0·38
≥32	26/263 (9·9)	43/250 (17·2)	0·51 (0·28-0·95, p=0·034)	
UDCA daily dosage (g/day)		**Placebo**		
<1	7/56 (12·5)	14/46 (30·4)	0·18 (0·05-0·70, p= 0·013)	p=0·069
≥1	68/383 (17·8)	93/383 (24·3)	0·69 (0·45-1·06, p=0·094)	

Analyses performed using individual participant data from participants of randomised controlled trials. Composite outcome: any one of stillbirth or preterm birth before 37/40, recorded once for each fetus. Odds ratios were calculated using logistic regression with Huber-White correction for clustering by fetus, adjustments were performed for parity and number of fetuses. UDCA: ursodeoxycholic acid, aOR: adjusted odds ratio

Table S10. Impact of bile acid concentration at baseline on perinatal outcomes using individual participant data, from all studies (Group A – Appendix p26)

Outcome	Baseline bile acid concentration (µmol/L) n/N (%)			Comparison <40 vs ≥40 aOR (95% CI, p value)	Comparison <100 vs ≥100 aOR (95% CI, p value)
	<40	40-99	≥100		
Neonatal unit admission	521/2478 (21·0)	312/1266 (24·6)	114/413 (27·6)	1·43 (1·15-1·78, p=0·001)	1·64 (1·23-2·19, p=0·001)
Meconium-stained amniotic fluid	310/2517 (12·3)	223/1278 (17·4)	109/406 (26·8)	1·93 (1·54-2·42, p<0·001)	2·27 (1·69-3·04, p<0·001)
Umbilical cord arterial pH<7·0	4/467 (0·9)	3/398 (0·8)	0/163 (0·0)	1·70 (0·24-12·14, p=0·60)	0·53 (0-3·54, p=0·57)
Apgar score <7 at 5 minutes	79/2581 (3·1)	50/1310 (3·8)	16/396 (4·0)	1·23 (0·81-1·87, p=0·33)	1·60 (0·91-2·83, p=0·11)
Neonatal death	1/1830 (0·1)	3/1117 (0·3)	4/371 (1·1)	10·80 (0·38-306·53, p=0·16)	8·31 (2·13-32·41, p=0·002)
Perinatal death	8/1830 (0·4)	9/1117 (0·8)	13/371 (3·5)	2·78 (0·99-7·82, p=0·053)	5·94 (2·65-13·29, p<0·001)
Small for gestational age					
Singleton	50/1470 (3·4)	35/895 (3·9)	12/332 (3·6)	1·24 (0·75-2·04, p=0·40)	0·90 (0·44-1·81, p=0·76)
Multifetal	159/824 (19·3)	64/351 (18·2)	11/60 (18·3)	0·89 (0·59-1·34, p=0·59)	0·79 (0·37-1·66, p=0·53)
Large for gestational age					
Singleton	233/1470 (15·9)	158/895 (17·7)	36/332 (10·8)	0·87 (0·66-1·13, p=0·30)	0·53 (0·36-0·79, p=0·001)
Multifetal	17/824 (2·1)	7/351 (2·0)	2/60 (3·3)	1·39 (0·50-3·88, p=0·53)	3·55 (0·24-53·23, p=0·36)

Analyses were performed using individual participant data from all studies. Logistic regression was performed with Huber-White correction for clustering, as the multilevel model failed to converge. n/N: number with outcome/total number, aOR: adjusted odds ratio, CI: confidence interval.

Table S11. Maternal outcomes according to ursodeoxycholic acid treatment using individual participant data, from all studies (Groups A, E – Appendix p26)

Outcome	All studies IPD			Randomised controlled trials IPD		
	UDCA n/N (%)	No UDCA n/N (%)	aOR (95% CI, p value)	UDCA n/N (%)	No UDCA n/N (%)	aOR (95% CI, p value)
Birth onset induced	1358/2358 (57·6)	785/1100 (71·4)	1·11 (0·85-1·46, p=0·44)	274/412 (66·5)	253/397 (63·7)	1·12 (0·83-1·51, p=0·48)
Postpartum haemorrhage	714/2456 (29·1)	363/1069 (34·0)	1·06 (0·81-1·39, p=0·67)	135/378 (35·7)	137/370 (37·0)	0·97 (0·71-1·33, p=0·85)
Mode of delivery						
Unassisted vaginal birth	1926/3842 (50·1)	1146/1853 (61·8)	Referent	261/412 (63·3)	253/397 (63·7)	Referent
Assisted vaginal delivery	196/3842 (5·1)	123/1853 (6·6)	0·85 (0·64-1·12, p=0·24)	29/412 (7·0)	40/397 (10·1)	0·68 (0·40-1·14, p=0·14)
Elective caesarean section	805/3842 (21·0)	240/1853 (13·0)	1·18 (0·97-1·44, p=0·092)	77/412 (18·7)	63/397 (15·9)	1·27 (0·87-1·87, p=0·22)
Emergency caesarean section	449/3842 (11·7)	158/1853 (8·5)	0·84 (0·65-1·67, p=0·15)	37/412 (9·0)	37/397 (9·3)	0·97 (0·58-1·61, p=0·90)
Unknown caesarean section	466/3842 (12·1)	186/1853 (10·0)	1·29 (1·02-1·64, p=0·036)	8/412 (1·9)	4/397 (1·0)	2·01 (0·59-6·81, p=0·27)

Adjustments were made for parity, multifetal pregnancy, baseline bile acid concentration, using multilevel modelling to compare with study and mother as separate levels. Women who had a stillbirth were not included in onset of birth or mode of delivery analyses. IPD: individual participant data, UDCA: ursodeoxycholic acid, n/N: number with outcome/total number, aOR: adjusted odds ratio, CI: confidence interval, n/a: not applicable (insufficient numbers reported for analysis).

Table S12. Impact of bile acid concentration at baseline on maternal pregnancy outcomes using individual participant data, from all studies (Group A – Appendix p26)

Outcome	Baseline bile acid concentration (µmol/L) n/N (%)			Comparison <40 vs ≥40 aOR (95% CI, p value)	Comparison <100 vs ≥100 aOR (95% CI, p value)
	<40	40-99	≥100		
Birth onset induced	925/1678 (55·1)	342/598 (57·2)	113/185 (61·1)	0·81 (0·66-1·01, p=0·059)	0·61 (0·43-0·88, p=0·007)*
Unassisted vaginal birth	1038/2117 (49·0)	393/807 (48·7)	131/234 (56·0)	1·07 (0·90-1·28, p=0·45)	1·11 (0·82-1·50, p=0·51)
Caesarean section	958/2117 (45·3)	358/807 (44·4)	85/234 (36·3)	0·93 (0·78-1·12, p=0·45)	0·97 (0·71-1·33, p=0·86)
Pre-eclampsia	94/1661 (5·7)	52/1008 (5·2)	16/324 (4·9)	0·69 (0·45-1·05, p=0·082)	0·83 (0·47-1·48, p=0·53)
Postpartum haemorrhage	536/1512 (35·4)	187/549 (34·1)	54/170 (31·8)	0·81 (0·65-1·01, p=0·057)	0·86 (0·59-1·25, p=0·42)

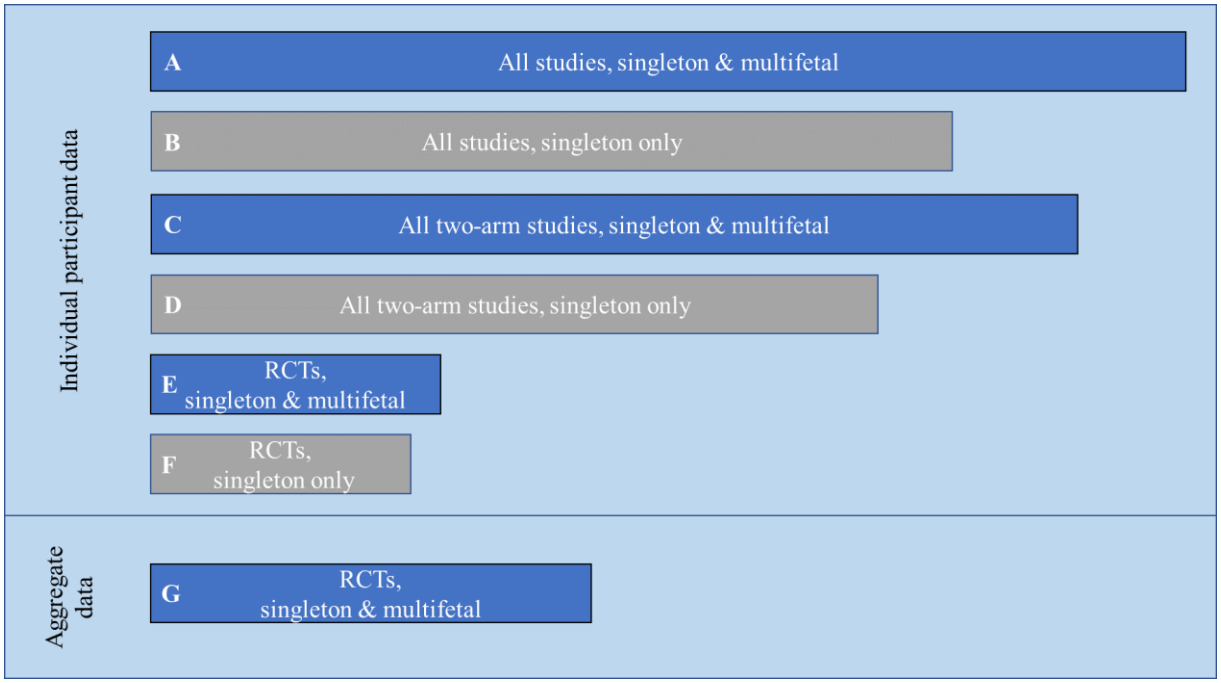
Analyses performed using individual participant data from all studies. Odds ratios are calculated using multilevel models, with mother and study considered as separate levels, including women from all studies. Adjustment is made for parity and number of fetuses. Women who had a stillbirth are not included in onset of birth or mode of delivery analyses. *Adjustment reversed the direction of the association, this was largely due to study effect. n/N: number with outcome/total number, aOR: adjusted odds ratio, CI: confidence interval

Table S13. Randomised controlled trials included in the aggregate data meta-analysis (Group G – Appendix p26)

Name of study	UDCA group	UDCA number	Comparator group	Comparator number	Use of masking	Intervention duration (days)	Included in IPD meta-analysis
Ai et al., 2002[88]	UDCA	15	Dexamethasone / Glucose + vitamin C + inosine + phenobarbital	31	No	14	No
Binder et al., 2006[41]	UDCA / UDCA + SAMe	53	SAMe	25	No	Until birth	No
Chappell et al., 2012[12]	UDCA	56	Placebo	55	Yes	Until birth	Yes
Chappell et al., 2019[13]	UDCA	305	Placebo	300	Yes	Until birth	Yes
Diaferia et al., 1996[89]	UDCA	8	Placebo	8	Yes	20	No
Floreani et al., 1996[90]	UDCA	10	SAMe	10	No	Until birth	No
Glantz et al., 2005[53]	UDCA	47	Placebo / Dexamethasone	83	Yes	21	No
Joutsiniemi et al., 2014[91]	UDCA	10	Placebo	8	Yes	14	No
Kondrackiene et al., 2005[25]	UDCA	42	Cholestyramine	42	No	14	Yes
Liu et al., 2006[65]	UDCA	34	Glucose + vitamin C + inosine	34	No	14	No
Nicastri et al., 1998[69]	UDCA / UDCA + SAMe	16	SAMe / Placebo	16	No	20	No
Palma et al., 1997[92]	UDCA	8	Placebo	7	Yes	21	No
Roncaglia et al., 2004[32]	UDCA	24	SAMe	22	No	Until birth	Yes
Zhang et al., 2015[86]	UDCA / UDCA + SAMe	82	SAMe	38	No	Until birth	No

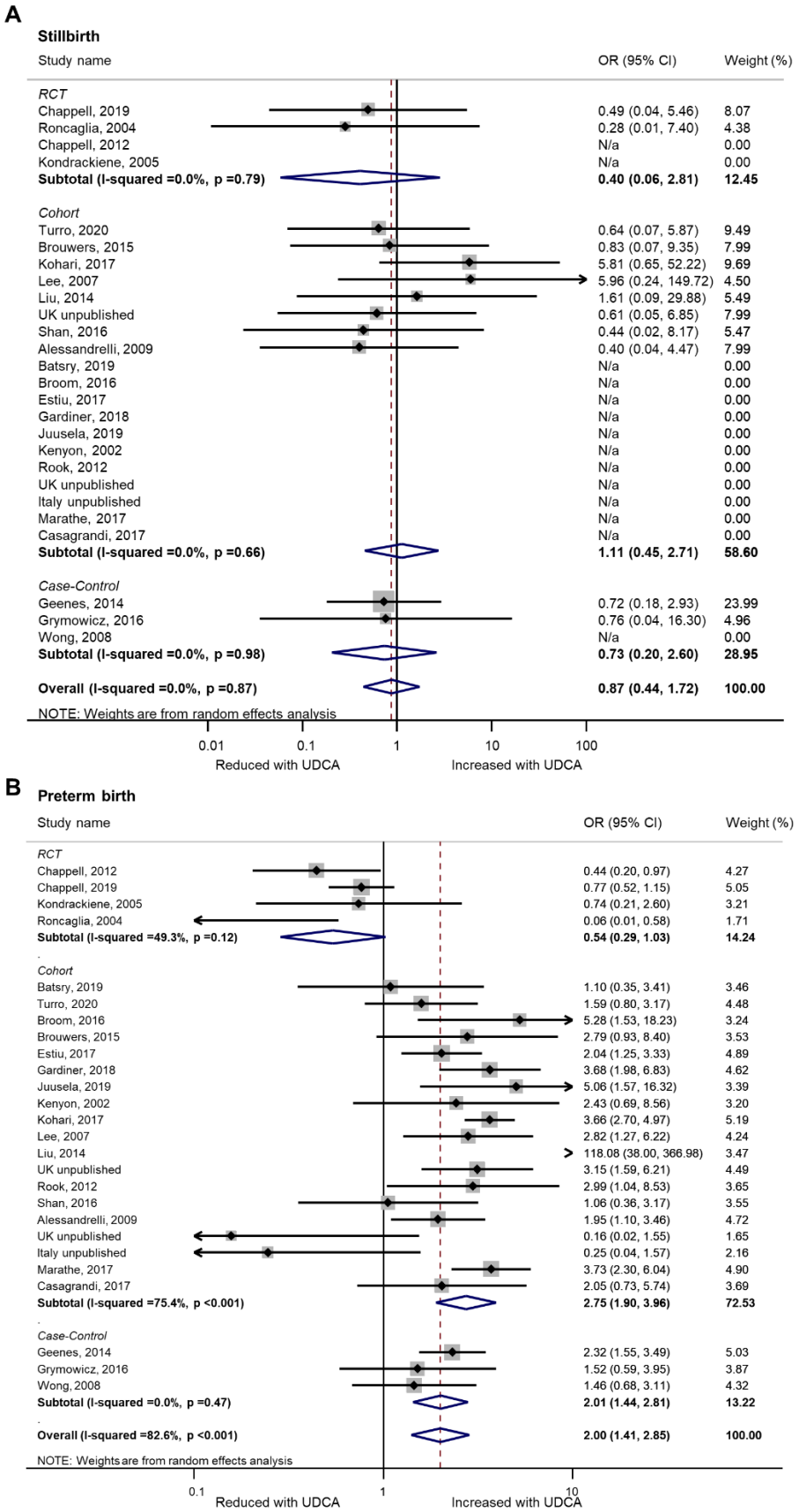
UDCA: ursodeoxycholic acid, IPD: individual participant data, SAMe: S-Adenosylmethionine

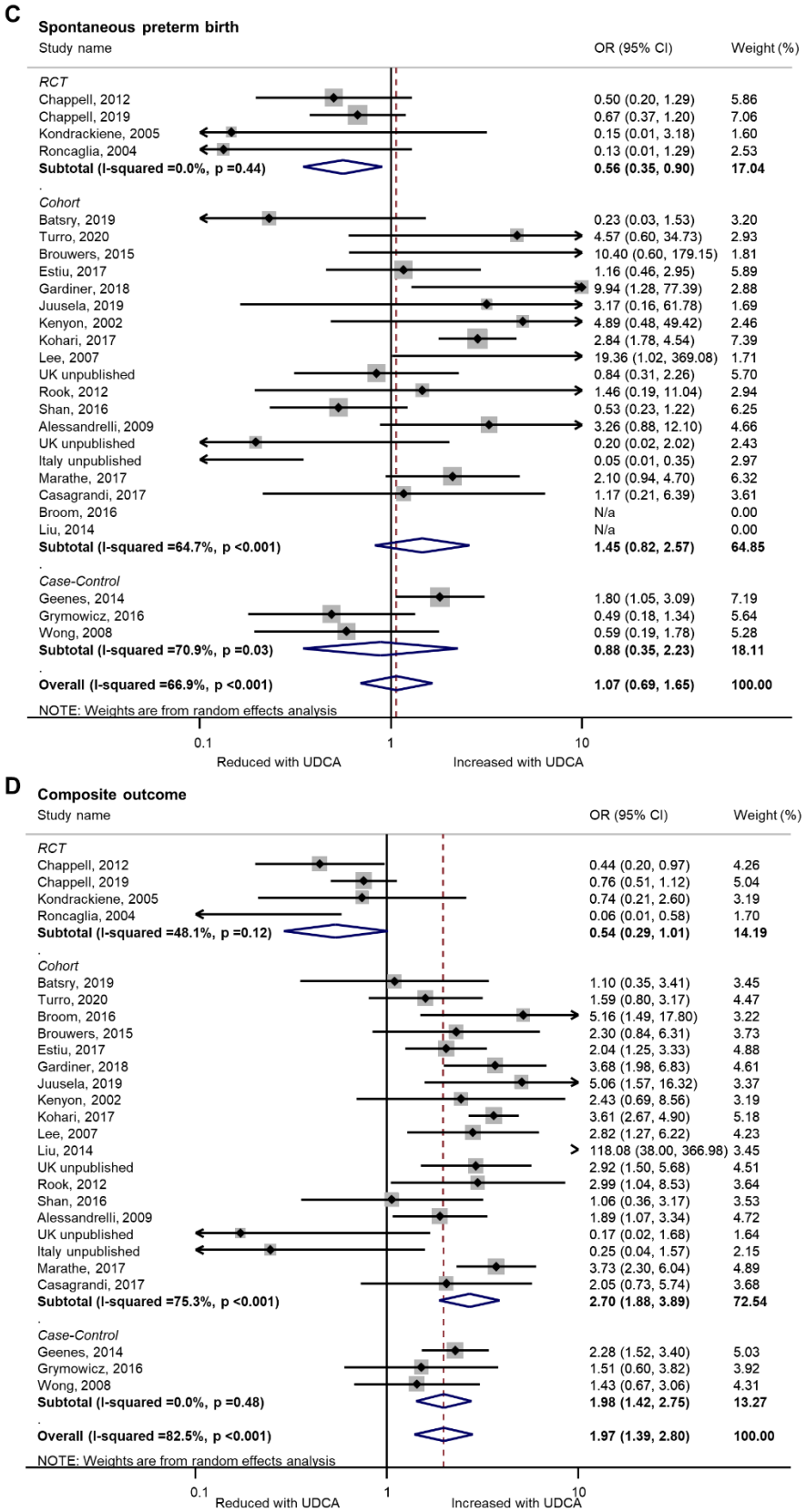
Figure S1. Schematic of dataset subgroups



RCTs: randomised controlled trial. Boxes not drawn to scale.

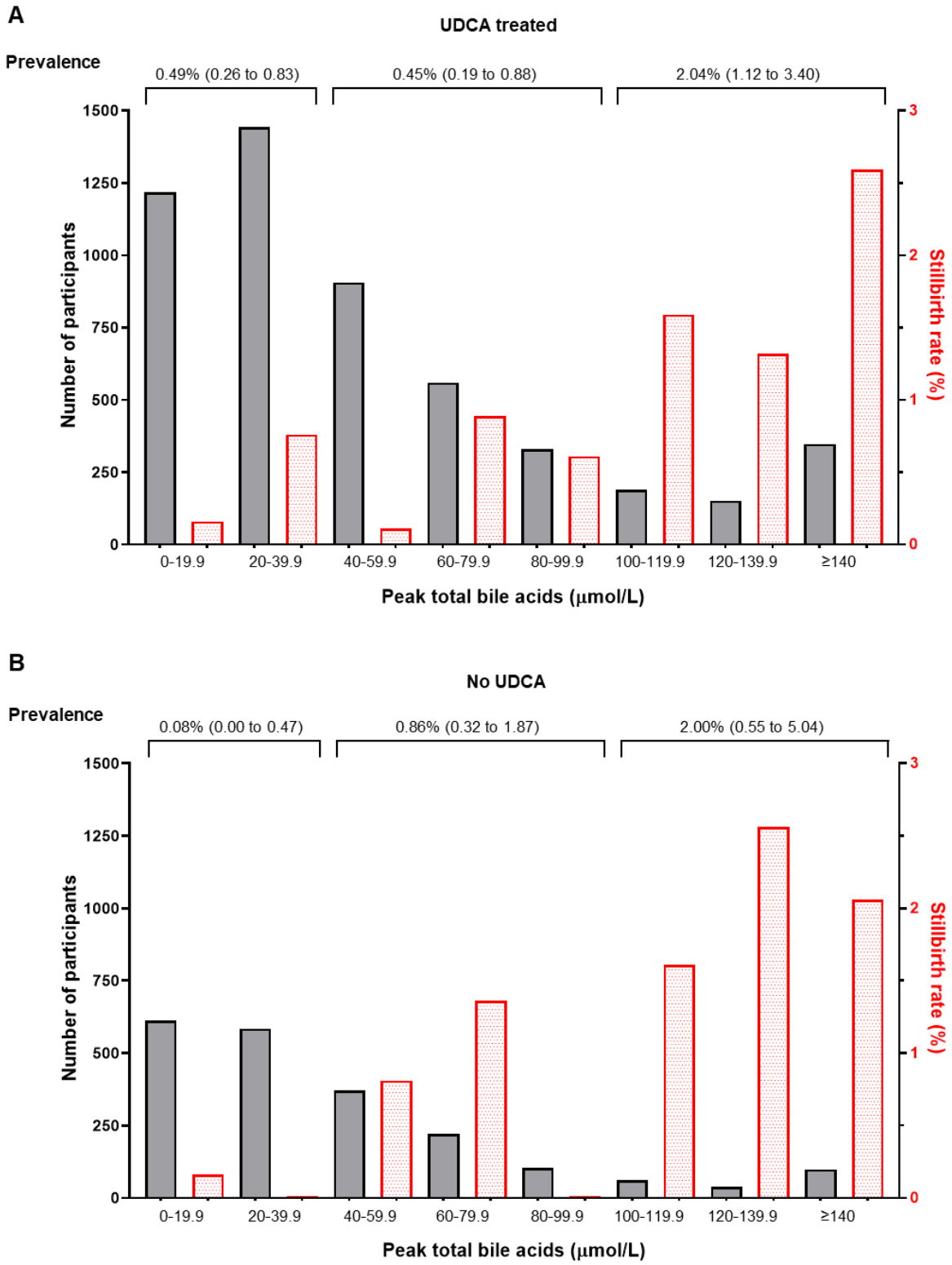
Figure S2. Rates of stillbirth and preterm birth for women receiving or not receiving ursodeoxycholic acid during their pregnancies, using individual participant data from all two-arm studies (Group C – Appendix p26)





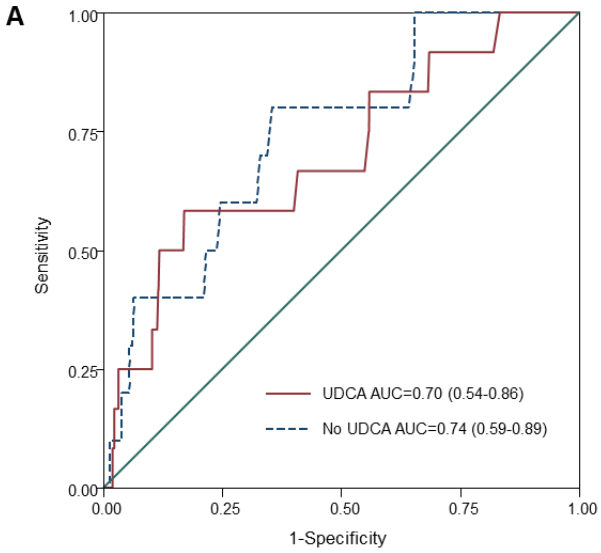
Comparisons performed by study type using a two-stage meta-analysis, with OR calculated for each study separately and combined with a random effects model. Only studies with participants in both arms (UDCA / no UDCA) were included. A: Stillbirth, B: All preterm birth <37 gestational weeks, C: Spontaneous preterm birth <37 gestational weeks, D: Composite outcome: any one of stillbirth or preterm birth. OR: odds ratio, CI: confidence interval, RCT: randomised controlled trial, UDCA: ursodeoxycholic acid, N/a: not applicable

Figure S3. Proportion and incidence of stillbirths and total number of singleton pregnancies by peak total bile acid concentration and ursodeoxycholic acid treatment using individual participant data, from all studies (Group B – Appendix p26)

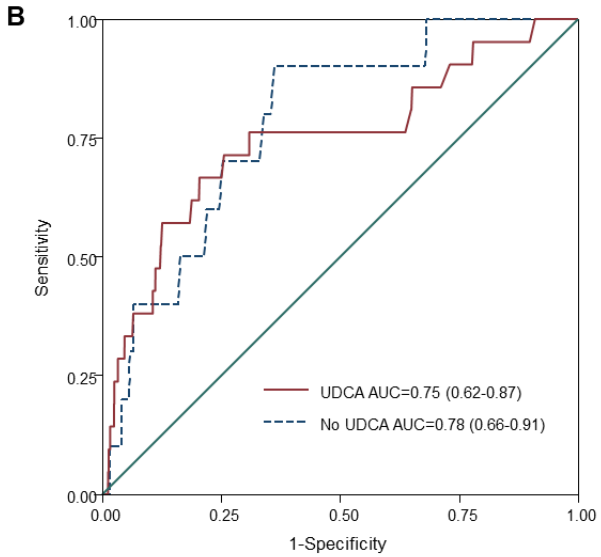


A: women treated with UDCA, B: women not treated with UDCA. Number of women with ICP (grey bars) and stillbirth proportion (red bars) by peak total bile acid category. Stillbirth prevalence from participants in all studies using individual participant data, by total bile acid groups <40 µmol/L, 40-99·9 µmol/L, and ≥100 µmol/L (95% confidence interval). UDCA: ursodeoxycholic acid

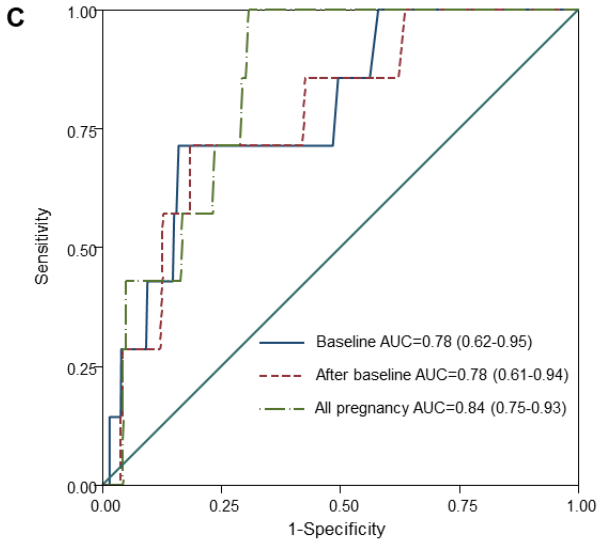
Figure S4. Receiver operating characteristic curves to determine the association between stillbirth and peak bile acid concentration for women with singleton pregnancies, using individual participant data, from all studies (Group B – Appendix p26)



A: Effect of UDCA on association between stillbirth and peak bile acids post baseline. No difference was found between women receiving UDCA or no UDCA (p=0·72). UDCA n=2138, no UDCA n=1821



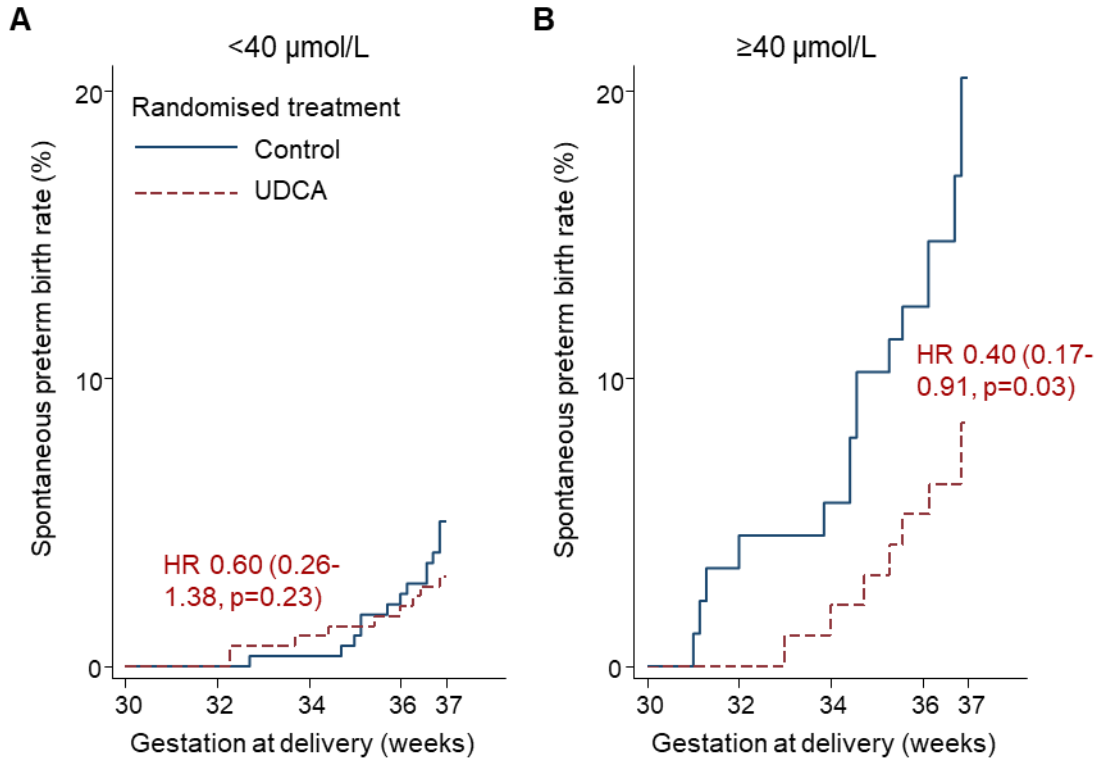
B: Effect of UDCA on association between stillbirth and peak bile acids for all of the pregnancy. No difference was found between women receiving UDCA or no UDCA (p=0·69). UDCA n=3775, no UDCA n=1936



C: Effect of timing of peak bile acid measurement on association with stillbirth. No difference was found between timings and association of stillbirth with bile acid levels (p=0·15). N=1417

Baseline: highest bile acid measurement taken before starting intervention, placebo or observation. After baseline: highest bile acid measurement taken after starting intervention, placebo or observation. All pregnancy: highest bile acid measurement recorded throughout the pregnancy. AUC: area under the curve (95% confidence interval), UDCA: ursodeoxycholic acid

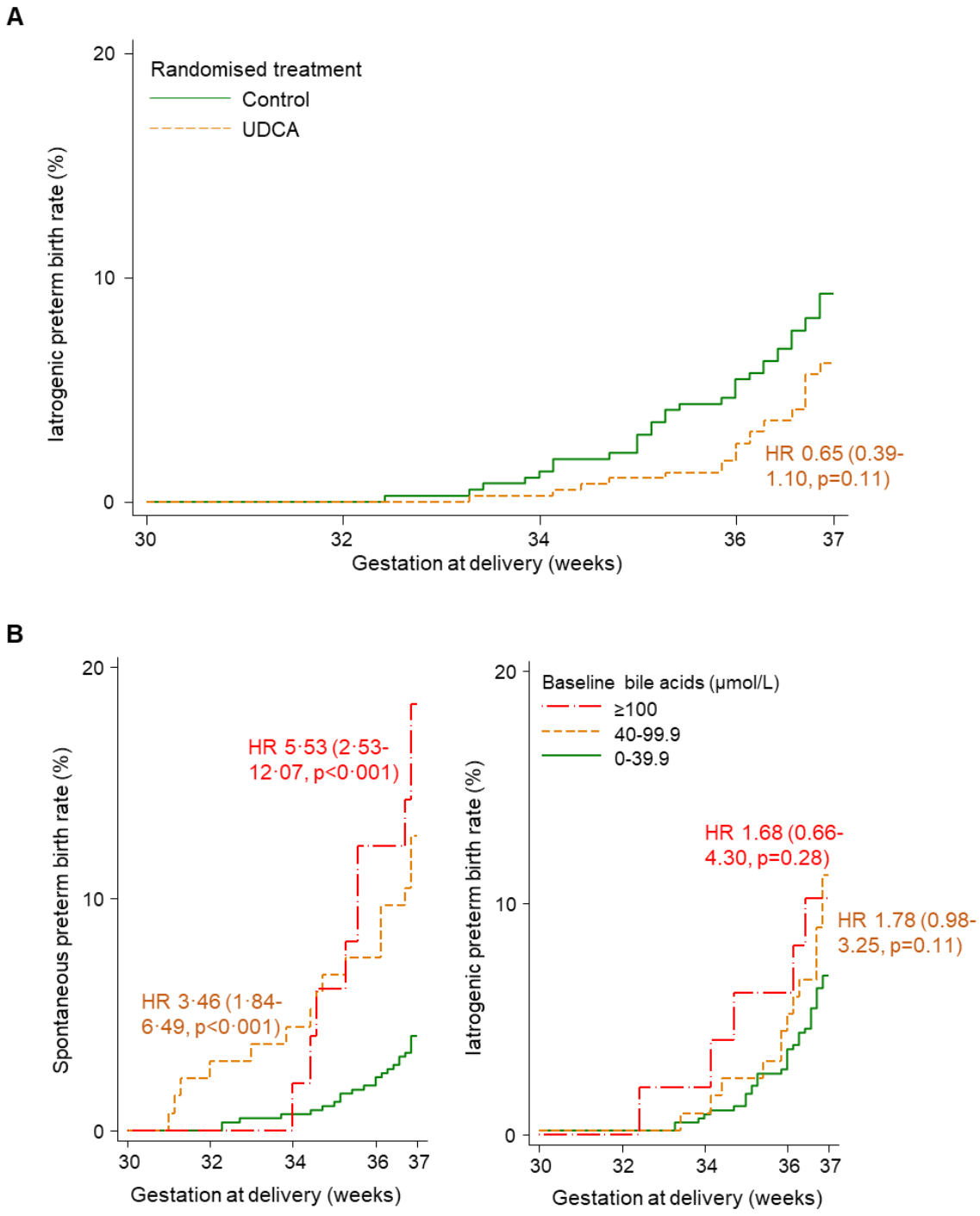
Figure S5. Kaplan-Meier survival plots of spontaneous preterm birth rate by gestational week of birth, according to ursodeoxycholic acid use and disease severity at randomisation for women with singleton pregnancies, using individual participant data from randomised controlled trials (Group F – Appendix p26)



A, B: Women with baseline bile acid concentration <40 and ≥40 µmol/L respectively, hazard ratios comparing the women randomised to UDCA with those randomised to placebo, calculated accounting for study effect. Interaction test for the groups: p=0·61

Women were censored at 37/40 if still pregnant at that time, or where birth onset was not spontaneous. HR: hazard ratio, UDCA: ursodeoxycholic acid. HR presented with 95% confidence interval

Figure S6. Kaplan-Meier survival plots of iatrogenic preterm birth rate by gestational week of birth, according to ursodeoxycholic acid use and disease severity at randomisation for women with singleton pregnancies, using individual participant data, from randomised controlled trials (Group F – Appendix p26)

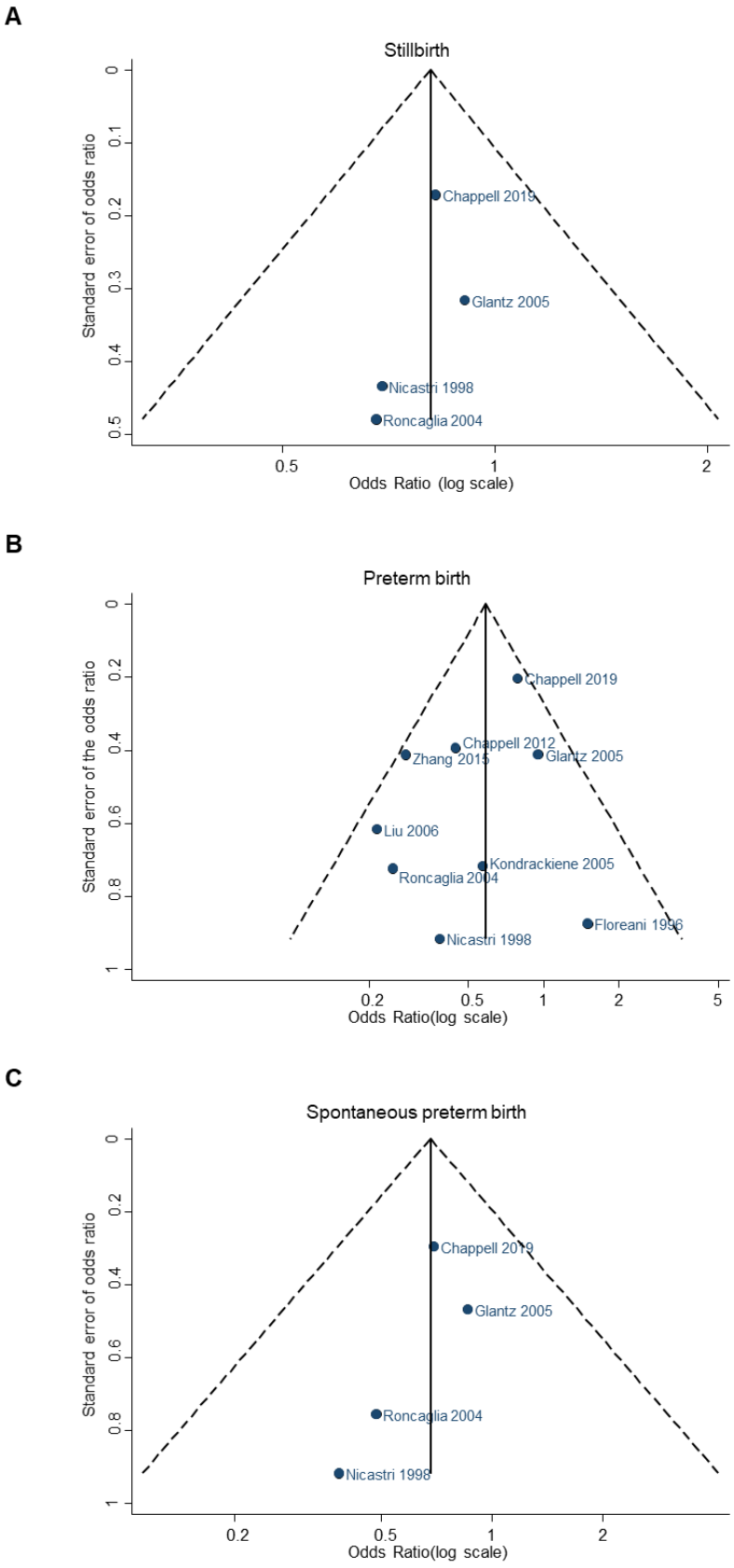


A: All women

B: All women by baseline bile acid concentration, hazard ratios comparing women with baseline bile acids 40-99.9 (red) and ≥100 µmol/L (orange) to those with baseline <40 µmol/L. The graph of spontaneous preterm birth is reproduced from Figure 2 for comparison.

Women were censored at 37/40 if still pregnant at that time, or where birth onset was not clinician-induced. Hazard ratios were calculated accounting for study effect and presented with 95% confidence interval. HR: hazard ratio, UDCA: ursodeoxycholic acid.

Figure S7. Funnel plots of studies in the aggregate data meta-analysis of randomised controlled trials (Group G – Appendix p26)



Funnel plots are presented showing pseudo 95% confidence intervals. A: stillbirth, B: preterm birth, C: spontaneous preterm birth

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