Ursodeoxycholic acid in intrahepatic cholestasis of pregnancy: an individual participant data meta-analysis

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Abstract

Background

Ursodeoxycholic acid (UDCA) is commonly used to treat intrahepatic cholestasis of pregnancy (ICP), yet its largest trial detected minimal benefit for a composite outcome (stillbirth, preterm birth, and neonatal unit admission). We aimed to determine whether UDCA affects specific adverse perinatal outcomes.

Methods

Following systematic review of the literature, authors of selected studies were invited to submit individual participant data for meta-analysis. Studies of all design without evidence of selection bias were eligible for inclusion, reported by January 2020. The primary outcome was stillbirth, although we anticipated insufficient data to achieve statistical power, and included a composite of stillbirth and preterm birth as a main secondary outcome. A mixed-effects meta-analysis was performed using multilevel modelling, adjusting for bile acid concentration, parity, and multifetal pregnancy. Analyses were performed in Stata version 16·0; the study was registered in PROSPERO: CRD42019131495.

Findings

Eighty-five studies were selected, from which data were provided for 6974 women from 34 studies, of whom 4726 (67·8%) took UDCA. With adjustment for confounders, the results including observational studies were similar to those of randomised controlled trials (RCT). In RCTs, UDCA treatment had no statistically significant effect on stillbirth (adjusted odds ratio (aOR) 0·29, 0·04 to 2·42, p=0·25), but was associated with a reduced composite outcome (aOR 0·60, 0·39 to 0·91, p=0·016), largely due to reduced total preterm birth (aOR 0·61, 0·40 to 0·92, p=0·019). This was likely due to reduced spontaneous preterm birth, which was reduced when comparing participants of all studies (aOR 0·55, 0·35 to 0·88, p=0·012).

Interpretation

IPD revealed no significant effect of UDCA on stillbirth, likely limited by the low overall event rate. However, rates in combination with preterm birth were reduced, providing evidence for the clinical benefit of antenatal UDCA treatment.

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300/300 words

Research in context

Evidence before this study

Pregnancies complicated by intrahepatic cholestasis of pregnancy (ICP) are known to have increased rates of perinatal complications, including preterm birth (both spontaneous and clinician-initiated), meconium stained amniotic fluid (MSAF), neonatal unit admission and, for women with the most severe disease (peak bile acid concentration greater than 100 µmol/L), stillbirth. Ursodeoxycholic acid (UDCA) is the most commonly used treatment for the management of ICP, yet there is not consensus as to its benefit for women or their babies. We searched PubMed, Web of Science, Embase, Medline, CINAHL, Global Health, MIDIRS and Cochrane databases for meta-analyses of UDCA use in ICP (search terms "meta$analysis", "cholestasis", "pregnancy", and "ursodeoxycholic acid"). Whilst multiple meta-analyses have been published, the majority were before publication of the 2019 PITCHES randomised placebo-controlled trial (Chappell and colleagues). This was of an equivalent size to the sum of all previous UDCA trials, many of which only administered UDCA for limited durations (2-3 weeks), often with treatment unmasked to participants and clinicians. The 2020 Cochrane Systematic Review of pharmacological treatments for ICP included the PITCHES trial, and concluded that UDCA was able to reduce itch to a minimal degree and improve serum liver

transaminase measurements and rates of MSAF, but the studies of its use for perinatal benefit were not of sufficient quality to provide clear evidence for its use in ICP. No study has reported the effect of UDCA using individual participant data, and no study has had sufficient statistical power to demonstrate any impact of UDCA on stillbirth.

Added value of this study

We performed a systematic review and individual participant data meta-analysis, including additional unpublished cohorts of women with ICP, to determine how UDCA treatment impacts adverse perinatal outcomes in ICP. Although the study was underpowered to show a statistically significant reduction in overall stillbirth with UDCA use, we demonstrated that a composite of stillbirth and preterm birth was lower for women treated with UDCA (with the number needed to treat (NNT) being 15), and also showed that preterm birth rates were reduced, particularly for women with singleton pregnancies, with the use of UDCA.

Implications of all the available evidence

Our study shows that women with ICP who are treated with UDCA have lower rates of preterm birth, and a composite outcome of stillbirth and preterm birth, than women who were not treated with UDCA in their pregnancy. We demonstrated that the benefit of UDCA treatment on reducing spontaneous preterm birth was more evident for women with higher bile acid concentrations (≥40μmol/L); as most adverse outcomes of ICP increase with rising bile acid concentrations, so this emphasises that women with more severe disease are likely to be those for whom UDCA has the greatest benefit. Particularly for women who experience disease before 36-37 gestational weeks and with moderate-severe bile acid elevations, this study suggests that UDCA should be offered as part of their antenatal treatment.

Introduction

Intrahepatic cholestasis of pregnancy (ICP) affects 0·3-5·6% of pregnant women, with marked differences by ethnicity.[1] Affected women experience pruritus and liver dysfunction, with raised serum total bile acid concentrations and, often, liver transaminases.[2] Increasing peak bile acid concentrations (particularly ≥40 μmol/L) are associated with higher rates of adverse perinatal outcomes, including spontaneous preterm birth, meconium-stained amniotic fluid, and neonatal unit admission;[3,4] when bile acids rise >100 μmol/L, women have an increased risk of stillbirth (3·44% versus 0·28% for women with peak bile acids between 40 and 100 μmol/L).[5,6]

Ursodeoxycholic acid (UDCA) is commonly used for the treatment of ICP.[1] It improves biliary flow,[7] enhances the protective bicarbonate environment on the surface of cholangiocytes,[8] and protects the liver from bile acid-induced apoptosis.[9] It has anti-inflammatory actions,[10] and can reduce fetal serum bile acid elevation by upregulating placental bile acid export.[11] As UDCA is a bile acid, its use results in alteration of the bile acid pool, constituting 60-70% of the measured total bile acids in treated women, and replacing more harmful (hydrophobic) bile acids.[12,13] Although not licensed for use in pregnancy, UDCA is thought to be safe, with gastrointestinal side-effects the most common; however no difference in overall side-effects were seen between UDCA and placebo tablets in previously reported studies.[14]

Studies have demonstrated that UDCA treatment is associated with reduced pruritus,[15] but not to a pre-determined clinically-beneficial degree.[16] Whether UDCA improves perinatal outcomes is unclear, with contradictory findings from previous aggregate data meta-analyses of trials of its use, dependent upon the method of comparison.[15,17–19] However, these meta-analyses were limited by study sizes, including between 600-700 women amongst all contributing studies. A subsequent randomised placebo-controlled trial (RCT) of UDCA in ICP studied 605 women, and demonstrated no improvement in the primary outcome (a composite of perinatal death, preterm birth, and neonatal unit admission) with UDCA; a lower incidence of meconium-stained amniotic fluid was the only

secondary perinatal outcome to improve with UDCA.[20] This is reflected in the most recent Cochrane review of ICP treatment, which demonstrated that the evidence for the impact of UDCA on fetal distress and stillbirth (the principal perinatal outcomes) was uncertain, due to limitations in study design and imprecision.[14] These findings are in contrast to the recent SMFM comment on the management of ICP, which suggest grade 1A evidence supports the use of UDCA.[21]

Thus, clear evidence for the benefit of UDCA in pregnancy is lacking, with a greater sample size required to achieve statistical power. Myometrium from women with ICP has greater oxytocin-mediated contractility than that from unaffected pregnancies[22] and, as exposure of human myometrium to cholic acid increases the expression of oxytocin receptors,[23] UDCA-mediated alteration in the bile acid pool may reduce spontaneous preterm birth in ICP.[12] There is experimental evidence that UDCA treatment reduces the impact of pathological processes that are implicated in the aetiology of stillbirth in ICP, such as placental vasospasm,[24] and fetal arrhythmia (abnormal heart rate variability and the elevation of umbilical venous NT-proBNP are associated with elevated maternal and fetal bile acid concentrations).[25,26] However, clinical trials powered to detect alterations in stillbirth rates would require participant numbers that are likely unfeasible, given the disease prevalence.[27]

We therefore aimed to utilise data from existing literature to determine whether UDCA affects adverse perinatal outcomes, predominantly stillbirth and preterm birth. We planned to use individual participant data to enable appropriate adjustment for main confounders, enabling inclusion of observational studies, in addition to RCTs.

Methods

Search strategy and selection criteria

A systematic review of the literature and individual participant data meta-analysis was performed.

The PubMed, Web of Science, Embase, Medline, CINAHL, Global Health, MIDIRS and Cochrane databases and manuscript reference lists were searched for relevant articles using search terms referencing ICP, UDCA and perinatal outcomes, following a prospective search with Ovid using the "Map Term to Subject Heading" feature, and Medical Search Heading (MeSH) additional search term permutations included in the search terms (Appendix p12). Duplicates were removed, relevant articles were selected by title and abstract, and adherence to inclusion / exclusion criteria (Appendix p12) determined in duplicate by JS and KP; any disparities were arbitrated by CO. Studies were included from inception of the database to 01/01/2020. There were no language limits; publications not in English were translated by fluent speakers of the original language or Google Translate. ICP was defined based upon the local criteria of the study, however studies were excluded where elevated bile acid concentrations were not reported; as the majority of adverse perinatal outcomes occur in women with "severe" ICP (bile acids ≥40μmol/L), we aimed to enrich our study by including only studies that included women with more severe disease. Corresponding authors of selected articles were contacted, initially via email, on at least two occasions; where no reply was received, at least one other author from the manuscript was contacted. Participating authors completed pseudoanonymised spreadsheets reporting simple maternal demographics, ICP diagnostic and treatment details, and perinatal outcomes (Appendix p12). The National Heart, Lung and Blood Institute (NHLBI) study quality assessment tools were used to provide a quality score for each publication included.[28] These were independently assessed by JS and NW, with arbitration by CO. The study protocol was pre-registered in PROSPERO (CRD42019131495),[29] and the data analysis plan pre-specified (Appendix p3). Modifications to the PROSPERO planned analyses are documented in the Appendix (p2); in response to the number of participants for whom data were available, we anticipated insufficient stillbirths would be reported for adequate power to determine the effect of UDCA; we therefore modified our objectives to evaluate a secondary composite outcome (stillbirth or preterm birth).

An additional (unpublished) cohort of 339 women with ICP, who had provided individual informed consent, was included (study approved by the Ethics Committee of Hammersmith Hospital National Health Service Trust, London, UK: 97/5197, 17/WA/0161, and 08/H0707/21). Ethical approval to share data was a prerequisite of inclusion of all studies.

Data analysis

Analyses were performed in Stata version 16·0. An IPD meta-analysis was performed using multi-level mixed-effects logistic regression using the Stata function "melogit", (or logistic regression with Huber-White correction where this did not converge), with participants nested within studies, and (for multiple pregnancy) infants within mothers,[30] comparing women treated with UDCA (at any dose / duration) with those not receiving UDCA. Adjustment was performed for bile acid concentrations, number of fetuses, and maternal parity, due to the established relationships between these confounders and adverse perinatal outcomes, and anticipated data availability.[3,5,31,32] IPD analyses were performed for all studies and limited to RCTs (Appendix p13), further excluding multifetal pregnancies and single-arm studies (a schematic of groups analysed is provided in the Appendix, p26). Results were presented as adjusted odds ratios (aOR), with 95% confidence intervals (95% CI) and p value reported. Missing data were handled by exclusion. Logistic regression of subgroups was performed to determine the effects of treatment by bile acid concentrations, separated at 40 μmol/L and 100 μmol/L;[3,5] by gestational age at diagnosis before or after 32 gestational weeks;[33] and by maximum daily UDCA dose <1 g versus ≥1 g (median value for the whole cohort). Interactions between groups were calculated using the likelihood ratio.

Associations between bile acid concentrations and stillbirth (by UDCA treatment) were compared using the "roccomp" function in Stata. Baseline bile acid concentration was defined as the highest bile acid concentration prior to treatment randomisation (for trials) or at diagnosis (assuming that most women treated with UDCA in observational studies commenced this rapidly after "baseline"). Women with bile acid concentrations recorded at commencement of the study (baseline) and later in their pregnancy were included in the comparison of timing of measurement and association with

stillbirth, whilst the effect of UDCA treatment on this association was determined based on peak concentrations during treatment and for the whole pregnancy.

A survival analysis was performed as outlined in the data analysis plan to determine the risk of spontaneous preterm birth (defined as birth before 37 gestational weeks following spontaneous labour onset) over time, stratified by UDCA treatment, for participants in RCTs using Cox's proportional hazards model. Participants were divided according to baseline bile acid concentrations into predefined categories and hazard ratios determined comparing UDCA treatment and bile acid category.

Given that we only received data from four of fourteen RCTs (822/1389 pregnancies, 59·2%, Appendix p13), aggregate data from all published RCTs were compared in a conventional fixed effects meta-analysis, *post hoc*, deriving summary effects using Mantel-Haenszel methods. Funnel plots were produced to review potential publication bias. No restriction on the number of participants was used; studies were otherwise selected based upon the original search strategy, using studies that reported clear randomisation in their design. Studies required participants of at least one arm to receive UDCA, with another arm not receiving UDCA. Aggregate data were extracted from the original manuscript in duplicate (CO, JS), collecting data on stillbirth, spontaneous, and overall preterm birth (defined as birth before 37/40).

Role of the funding source

The funders of the study had no roles in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

A total of 85 studies fulfilled the inclusion criteria, from which individual participant data were provided for 32 studies (6670 pregnancies), including four RCTs; these were enriched with data from unpublished cohorts (339 pregnancies) (Figure 1, Appendix p13, 17). Of the 7009 pregnancies for which data were provided, 6974 reported sufficient data for inclusion (822 from four RCTs), of whom 4726 (67·8%) took UDCA (Appendix p18).

The stillbirth rate was not statistically different in women treated with UDCA compared to non-UDCA treated women (adjusted odds ratio (aOR) 1·04, 95% confidence interval (CI) 0·35 to 3·07, p=0.95)(Table 1, Appendix p27); this did not differ when considering singleton pregnancies alone (Table 2). Women with peak bile acid concentrations ≥100 μmol/L (compared to those <100 μmol/L) from both treatment groups had similarly increased stillbirth prevalence (2·04% with UDCA vs. 2·00% without) (Appendix p29). In women with singleton pregnancies, UDCA treatment did not affect the association between peak bile acid concentration and stillbirth, whether the highest bile acid measurement for the whole pregnancy was used (p=0·69 comparing groups) or only after treatment initiation (p=0·72 comparing groups) (Appendix p30). Peak bile acid concentration for the whole pregnancy had the highest prediction of stillbirth compared to other timepoints (area under receiver operating curve (AUC) 0·84, 95% CI 0·75 to 0·93).

Adjusted analysis of the entire dataset revealed that UDCA treatment was associated with a reduced risk of spontaneous preterm birth (aOR 0·55, 95% CI 0·35 to 0·88, p=0·012), and this reduction was seen in RCTs when restricted to singleton pregnancies (aOR 0·46, 95% CI 0·25-0·86, p=0·015) (Tables 1, 2, Appendix p27). UDCA treatment was also associated with a reduced risk of total preterm birth, for women in RCTs (singleton and multifetal pregnancies) (aOR 0·61, 95% CI 0·40-0·92, p=0·019) and when considering only singleton pregnancies for all studies (aOR 0·69, 95% CI 0·48-0·98, p=0·040). UDCA did not reduce early preterm birth (<34 gestational weeks) (Appendix p19). Heterogeneity at the study level was significant for iatrogenic preterm birth (OR 2.31, 95% CI 1.10 to 4.82) when considering all studies (observational and RCTs); removal of single-arm studies did not alter findings

for singleton pregnancies, although suggested a reversed impact of UDCA on preterm birth outcomes when multifetal pregnancies were also included (Appendix p20).

A survival analysis performed for women participating in RCTs with singleton pregnancies demonstrated that spontaneous preterm birth was lower for UDCA-treated women (hazard ratio 0·49, 95% CI 0·27 to 0·88, p=0·017), compared with non-UDCA treated women (Figure 2A). When the impact of UDCA treatment was compared in women with different peak bile acid concentrations, UDCA was of benefit in those with serum concentrations between 40 and 100 µmol/L (Figure 2B-D, Appendix p31), although interaction testing between the groups was not significant. Overall, peak bile acid concentration was associated with spontaneous preterm birth (Figure 2E). The impact of UDCA treatment on iatrogenic preterm birth was less marked, although the association with increased bile acid concentrations remained (Appendix p32).

For RCTs alone, UDCA significantly reduced the composite outcome (aOR 0·60, 95% CI 0·39 to 0·91, p=0·016), with the number needed to treat (NNT) being 15 (95% CI 9 to 54) (Table 1). We confirmed these findings in singleton pregnancies (Table 2), demonstrating the NNT was 14 (95% CI 8 to 42). There was no difference in the rate of composite outcome between groups with differing baseline bile acid concentrations (using both 40 and 100 µmol/L thresholds), p=0·74 and p=0·79 for the interactions, respectively, between women diagnosed before or after 32 gestational weeks (p=0·38), or by the dose of UDCA prescribed (p=0·069) (Appendix p21).

UDCA-treated women had lower rates of meconium-stained amniotic fluid than non-UDCA treated (for RCTs, aOR 0·51, 95% CI 0·34 to 0·77, p=0·001) (Table 1). There were no differences in rates of neonatal unit admission, umbilical cord arterial pH <7·0, Apgar score <7 at five minutes, small for gestational age babies, or perinatal death (p>0·05 throughout) between UDCA-treated and non-UDCA treated groups. There were higher rates of neonatal unit admission (aOR 1·43, 95% CI 1·15 to 1·78, p=0·001 and aOR 1·64, 95% CI 1·23 to 2·19, p=0·001) and meconium-stained amniotic fluid (aOR 1·93, 95% CI 1·54 to 2·42, p<0·001 and aOR 2·27, 95% CI 1·69 to 3·04, p<0·001) for all

participants with bile acid concentrations greater than both 40 μmol/L and 100 μmol/L, respectively (Appendix p22). Bile acids ≥100 μmol/L were associated with higher neonatal death than lower levels (aOR 8·31, 95% CI 2·13 to 32·41, p=0·002).

There were no significant differences in maternal outcomes (induction of labour, unassisted vaginal birth, and postpartum haemorrhage) for UDCA treated or non-UDCA treated women (p>0·05 throughout), for women participating in all studies and limited to RCTs (Tables 1, 2, Appendix p23). Insufficient data were reported on development of pre-eclampsia in women participating in RCTs to perform a reliable analysis, although there was no difference with UDCA treatment in pre-eclampsia rates for the entire cohort (aOR 1·14, 95% CI 0·53 to 2·47, p=0·74)(Table 1). Maternal outcomes were not related to bile acid concentrations (Appendix p24).

Given the magnitude of effect of data adjustment on the observational studies compared to RCTs, and the limitation of the RCT IPD to only four studies (822/1389 pregnancies, 59·2%, Appendix p13), we then performed an aggregate data meta-analysis on published RCTs comparing the impact of UDCA with any other treatment on the primary outcomes. We identified 14 studies (Appendix p25) for inclusion; and defined high quality, for this purpose, as being those that were double-blinded, placebo-controlled, and with the intervention administered until delivery. No effect of UDCA treatment was seen on stillbirth, but it did reduce the risk of total preterm birth (OR 0·55, 95% CI 0·42 to 0·72, p<0·001) (Figure 3a,b), although the reduction in spontaneous preterm birth specifically was not significant (OR 0·69, 95% CI 0·43 to 1·09, p=0·11) (Figure 3c). For all comparisons, publication bias was not evident on funnel plots (Appendix p33).

Discussion

Using IPD, we demonstrated the new finding that UDCA treatment is associated with a lower rate of a composite of stillbirth and preterm birth, and total preterm birth in trials, and reduced rates of

spontaneous preterm birth (when considering singleton pregnancies for all studies), although this study did not establish that UDCA treatment in ICP significantly reduces the stillbirth rate. This was supported by analysis of aggregate data from published trials, which also demonstrated reduced total preterm birth with UDCA treatment. Of the pre-specified secondary maternal and fetal outcomes, meconium-stained amniotic fluid reduced with UDCA treatment.

Whilst UDCA did not reduce preterm births before 34 gestational weeks, prevention of late preterm birth is of considerable benefit: these babies are at a higher risk of postpartum respiratory impairment, delayed feeding, early childhood mortality, neurodevelopmental disability, and longer-term cognitive defects than children born at term.[34] Recent IPD evidence demonstrated that, for women with ICP with serum bile acid concentrations <100 μmol/L, stillbirth rates are no higher than the background population,[5] meaning that iatrogenic preterm delivery rates for women with lower bile acid concentrations are likely to fall,[35] which may result in more fetuses that could benefit from UDCA-associated reduced spontaneous preterm birth.

This IPD meta-analysis has demonstrated the value of well-designed RCTs in intervention studies. When considering IPD from all study designs, adjustment of comparisons by the main confounders reversed the effect of UDCA, reflecting how poorly matched treatment groups were in these studies by the main influencers of perinatal outcomes in ICP. Similarly, removal of single-arm studies from comparisons of IPD from all studies altered the effect of UDCA on the main primary outcomes when multifetal pregnancies were included (although not for singletons). This may suggest different mechanisms by which ICP impacts preterm birth or stillbirth in multifetal pregnancies, consistent with a previously reported lack of association between bile acid concentration and stillbirth in multifetal pregnancies that is in contrast to singletons.[5] Alternatively, this may demonstrate the impact of unmatched comparator groups, particularly when outcomes are analysed by number of fetuses, rather than by pregnancy. The results of the aggregate meta-analysis are consistent with previous studies that have demonstrated effect sizes to be over-estimated in unconcealed or non-

masked RCTs;[36] only two of the RCTs of UDCA treatment, where treatment was continued until delivery, were masked to investigators and participants and, for these studies, the effect size on preterm birth reduction was less than that of non-masked studies. This over-estimation of effect size may explain why historical studies have suggested additional perinatal benefits that have not been revealed in this meta-analysis,[15] such as no effect on neonatal unit admission and Apgar scores. Similarly, the magnitude of change in effect seen in the observational studies when adjustment for baseline characteristics was performed is consistent with previous concerns about the validity of inadequately balanced groups in observational studies without attempt to eliminate bias,[37] hence the limitation on what conclusions can be drawn from these studies alone. Differences between studies and data collected limited the baseline adjustments that we were able to perform and prevented use of an inverse probability treatment weighting approach; thus results from the more comparable groups participating in RCTs are likely to be more reliable; the risk of selection bias for studies included in the IPD is a further limitation to interpretation of our findings, which was mitigated in part by use of the aggregate data meta-analysis.

This study did not demonstrate a significant reduction in stillbirth with UDCA treatment, despite attempting to include all data available. Stillbirth is a relatively rare outcome, and therefore the number of participants required to obtain sufficient power to detect any difference is likely to be prohibitive to study. Limiting future studies to those women at greatest risk (for example those with bile acid concentrations ≥100 μmol/L) would reduce the numbers needed to evaluate the impact of UDCA on stillbirth risk, but may remain unfeasible. Whilst we were able to include data from the largest RCT of UDCA,[20] data were not available for many other studies, which limited the sample size available for comparison. Clinicians cannot, therefore, reassure women that treatment with UDCA abrogates the risk of stillbirth. Similarly, comprehensive data on UDCA treatment duration and dose escalation were not available in this study, limiting specific prescribing guidance for the clinician; differences in laboratory bile acid measurement method and reference range between centres also complicate interpretation.

Our findings regarding the effect of UDCA on total preterm birth reveal a reduction in spontaneous preterm birth in singleton pregnancies with UDCA treatment for the first time. This was not evident from the aggregate data meta-analysis, due to limited reporting of this outcome with a standardised definition, and incomplete reporting of this outcome by number of fetuses. The recent Cochrane review also did not demonstrate this reduction in spontaneous preterm birth, likely due to incomplete reporting in all studies and separate comparisons of UDCA by comparator group (e.g. placebo, S-adenosyl methionine).[14] We compared UDCA treatment with any other treatment based upon the lack of evidence for perinatal benefit for other treatments.[38] Similarly, by combining IPD from multiple studies, we were able to identify significant treatment benefits not revealed in the largest RCT of UDCA.[20] For policy-makers, it is reassuring that the 2019 UK RCT did not show statistical difference in the total cost for UDCA treatment compared with placebo (adjusted difference cost per patient −£429 (95% CI −1235 to 377), adjusted p=0·30), and there was no difference in reported adverse events.[20] However, we did not show that UDCA treatment improved all adverse perinatal outcomes, and it seems clear that UDCA cannot prevent all cholestasis-related adverse perinatal effects. Similarly, the benefit of UDCA on maternal pruritus is limited,[14] and an effective alternative treatment is currently lacking. Thus, there is a clear need for complementary treatment targets for gestational cholestasis.

In summary, this meta-analysis suggests that UDCA treatment in ICP reduces the risk of preterm birth. Previous work has shown that there is an increased risk of preterm birth in women with peak bile acid concentrations ≥40 μmol/L (compared to those <40 μmol/L);[5] UDCA treatment should therefore be considered for these women with disease onset prior to 37 weeks' gestation.

3425 words

Declaration of Interests

CW, CO and HUM are consultants for Mirum Pharmaceuticals. CW is a consultant for Glaxo Smith Kline. KK is an unpaid consultant for Myriad Pharmaceuticals. BH reports non-financial support from Falk Foundation, during the conduct of the study; and Co-author of the Cochrane Review on Pharmacological interventions for treating intrahepatic cholestasis of pregnancy (Walker et al 2020). RT reports grants from Tommy's Charity and from Lauren Page Trust during the conduct of the study. The other authors declared no conflicts of interest.

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Data sharing

De-anonymised and summary data will be available for sharing by reasonable request from the corresponding author. Individual participant data from the unpublished UK cohort will be available, unless consent for data-sharing was withheld by the participant, upon request of the corresponding author. Unpublished data for the purpose of meta-analysis from the Italian cohort is available online: Indraccolo U, Catagini S, Bianchi B, Morano D, Borghi C, Greco P (2020). Intrahepatic cholestasis of pregnancy - Database Arcispedale Sant'Anna of Ferrara. DOI: 10.13140/RG.2.2.32304.30722.

Author Contributions

CO and CW conceived the study; CO, PTS, JS and CW wrote the study protocol and data analysis plan; JS and KP performed the systematic review and requested IPD; JS and NJW performed the study quality assessments; JS, KP, GA, FA, YB, LB, KB, RBF, LB, JC, YC, MD, PHD, MCE, FWG, VG, MG, BG, WMH, CH, YH, UI, AJ, SCK, AK, LK, KK, JK, MPHK, RHL, XL, AL, RIRM, RM, AM, KM, JM, AM, MAO,

DO, MJP, AHS, RMT, VT, NTO, TV, LFAW, YY, QX, KZ, LCC, JT and CW provided IPD; PTS, CO, JS and CW performed the statistical analysis; CO, JS, PTS, HUM, LCC, JT and CW interpreted the data; CO, JS and CW wrote the first draft of the manuscript; all authors reviewed and approved the final manuscript.

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Figure Legends

Figure 1. Flow chart of search results.

Adapted from PRISMA and PRISMA IPD. ICP: intrahepatic cholestasis of pregnancy, IPD: individual participant data, UDCA: ursodeoxycholic acid

Figure 2. Kaplan-Meier plots of spontaneous preterm birth rate by gestational week of birth, according to ursodeoxycholic acid use and disease severity at randomisation

Analyses performed using individual participant data from women with singleton pregnancies participating in randomised controlled trials (Group F, Appendix p26), with hazard ratios calculated accounting for study effect.

A: All women, B-D: Women with baseline bile acid concentration <40, 40-99·9 and ≥100 µmol/L respectively, hazard ratios comparing the women randomised to UDCA with those randomised to placebo. Interaction test for the groups: p=0·67

E: 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

IPD: individual participant data, HR: hazard ratio, UDCA: ursodeoxycholic acid. HR presented with 95% confidence interval

Figure 3. Rates of stillbirth and preterm birth for women receiving ursodeoxycholic acid or not as part of a randomised controlled trial using aggregate published data

Studies separated by quality: high – placebo controlled, masked, intervention provided until delivery; lower quality – those not fulfilling all high quality criteria. A: stillbirth, B: all preterm birth <37 gestational weeks, C: spontaneous preterm birth <37 gestational weeks. Stillbirth analysed by number of fetuses, except Glantz (number of pregnancies); preterm birth analysed by number of fetuses, except Glantz, Kondrackiene, Roncaglia, and Palma (number of pregnancies). OR: odds ratio, CI: confidence interval, UDCA: ursodeoxycholic acid