The Effects of Ursodeoxycholic Acid Treatment for Intrahepatic Cholestasis of Pregnancy on Maternal and Fetal Outcomes: A Meta-Analysis Including Non-Randomized Studies

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Abstract

Objective: The benefits of ursodeoxycholic acid (UDCA) use for treating intra-hepatic cholestasis of pregnancy (ICP) remain uncertain. A 2010 Cochrane Review of randomized control trials was unable to recommend either for or against the use of UDCA in treating ICP. We conducted a meta-analysis of the literature, including both non-randomized studies (NRSs) and RCTs. The objective of the study was to determine if patients included in NRSs were comparable to those in RCTs, and to determine whether the inclusion of NRSs could strengthen the available evidence and guide clinical practice on UDCA use in women with ICP.

Data sources: We searched Medline (Ovid), Embase (Ovid), EMB Reviews, CINAHL (Ebsco), and Web of Knowledge (Thomson Reuters) for articles published from 1966 to June 2012.

Study Selection: We included all eligible RCTs of UDCA versus placebo or other treatments, and all NRSs comparing UDCA with any other treatment in women with ICP.

Data Synthesis: We included 11 RCTs (n = 625 pregnancies) and six NRSs (n = 211 pregnancies). The women included in RCTs and NRSs were comparable, but study quality was poorer for NRSs. Overall, women treated with UDCA had decreased pruritus in 73% of RCTs and in 100% of NRSs with available data. Liver function tests were improved in 82% of RCTs and in 100% of NRSs with available data. UDCA use did not affect the Caesarean section rate, but was associated with less prematurity, less use of neonatal intensive care units (data available in only 3/17 studies), and trends towards increased birth weight and decreased meconium staining. There were 0/356 stillbirths with UDCA and 3/399 stillbirths with comparator.

Conclusion: UDCA treatment should be recommended for women with ICP to reduce adverse maternal and fetal outcomes.

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Key Words: Intrahepatic cholestasis of pregnancy, ursodeoxycholic acid, maternal, prematurity, treatment

Competing Interests: None declared.

Résumé

Objectif : Les avantages de l'utilisation d'acide ursodésoxycholique (AUDC) pour la prise en charge de la cholestase intrahépatique de la grossesse (CIG) demeurent incertains. Une analyse Cochrane de 2010 ayant porté sur des essais comparatifs randomisés n'a pas été en mesure de se prononcer pour ou contre l'utilisation d'AUDC pour la prise en charge de la CIG. Nous avons mené une méta-analyse de la littérature, en englobant tant les études non randomisées (ENR) que les ECR. Nous avions pour objectif de déterminer si les patientes ayant participé aux ENR étaient comparables à celles qui avaient participé aux ECR; nous avions également pour objectif de déterminer si l'inclusion des ENR pouvait renforcer les données probantes disponibles et orienter la pratique clinique quant à l'utilisation d'AUDC chez les femmes qui présentent une CIG.

Sources de données : Nous avons mené des recherches dans Medline (Ovid), Embase (Ovid), *EMB Reviews*, CINAHL (Ebsco) et *Web of Knowledge* (Thomson Reuters) en vue d'en tirer les articles publiés entre 1966 et juin 2012.

Sélection des études : Nous avons inclus tous les ECR admissibles ayant comparé l'AUDC à un placebo ou à d'autres traitements et toutes les ENR ayant comparé l'AUDC à tout autre traitement chez des femmes présentant une CIG.

Synthèse des données : Nous avons inclus 11 ECR (n = 625 grossesses) et six ENR (n = 211 grossesses). Bien que les femmes ayant participé aux ECR et aux ENR aient été comparables, la qualité des études était plus faible dans le cas des ENR. De façon générale, les femmes traitées à l'AUDC ont connu une atténuation du prurit dans 73 % des ECR et dans 100 % des ENR disposant de données disponibles. Les épreuves de fonction hépatique ont présenté une amélioration dans 82 % des ECR et dans 100 % des ENR disposant de données disponibles. Bien que l'utilisation d'AUDC n'ait pas affecté le taux de césarienne, elle a été associée à une prématurité moindre, à une utilisation moindre des unités néonatales de soins intensifs (données disponibles pour seulement trois des 17 études) et à des tendances à l'augmentation du poids de naissance et à l'atténuation de la teinte méconiale du liquide amniotique. Aucune mortinaissance n'a été constatée dans le cadre de 356 grossesses ayant fait l'objet d'un traitement à l'AUDC et trois mortinaissances ont été constatées dans le cadre de 399 grossesses ayant fait l'objet d'un traitement au moyen d'un agent de comparaison.

Conclusion : Le traitement à l'AUDC devrait être recommandé aux femmes qui présentent une CIG en vue d'atténuer les issues indésirables maternelles et fœtales.

INTRODUCTION

Intrahepatic cholestasis of pregnancy is a pregnancy-related liver disease. It occurs in approximately 0.1% to 1.5% of pregnancies in Europe and the United States,[1] although it is much more prevalent in South America and Scandinavia, where occurrence is approximately 6% to 29%.[2] ICP is defined as an intractable pruritus that usually begins on the palms and soles and spreads to involve the whole body. It is much worse at night and disturbs sleep.[3] It usually begins during the second half of pregnancy and resolves after delivery. It can be accompanied by elevated serum concentrations of liver enzymes and bile acids (> 10 μmol/L).[4]

Although pruritus can be very disturbing, ICP typically remains a benign disease for mothers. However, studies confirm that the presence of ICP is associated with an increased risk of perinatal morbidity and mortality.[5] The rates of preterm delivery (10% to 60%), fetal distress (22% to 41%), and stillbirth (1% to 4%) are increased when bile acid levels exceed 40 μmol/L.[6–8] Because of an increased risk of neonatal complications after 38 weeks of gestation, most women with ICP have induction of labour at 37 weeks.[9]

Ursodeoxycholic acid is currently the most effective treatment for ICP and is thought to reduce pruritus and neonatal complications.[10] The recommended dose of UDCA is 15 mg/kg/day divided into two or three doses, and it is usually well tolerated. Many research groups have studied the effects of UDCA versus placebo or other treatments in treating ICP. However, a recent Cochrane review of RCTs failed to find sufficient evidence of UDCA's benefit to recommend it for treatment of ICP.[11]

There have been many non-randomized studies focusing on the use of UDCA to treat ICP, but these were not included in the Cochrane review. We hypothesized that a review of these studies would augment available evidence and help in making clinical decisions on the use of UDCA in women with ICP.

The objectives of our study were to determine if the patients and clinical conditions in NRSs were comparable to those in RCTs, to evaluate if the inclusion of data from NRSs could add to the evidence supporting the use of UDCA as a treatment for ICP, and to investigate if UDCA reduces adverse fetal and maternal outcomes in women with ICP compared to other treatments.

ABBREVIATIONS

ICP	intrahepatic cholestasis of pregnancy
IUGR	intrauterine growth restriction
NRS	non-randomized study
RR	risk ratio
UDCA	urdodeoxycholic acid

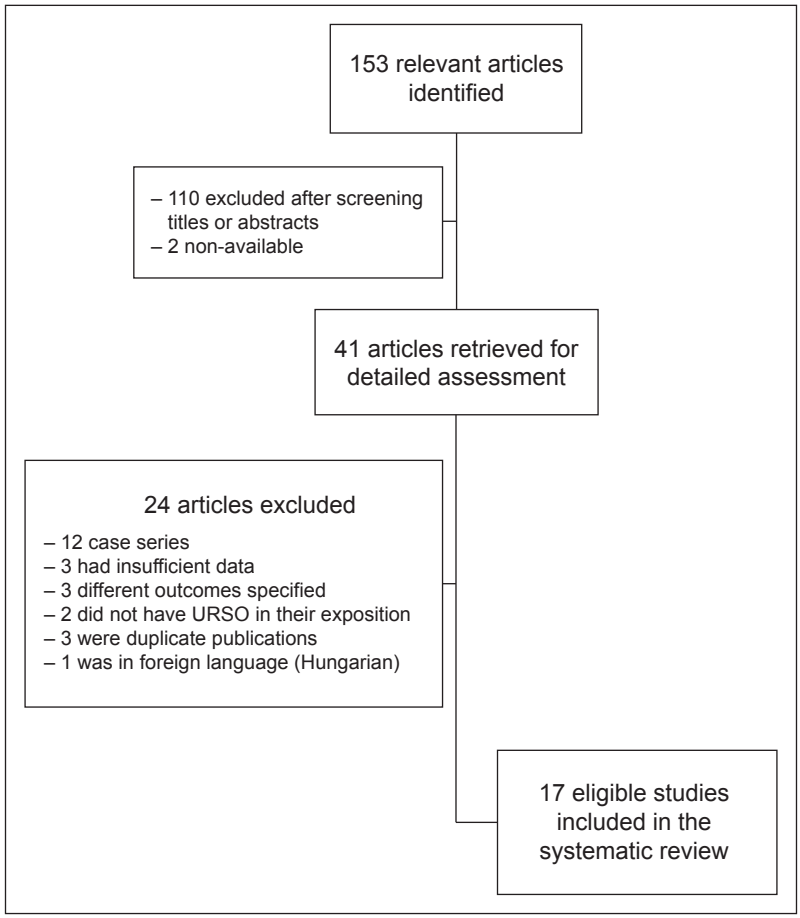
METHODS

We conducted a systematic review of the literature. We searched Medline (Ovid), Embase (Ovid), EMB Reviews, CINAHL (Ebsco), and Web of Knowledge (Thomson Reuters) for studies from 1966 to June 2012. We used the MeSH terms "therapeutics," "cholestasis intrahepatic," "pregnancy," "mothers," "fetus," and non-MeSH terms "ursodeoxycholic acid/therapeutic use," "treatment," "therapy," "cholestasis," "intrahepatic," "maternal," and "fetal." No language restrictions were applied. We later reviewed the reference lists of the primary articles to identify relevant articles not identified in the initial database search.

Two reviewers (M.M. and S.G.M.) screened the titles and abstracts of all publications identified by the initial search. Full-text articles were obtained when abstracts were insufficiently informative. We included all RCTs or NRSs that analyzed the effects of UDCA versus placebo or any other comparator for treatment of ICP in humans. Data from two studies were not available: one had no corresponding author, and the authors of the second study did not respond to our enquiries. Each study had a different definition of ICP, but most included the presence of pruritus and elevated liver enzyme concentrations (aspartate aminotransferase–alanine aminotransferase) during pregnancy. Studies were excluded if they reported case series, were in a language other than French or English (one case report in Hungarian was not included), had insufficient data, used no UDCA in the intervention groups, reported duplicate data, or did not report maternal or fetal outcomes. Each of the reviewers independently compiled her own list of articles to include, and the two lists were then compared. Discrepancies were resolved by discussion.

We used the MOOSE[12] and the PRISMA[13] guidelines to perform our meta-analysis. We extracted data on study design, population (number of patients, maternal age, personal history of ICP, bile acid levels), and the medication and dosages used. We also extracted data on fetal and neonatal outcomes including stillbirth, prematurity (< 37 weeks of gestation), stay in NICU, meconium staining (from amniotic fluid), neonatal respiratory distress (defined as a need for positive pressure ventilation at birth), intrauterine growth restriction (IUGR; fetal weight

Figure 1. Flow diagram of the article selection process



below the 10th percentile for gestational age), birth weight, gestational age, and maternal outcomes (improvement of pruritus, improvement of liver function, spontaneous delivery, and Caesarean section).

The internal validity of each study was assessed by using the validity criteria of the U.S. Preventive Services Task Force, which rates quality of evidence as poor, fair, or good on the basis of a set of criteria according to the study design.[14]

Data concerning participants' characteristics were summarized using means and percentages. No formal statistical tests were done to compare results, as individual patient data were not available from all trials. Pooled risk ratios and weighted mean differences and their 95% confidence intervals for outcomes were obtained using the meta-analysis commands of Stata 11 (StataCorp LLP, College Station, TX).

Heterogeneity was assessed by the use of the I-squared statistic. Random effects were used for all meta-analyses, as each of the studies was conducted in different populations. We presented a pooled estimate for data from RCTs and NRSs. Pooled results from RCTs and NRSs must be viewed with caution because of crucial differences in design, but some authors consider this approach to be acceptable.[15]

RESULTS

The results of the literature search are shown in Figure 1. Forty-one articles were retrieved for detailed assessment. Seventeen studies were included in the analysis: 11 RCTs and six NRSs, for a total of 836 pregnancies. The definition of ICP was approximately the same in every article: pruritus with elevated liver enzyme levels and bile acids. However, the level of bile acids needed for the diagnosis differed.

The studies' characteristics and internal validity assessment are shown in Table 1. UDCA was compared with placebo, dexamethasone, S-adenosylmethionine, cholestyramine, no treatment, or antihistamine. Among the RCTs, only two studies were of good quality.[16,17] Four studies had fair quality: the inclusion or exclusion criteria data were

Table 1. Characteristics of the studies included in the review

Randomized controlled studies					
Author	Double blinding/ randomization/ intent-to-treat	Number of pregnancies (on UDCA)	Comparator	Outcomes	Quality
Diaferia et al. 1996[10]	Yes/Not specified/No	16 (8)	Placebo	Stillbirth, prematurity, birth weight, pruritus, bile acids, liver function, gestational age, CS	Poor
Glantz et al. 2005[16]	Yes/Allocation blocks/ Yes	130 (47)	Dexamethasone or placebo	Stillbirth, prematurity, meconium staining, neonatal respiratory distress, pruritus, bile acids, liver function, spontaneous delivery	Good
Chappell et al. 2012 [17]	Yes/Computer generated/ Yes	111 (56)	Placebo	Stillbirth, prematurity, NICU, meconium staining, birth weight, pruritus, bile acids, liver function, gestational age, spontaneous delivery, CS	Good
Binder et al. 2006[18]	No/Sealed envelopes/No	78 (25)	SAMe, UDCA + SAMe	Stillbirth, prematurity, NICU, meconium staining, neonatal respiratory distress, IUGR, birth weight, pruritus, bile acids, liver function, gestational age, spontaneous delivery, CS	Fair
Roncaglia et al. 2004[19]	No/Computer-generated random number tables/No	46 (24)	SAMe	Stillbirth, prematurity, NICU, meconium staining, IUGR, birth weight, pruritus, bile acids, liver function, gestational age, CS	Fair
Kondrackiene et al. 2005[20]	No/Sealed envelopes/ Yes	84 (42)	Cholestyramine	Stillbirth, prematurity, pruritus, bile acids, liver function, gestational age, CS	Fair
Palma et al. 1997[21]	Yes/Coded boxes/No	15 (8)	Placebo	Stillbirth, prematurity, IUGR, birth weight, pruritus, liver function, gestational age, CS	Fair
Floreani et al. 1996[22]	No/Closed envelope/No	20 (10)	SAMe	Stillbirth, prematurity, birth weight, pruritus, bile acids, liver function, gestational age, CS	Poor
Nicastri et al. 1998[23]	No/Random permuted blocks/No	32 (8)	SAMe, UDCA+ SAMe, placebo	Stillbirth, prematurity, IUGR, pruritus, bile acids, liver function	Poor
Liu et al. 2006[24]	No/Not specified/No	68 (38)	Placebo	Stillbirth, prematurity, meconium staining, birth weight, pruritus, bile acids, liver function, spontaneous delivery, CS	Poor
Isla et al. 1996[25]	No/Not specified/Yes	25 (13)	Placebo	Stillbirth, pruritus, liver function	Poor
Non-randomized studies					
Author	Study design	Number of pregnancies (on UDCA)	Comparative groups	Outcomes	Quality
Zapata et al. 2005[26]	Retrospective cohort	48 (32)	Historic control group	Stillbirth, prematurity, IUGR, birth weight, pruritus, liver function, gestational age, bile acids, CS	Poor
Mazzella et al. 2001[27]	Prospective cohort	30 (20)	Non-treated	Stillbirth, meconium staining, pruritus, liver function, gestational age	Poor
Milkiewicz et al. 2003[28]	Retrospective cohort	81 (57)	Non-treated	Pruritus, liver function	Fair
Rodrigues et al. 1999[29]	Prospective cohort	16 (9)	Non-treated	Stillbirth, meconium staining, birth weight, bile acids, liver function, gestational age	Poor
Laifer et al. 2001[30]	Retrospective cohort	20 (8)	Cholestyramine antihistamine, non-treated	Stillbirth, IUGR, liver function, gestational age	Poor
Brites and Rodrigues 1998[31]	Prospective cohort	16 (7)	Non-treated	Stillbirth, meconium staining, birth weight, gestational age, spontaneous delivery, CS	Poor

SAMe: S-adenosylmethionine.

Table 2. Baseline characteristics of patients included in randomized and non-randomized studies

	Randomized controlled trials n = 11	Non-randomized trials n = 6
Number of pregnancies	625	211
Mean maternal age, years*	29.1	27.8
Number of women	554	80
Personal history of ICP, n (%)*	139 (36)	32 (29)
Number of women	388	110
Mean bile acid levels, umol/L*	40.3	47.3
Number of women	585	64
Mean alanine transferase, U/L*	193.5	223.9
Number of women	539	114
Mean aspartate transferase, U/L*	129	103.5
Number of women	293	98

*Differences were not statistically significant.

The number of women in each category is different because of unavailable data.

missing,[18,19] the outcomes were not well specified,[18] or the type of randomization was not well described.[18–20] In some of these there was no intention-to-treat[18,19,21] or there was excessive loss to follow-up,[20,21] as defined by the US Preventive Services Task Force (important differential loss to follow-up or overall high loss to follow-up).[14] The remaining five RCTs were of poor internal validity: there was no blinding, the type of randomization was not well defined,[10,22–25] or the inclusion and exclusion criteria were not well specified.[23] Additionally, in some studies the outcomes were not well specified,[10,22–24] there was no intention-to-treat,[10,22–24] or there was excessive loss to follow-up.[25] The NRSs had poorer internal validity: historical control subjects were used,[26,27] control groups received no treatment,[28–31] or no inclusion and exclusion criteria were defined.[26,27,29,31] Furthermore, the outcomes were not well specified[31] or no follow-up data were described (Table 1).[26,28,30,31]

The characteristics of the women included in RCTs compared with NRSs are shown in Table 2. In RCTs, 625 pregnancies were included compared with 211 in NRSs. The mean age of the patients was similar between RCTs and NRSs (29.1 vs. 27.8). Women included in RCTs were more likely to have a history of ICP (36 vs. 29%). Overall bile acid and liver enzymes levels were comparable.

Assessment of Publication Bias

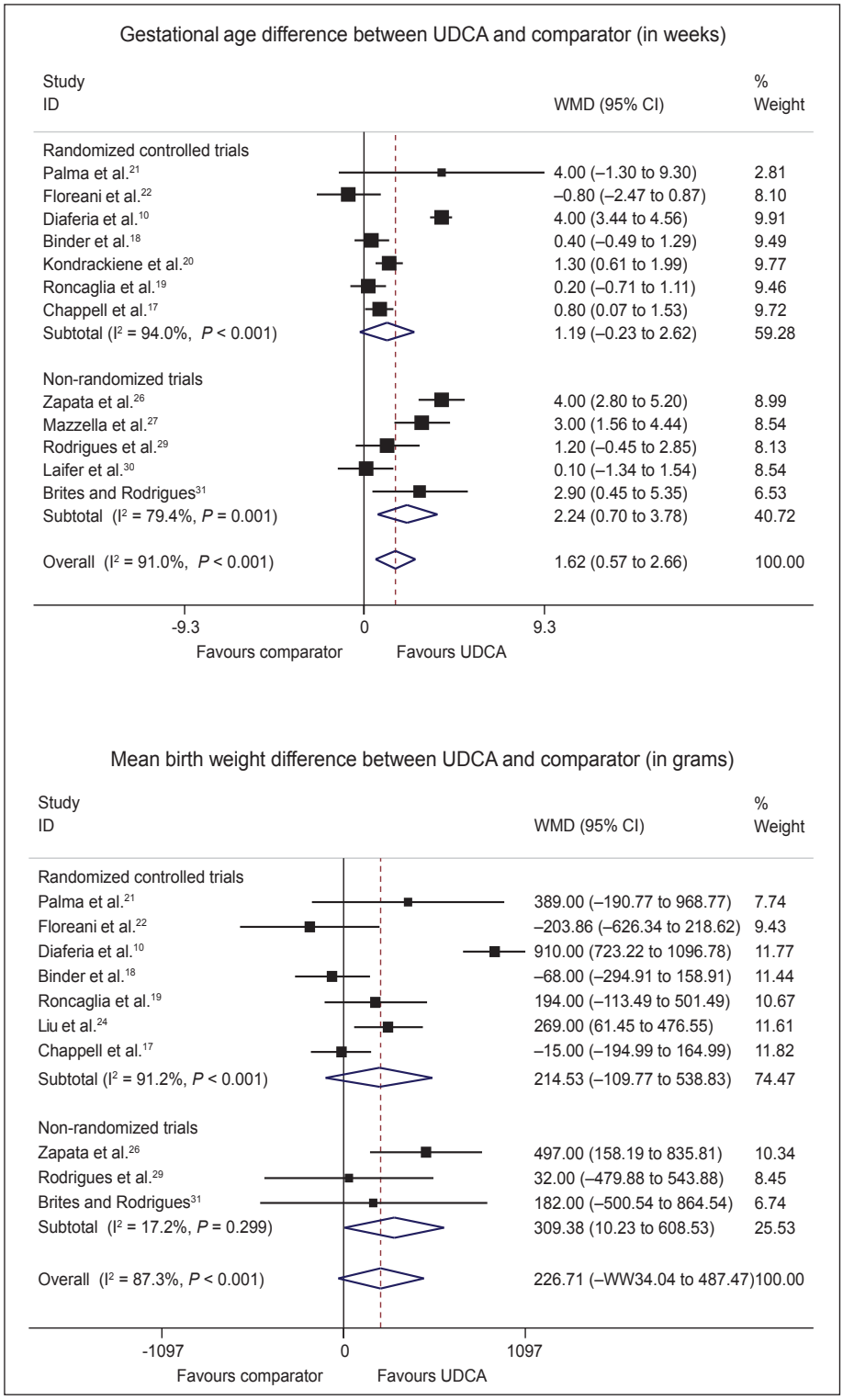
Funnel plots for all meta-analyses presented in Figure 2 are available in online eAppendix 1. No publication bias was evident, although the small number of published studies for some outcomes limited interpretation of the funnel plots. Publication bias did not seem to affect NRSs more than RCTs.

Fetal and Neonatal Outcomes

Neonatal intensive care unit stay was specified in three of 11 RCTs, and in none of six NRSs. There were 11 of 235 admissions to NICU (4.7%) in the UDCA treatment group compared with 24 of 235 (10.2%) in the control group (pooled RR 0.46; 95% CI 0.23 to 0.91, $P = 0.026$). IUGR was specified in four of 11 RCTs and in two of six NRSs, and was seen in six of 66 babies (9.1%) whose mother was treated with UDCA compared with seven of 105 control subjects (6.7%) in RCTs. In NRSs there were no cases of IUGR in two studies including 40 pregnancies with UDCA treatment and 28 pregnancies with the comparator. Respiratory distress was described in two of 11 RCTs and in none of six NRSs. In the UDCA treatment group four of 73 neonates (5.5%) had respiratory distress, compared with 12 of 135 (8.9%) with no treatment (pooled RR 0.63, 95% CI 0.21 to 1.87). There were no stillbirths in 280 pregnancies treated with UDCA in RCTs and two stillbirths in 345 pregnancies treated with comparator in RCTs. In the NRSs there were no stillbirths in 76 pregnancies with UDCA treatment compared with one stillbirth in 54 pregnancies without treatment. Details about the number of each outcome per study are available in online eAppendix 2.

Forest plots for outcomes with sufficient data to provide pooled estimates for RCTs and NRSs are shown in Figure 2. UDCA treatment was associated with less prematurity than other treatments, with a risk ratio of 0.62 (95% CI 0.41 to 0.94) in RCTs and 0.39 (95% CI 0.24 to 0.66) in NRSs (pooled RR 0.57, 95% CI 0.40 to 0.83). No difference was noted between spontaneous and iatrogenic prematurity with the data available. There was a trend

Figure 2. Meta-analysis of adverse outcomes in RCTs and NRSs with UDCA versus comparators



All summaries are from random effect meta-analysis.

WMD: weighted mean difference.

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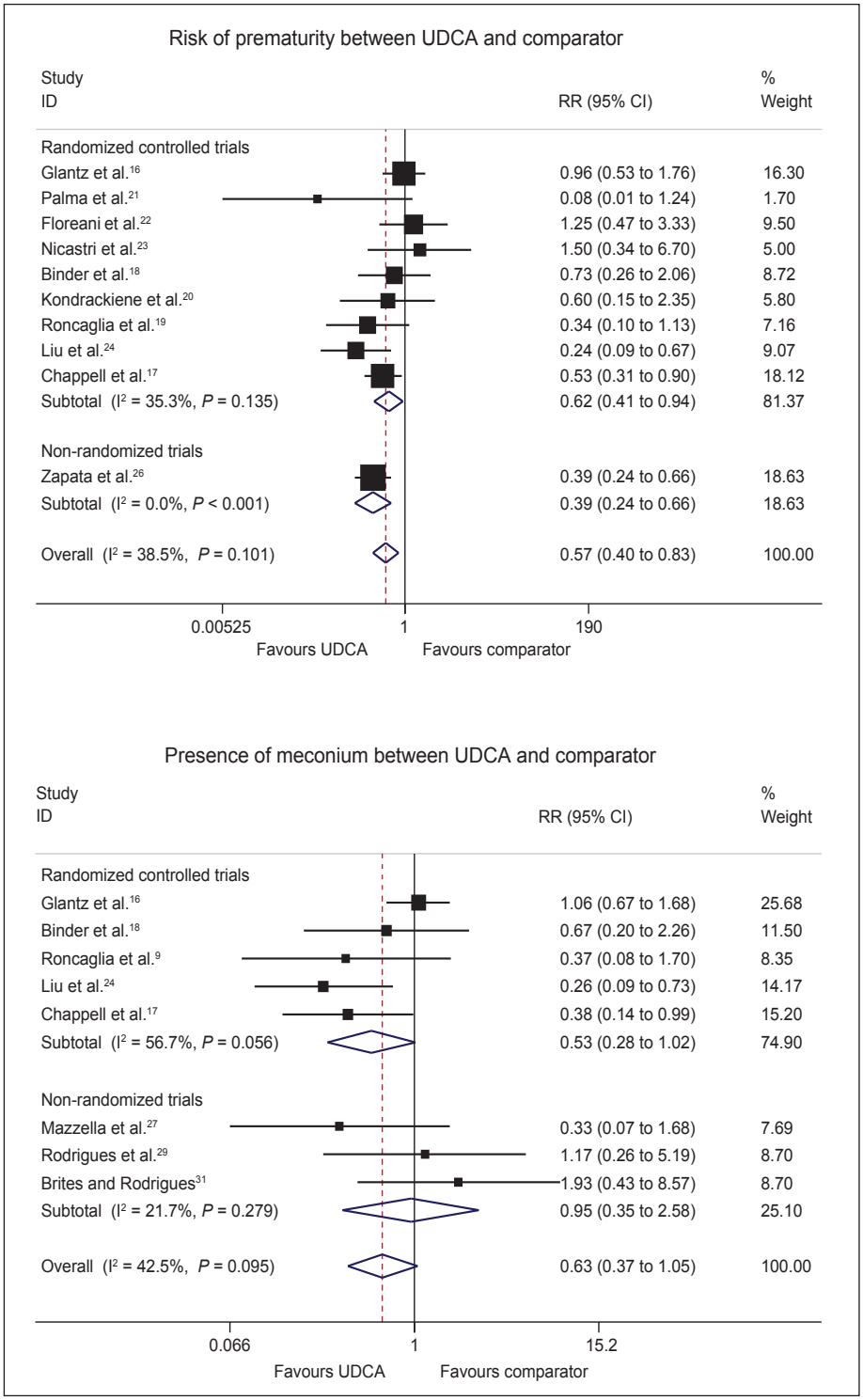
Figure 2. Continued



All summaries are from random effect meta-analysis.

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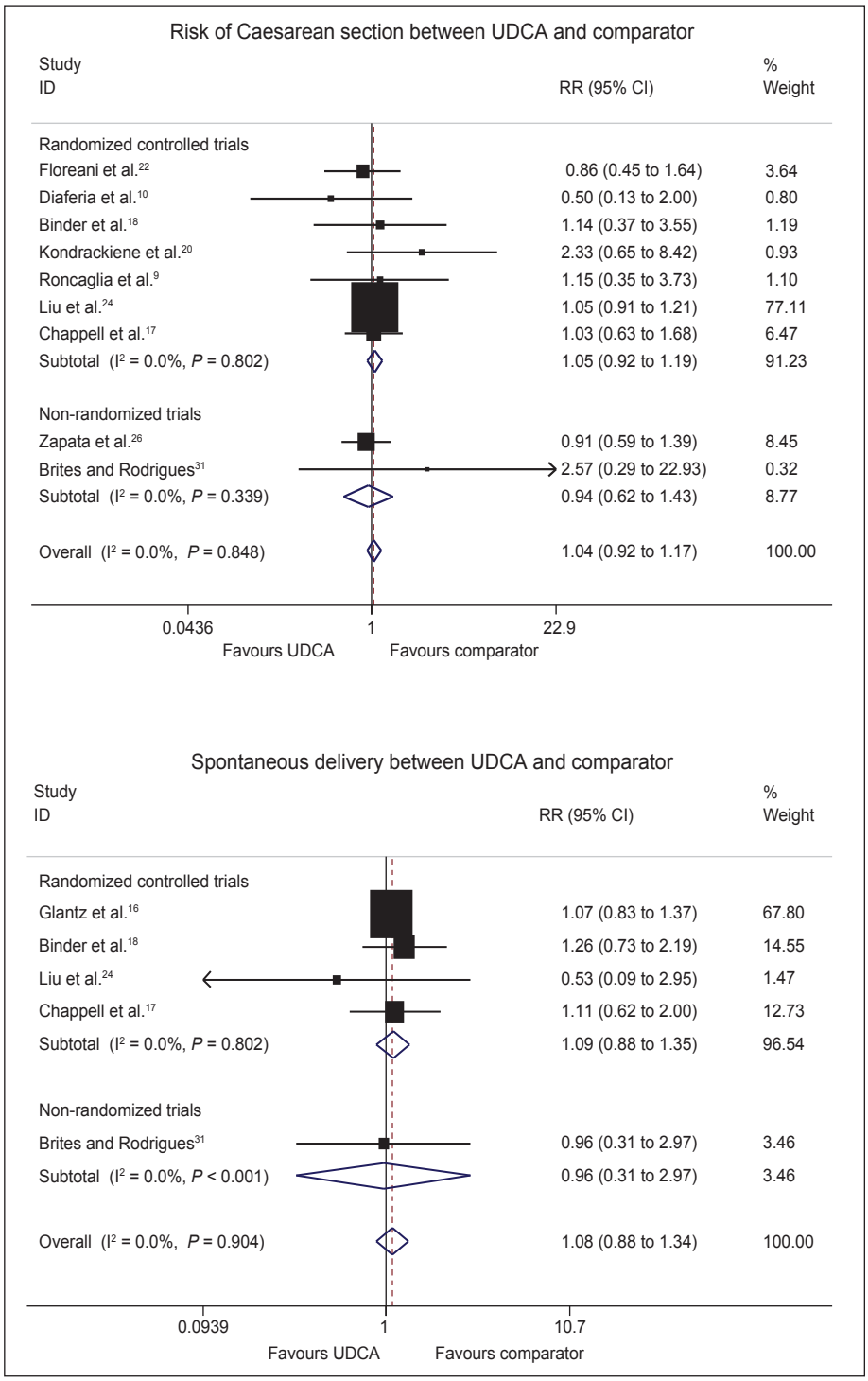
Figure 2. Continued



All summaries are from random effect meta-analysis.

towards an increase in mean birth weight of 214.53 g (95% CI −109.77 to 538.83 g) associated with UDCA in two RCTs. There was an increase in mean birth weight of 309.38 g (95% CI 10.23 to 608.53 g) associated with UDCA in two NRSs (pooled RR 226.71; 95%CI −34.04 to 487.47). There was no difference in rates of meconium staining between the two groups.

Maternal Outcomes

We found no difference in rates of Caesarean section associated with UDCA use (Figure 2).

Results for maternal outcomes such as decrease in pruritus and improvement in liver enzymes could not be pooled due to the paucity of data and the heterogeneity of reporting. Scores used to measure pruritus varied widely. When analyzed separately, eight of 11 RCTs (73%) and all three NRSs (100%) with data on pruritus showed a statistically significant reduction in pruritus with UDCA treatment. There was also a significant improvement in hepatic function with use of UDCA vs. comparators in nine of 11 RCTs (82%) and in all five NRSs (100%) with available data. In four RCTs with available data, spontaneous delivery was achieved in 63 of 167 pregnancies (38%) in UDCA-treated women compared with 90 of 220 pregnancies (41%) treated with comparator (RR 1.09; 95% CI 0.88 to 1.35). Only one NRS reported three of seven spontaneous deliveries (43%) with UDCA and four of nine (44%) with the comparator (RR 0.96; 95% CI 0.31 to 2.97: pooled RR 1.08; 95% CI 0.88 to 1.34). Insufficient data were available to assess bile acid levels post treatment.

Heterogeneity in Meta-analyses

There was significant heterogeneity for the outcomes of gestational age and mean birth weight (P for $I^2 < 0.001$). The study by Diaferia et al.[10] was primarily responsible for the heterogeneity. Repeating the meta-analysis after exclusion of this study did not alter the results (online eAppendix 3).

DISCUSSION

In this meta-analysis examining the use of UDCA in the management of intrahepatic cholestasis of pregnancy, including both RCTs and NRSs, we found that UDCA was associated with improvement in some maternal outcomes (liver function, pruritus) and some fetal and neonatal outcomes (preterm birth, NICU). Use of UDCA is associated with lower rates of prematurity and less frequent use of neonatal intensive care units. There was a trend towards increased birth weight associated with use of UDCA, and use of UDCA was also associated with a reduction in pruritus and improvement in liver function in most studies. However, the rates of Caesarean section, neonatal respiratory distress, and meconium staining were not decreased in women taking UDCA versus comparators.

Meta-analyses such as Cochrane reviews exclude NRSs in their analysis. By analyzing the effect of UDCA treatment in NRSs, we hoped to add to the body of evidence assisting clinicians to make decisions in treating women with ICP. For practical, ethical, and financial reasons, RCTs in obstetrics are difficult to perform; we therefore felt that the analysis of NRSs could be informative for clinicians. We showed that patients' characteristics in these two forms of study were comparable. There was no significant difference between RCTs and NRSs on maternal and fetal/neonatal outcomes with UDCA treatment.

The internal validity of most of the NRSs was of poorer quality, which was usually due to important methodological errors. The study of Isla et al. was available only as an abstract, and because of its low level of evidence, we concluded it was of poor quality.[25] Excluding this study from our analysis does not change our conclusions. This is why we can conclude that results seen in NRSs were consistent with those of RCTs, which should reassure clinicians who use UDCA in the treatment of ICP. We believe that the inclusion of NRSs in this meta-analysis allows a more complete picture of the available evidence.

We found significant heterogeneity between studies, both in study design and as measured by the I-squared statistic. This is probably due to the different populations being studied, the different comparators being used, and differences in the outcome ascertainment. The study showing most heterogeneity in results, by Diaferia et al.,[10] had a very small number of patients (8 in each treatment group). We do not feel that this affected the overall conclusions of our study; repeating the meta-analysis after exclusion of that study did not significantly alter the results.

Our results are comparable to those reported in the Cochrane review.[11] However, we found associations between the use of UDCA and reductions in both prematurity and NICU stay. The Cochrane review included four of the RCTs included in our review.[10,21–23] We added one study[19] that was excluded from the Cochrane review because the completed article was published in 2004 and was available only as an abstract in 2001. We also included three studies that were excluded from the Cochrane review because they were "awaiting assessment."[16,18,20] Three additional studies included in our review included one available only as an abstract,[25] one that was published in 2006,[24] and one published in 2012.[17,] The addition of these studies explains the different findings between our group and the Cochrane review.

Our study is limited by the differing definitions of ICP used among the studies. Additionally, data are missing for some outcomes, and we also included some studies of limited quality. The strength of our study relies on our extensive literature review and data extraction. We believe that our review accurately represents information currently available in the literature.

CONCLUSION

Intrahepatic cholestasis of pregnancy is a pregnancy-related liver disease in which the rates of preterm delivery, fetal distress, and stillbirth are increased. Although UDCA is the treatment most widely used in women with this condition, there is currently no strong recommendation on its effectiveness. By examining all available evidence from both RCTs and NRSs, we sought to present the best available data to guide clinical decisions. We suggest that with the possible benefits of lower rates of prematurity, increased birth weight, reduction of pruritus, improved liver function, and safety, UDCA should be used in the treatment of ICP.

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