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Original Article

Treatment of intrahepatic cholestasis of pregnancy using ursodeoxycholic acid: a meta-analysis

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Abstract: Intrahepatic cholestasis of pregnancy (ICP) is one pregnant-associated complication that is manifested as skin itches, liver dysfunction and elevated bile acid. ICP significantly increases the rate of perinatal death. This study thus performed a systematic analysis for the treatment efficacy of ursodeoxycholic acid (UDCA) on IPC and its effect on pregnancy outcomes. A systematic literature review was performed in both English and Chinese database including PubMed, Cochrane Library, MEDLINE, OVID, CNKI, Wanfang Database, and VIP. All randomly controlled experiments using UDCA for treating ICP until July 2015 were collected for extracting data for quality control. RevMan 5.3 software was then used for meta-analysis. In all 17 RCTs studies involved, meta-analysis indicated the significant improvement of TBA, ALT, skin itches, premature birth and neonatal asphyxia incidence by UDCA as compared to placebo group. However, no significant improvement has been obtained regarding the cesarean section rate and in uteri distress rate by UDCA. The application of UDCA may have satisfactory efficacy in improving biochemical indexes, itch symptom and pregnancy outcomes in ICP patients.

Keywords: Intrahepatic cholestasis of pregnancy, ursodeoxycholic acid, meta-analysis

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is one pregnant-associated complication that is manifested as skin itches, liver dysfunction and elevated bile acid. ICP significantly increases the rate of perinatal death [1]. The incidence of ICP is variable across different regions, with highest rate in Chile and Sweden. In China, Shanghai City and Sichuan Province had the highest frequency of ICP. ICP severely affects the prognosis of perinatal fetus, as it can cause fetal distress, amniotic fluid turbidity, neonatal asphyxia and even perinatal death. The risk of ICP mainly resides in causing pre-mature death, which is closely correlated with the disease severity. Common symptoms of ICP automatically disappear after delivery. However, higher probability of reoccurrence may occur, especially under the oral application of estrogen or re-pregnancy. Currently the major goal of ICP treatment is to improve symptoms including itches, decrease bile acid level, restore liver function, and decrease the rate of neonatal asphyxia and even perinatal death.

Currently available drugs for treating ICP include ursodeoxycholic acid (UDCA), S-adenosine methionine (SAMe), dexamethasone and certain Chinese herbs [2, 3]. UDCA belongs to double hydroxyl bile acid and is widely applied in treating intrahepatic liver diseases. Since 1992, UDCA has become the standard medication for ICP. The mechanism of UDCA mainly includes decreasing bile acid reabsorption, correcting liver-intestine circulation dysfunction, protecting hepatocytes and modulating immune response. Although having remarkable efficacy in treating ICP, further substantiation is required due to inherent different scenarios in these previous studies. This study thus performed a meta-analysis based on all public accessed clinical randomized controlled trials from both China and abroad, in order to investigate the clinical safety and efficacy of UDCA in treating ICP and to provide evidences for drug application.

Materials and methods

Inclusive and exclusive criteria

We retrieved all randomly controlled or clinical control studies. All subjects fitted the diagnostic criteria of ICP [4] including skin itches, elevated total bile acid (TBA), and abnormal amino-

Table 1. General information of included literatures

First author	Year	N	Intervention in control group	N	Intervention in experimental group
Binder T [6]	2006	25	SAMe	26	UDCA, 750 mg/d
Chappell L [14]	2012	55	Placebo	56	UDCA, 1000 mg/d
Diaferia A [7]	1996	8	Placebo	8	UDCA, 600 mg/d, 20 d
Floreani A [8]	1996	10	SAMe	10	UDCA, 450 mg/d
Glantz A [9]	2005	47	Placebo	47	UDCA, 1000 mg/d, 21 d
		36	Dexamethasone		
Kondrackiene J [10]	2005	42	Safety of bile	42	UDCA, 750 mg/d, 14 d
Liu Y [18]	2006	34	Placebo (Vitamin C)	34	UDCA, 900 mg/d, 14 d
Nicastri PL [11]	1998	8	SAMe	8	UDCA, 600 mg/d, 20 d
		8	SAMe+UDCA		
		8	Placebo		
Palma J [12]	1997	7	Placebo	8	UDCA, 1000 mg/d
Roncaglia N [13]	2004	22	SAMe	24	UDCA, 600 mg/d
Joutsiniemi T [15]	2015	60	Dexamethasone	60	UDCA, 800 mg/d, 14 d
		60	Dexamethasone+UDCA		
Grymowicz M [16]	2016	30	SAMe+UDCA	30	UDCA, 600 mg/d, 10 d
Grand'Maison S [17]	2014	30	SAMe+UDCA	30	UDCA, 300 mg/d, 7 d
		30	SAMe		
Estiú MC [21]	2015	70	SAMe+UDCA	70	UDCA, 300 mg/d, 10 d
Zhou F [19]	2014	60	Yinzhihuang+UDCA	60	UDCA, 900 mg/d, 20 d
Geenes V [22]	2014	40	SAMe+UDCA	40	UDCA, 500 mg/d, 10 d
Joutsiniemi T [20]	2014	30	SAMe+UDCA	21	UDCA, 100 mg/d, 10 d
			SAMe	21	

transferase. All those abnormal indicators were restored after delivery. Those patients with liver, gall bladder or skin diseases that may interfere with observed indexes were excluded. Those patients already had treatment were included.

Patients in experimental group received UDCA alone as the treatment. While control group received other medicines including placebo, Safety of bile, dexamethasone, SAMe or non-specific treatment. Those studies using UDCA and other medications in a combined scenario were excluded.

Observation indexes

Serum indexes including TBA, total bilirubin (TBIL), alanine aminotransferase (ALT) and itchy scales [5] were analyzed. The pregnant outcome indexes including premature rate, cesarean section rate, fetal distress rate and neonatal Apgar score were also recorded. Some indexes were excluded due to small sample size.

Literature retrieval

Using "ursodeoxycholic acid (or UDCA)" and "intrahepatic cholestasis of pregnancy (or ICP)" as keywords, both English and Chinese databases including PubMed, Cochrane Library, MEDLINE, OVID, CNKI, Wanfang Database, VIP and CBM were searched to extract relevant literatures until July 2015. Two independent individuals then performed a screening on all studies based on inclusive/exclusive criteria to extract data, which include authors and year, number of cases and intervention measures, pregnant outcomes and indexes. Jadad scale was used for quality control.

Statistical analysis

RevMan 5.3 software was used in meta-analysis on all included data. The homogeneity was firstly tested on all data. Those with homogeneity ($P>0.1$ and $I^2<50\%$) were analyzed in a fixed effect model. While those data with statistical heterogeneity ($P<0.1$ and $I^2>50\%$) were analyzed by random effect model.

Table 2. Jadad scale of inclusive literatures

Inclusive study	Random	Appropriate random	Double blinded?	Appropriate double blinded	Follow-up	Jadad scale
Binder T [6]	Yes (1)	Yes (1)	No (0)	No (0)	No (0)	2
Chappell L [14]	Yes (1)	Yes (1)	Yes (1)	No (0)	No (0)	3
Diaferia A [7]	Yes (1)	No (0)	Yes (1)	Yes (1)	No (0)	3
Floreani A [8]	Yes (1)	No (0)	No (0)	No (0)	No (0)	1
Glantz A [9]	Yes (1)	No (0)	Yes (1)	Yes (1)	No (0)	3
Kondrackiene J [10]	Yes (1)	Yes (1)	No (0)	No (0)	No (0)	2
Liu Y [18]	Yes (1)	No (0)	No (0)	No (0)	No (0)	1
Nicastri PL [11]	Yes (1)	Yes (1)	No (0)	No (0)	No (0)	2
Palma J [12]	Yes (1)	Yes (1)	Yes (1)	Yes (1)	No (0)	4
Roncaglia N [13]	Yes (1)	No (0)	No (0)	No (0)	No (0)	1
Joutsiniemi T [15]	Yes (1)	No (0)	No (0)	No (0)	No (0)	1
Grymowicz M [16]	Yes (1)	Yes (1)	Yes (1)	No (0)	No (0)	3
Grand'Maison S [17]	Yes (1)	Yes (1)	No (0)	No (0)	No (0)	2
Estiú MC [21]	Yes (1)	No (0)	No (0)	No (0)	No (0)	1
Zhou F [19]	No (0)	No (0)	No (0)	No (0)	No (0)	0
Geenes V [22]	Yes (1)	No (0)	No (0)	No (0)	No (0)	1
Joutsiniemi T	Yes (1)	Yes (1)	No (0)	No (0)	No (0)	2

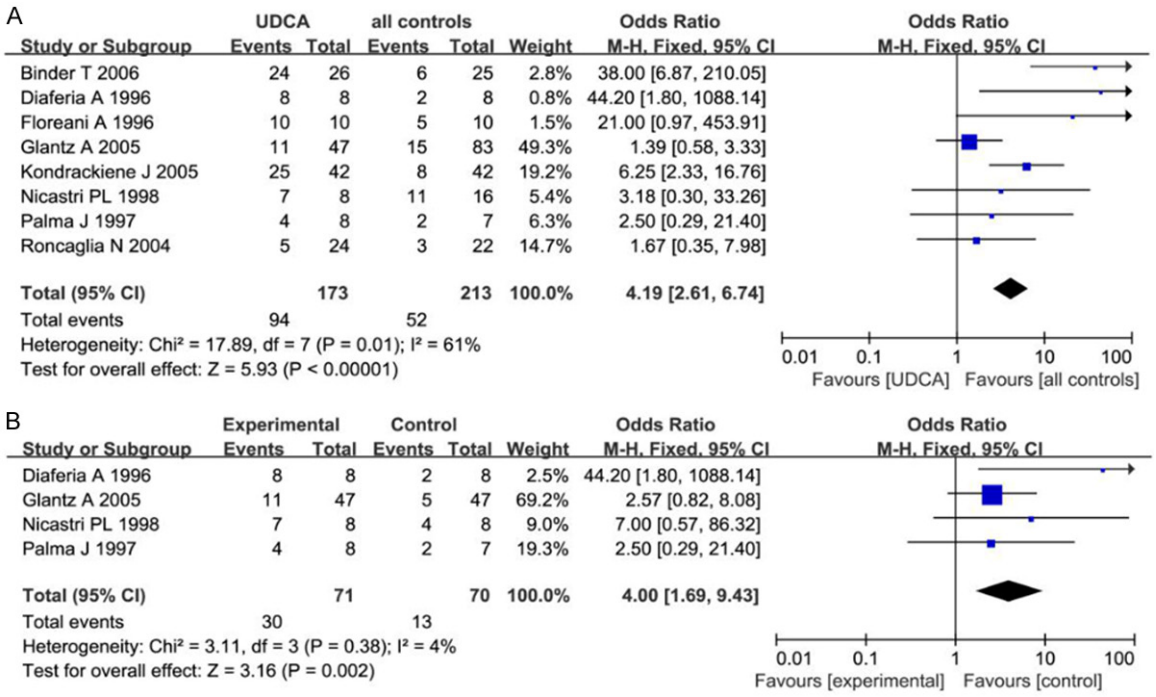

Figure 1. Meta-analysis of TBA. A. P<0.001 compared to control group; B. P<0.01 compared to placebo group.

Results

Literature search

Using online database, there were 18 English literatures screened out. Among those 10 studies were included based on the criteria. After primarily searching on Chinese papers, 65 studies were identified. While only 7 of them were eventually included by the standard. A total of 17 literatures were thus included in this analysis, as shown in **Table 1**.

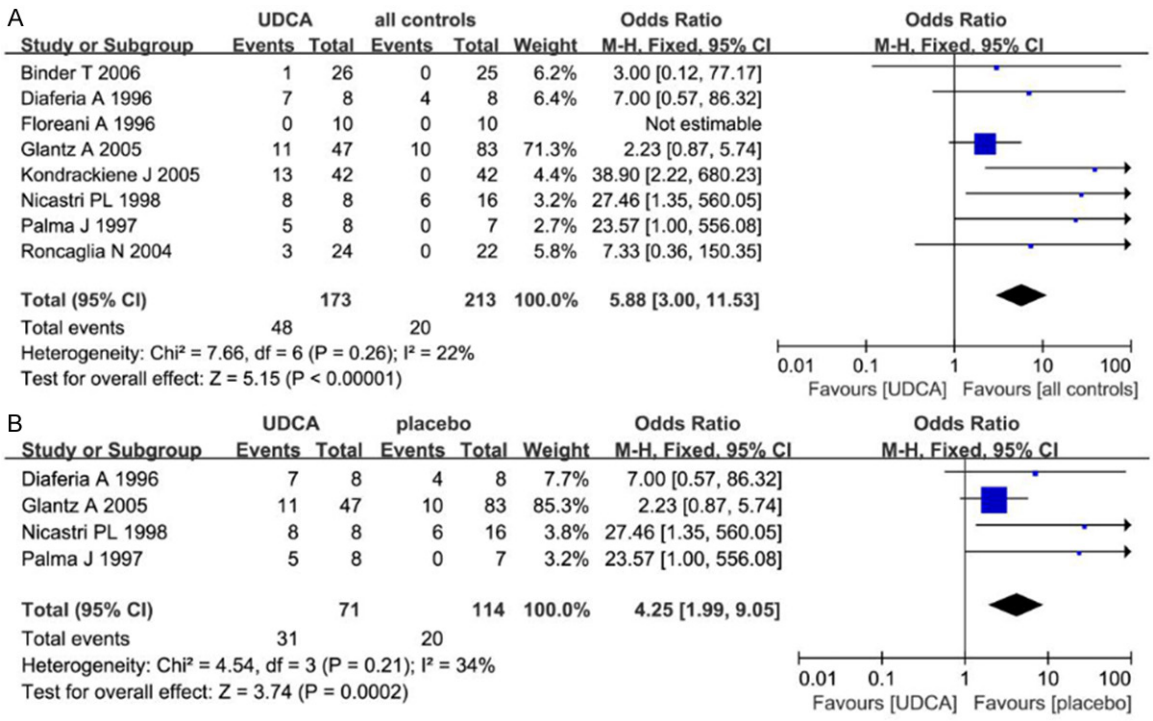

Figure 2. Meta-analysis of ALT. A. P<0.001 compared to control group; B. P<0.001 compared to placebo group.

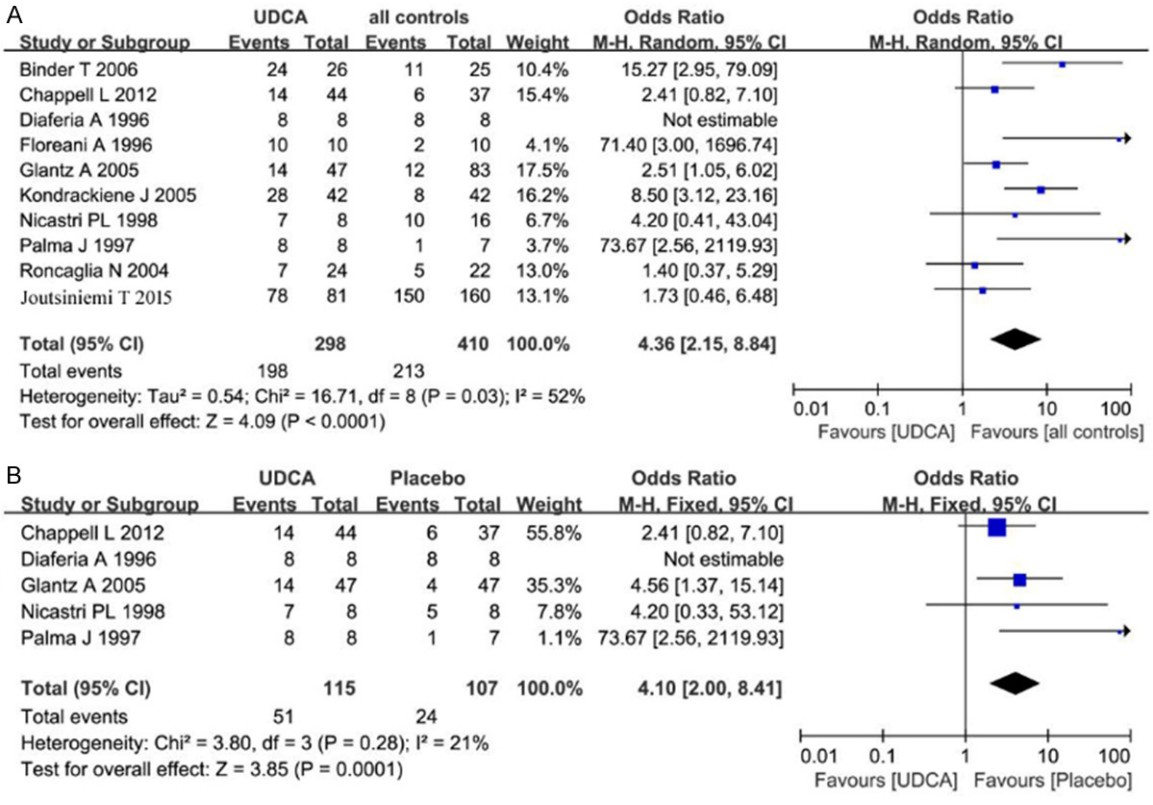

Figure 3. Meta-analysis of skin itches. A. P<0.001 compared to control group; B. P<0.001 compared to placebo group.

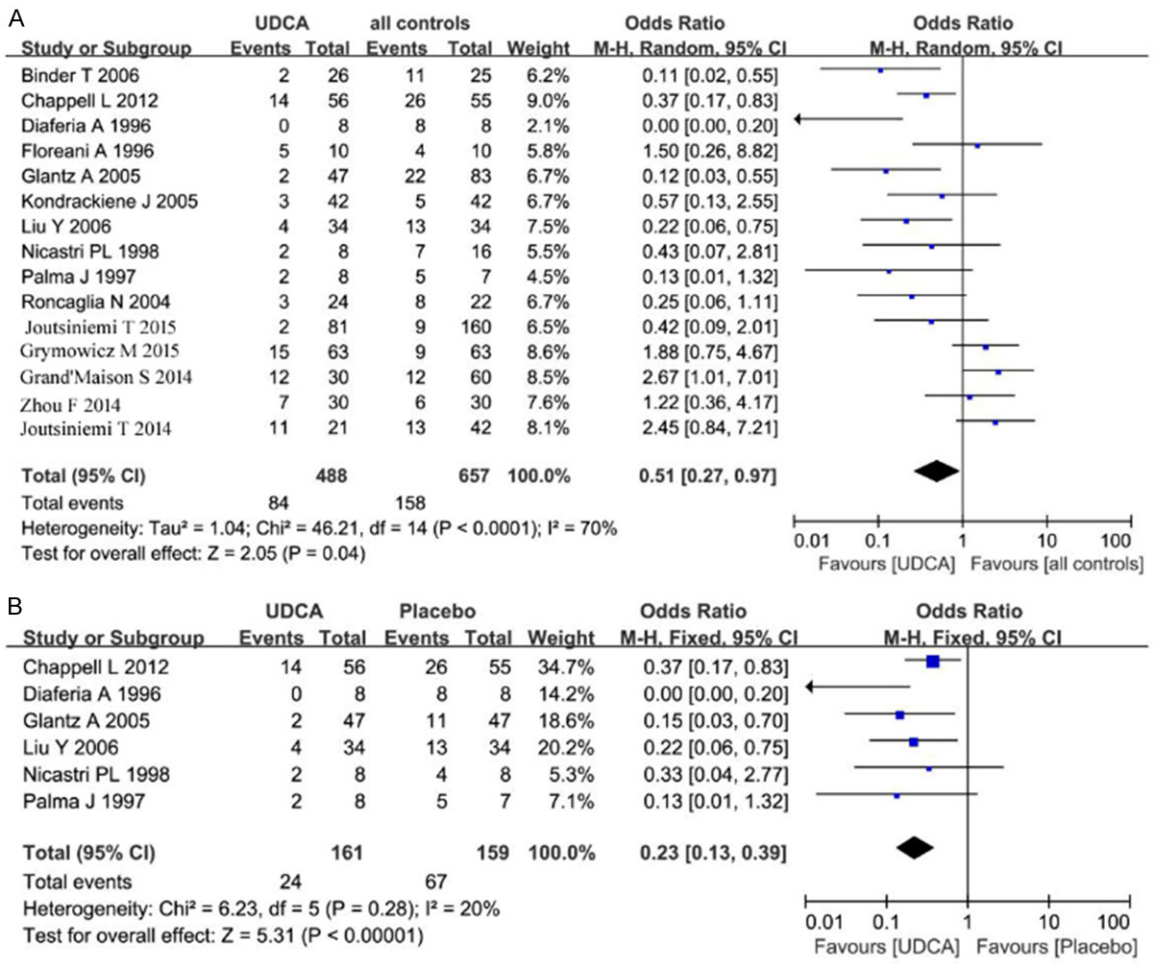

Figure 4. Meta-analysis of pre-mature birth rate. A. P<0.05 compared to control group; B. P<0.001 compared to placebo group.

Quality control

In all 17 inclusive studies, the quality of methodology is variable as shown in **Table 2**. Although 16 out of 17 literatures mentioned "random study", only 8 of them described detailed methodology for random study. Five studies performed blinded method, while 3 of them described the methodology and process of blinded study. Most of studies did not include post-delivery follow-up results. All studies described basal levels, which were statistically indifferent (**Table 2**).

Clinical treatment efficacy

In a total of 8 studies [6-13], the rate of significant improvement of TBA by UCDA was 54.3% (94/173), in contrast to 24.4% (52/213) and 18.6% (13/70) in control and placebo groups. A fixed effect model showed more significantly improved TBA by UDCA compared to control (OR = 4.19, 95% CI = 2.61-6.74, P<0.001) or placebo group (OR = 4.00, 95% CI = 1.69-9.43, P<0.01, **Figure 1**).

In those 8 studies included, the rates of improvement of ALT were 27.7% (48/173), 9.4% (20/213) and 17.5% (20/114) for UDCA, control and placebo groups, respectively. A fixed effect model meta-analysis showed more significant improvement of ALT by UDCA compared to control (OR = 5.88, 95% CI = 3.0011.53, P<0.001) or placebo group (OR = 4.25, 95% CI = 1.999.05, P<0.001, **Figure 2**).

In evaluating skin itches, we recruited 10 studies [6-15]. The rate of improvement of skin itches were 66.4% (198/298), 51.9% (213/410) and 22.4% (24/107) for UDCA, control and placebo groups, respectively. A random effect model meta-analysis showed more significant

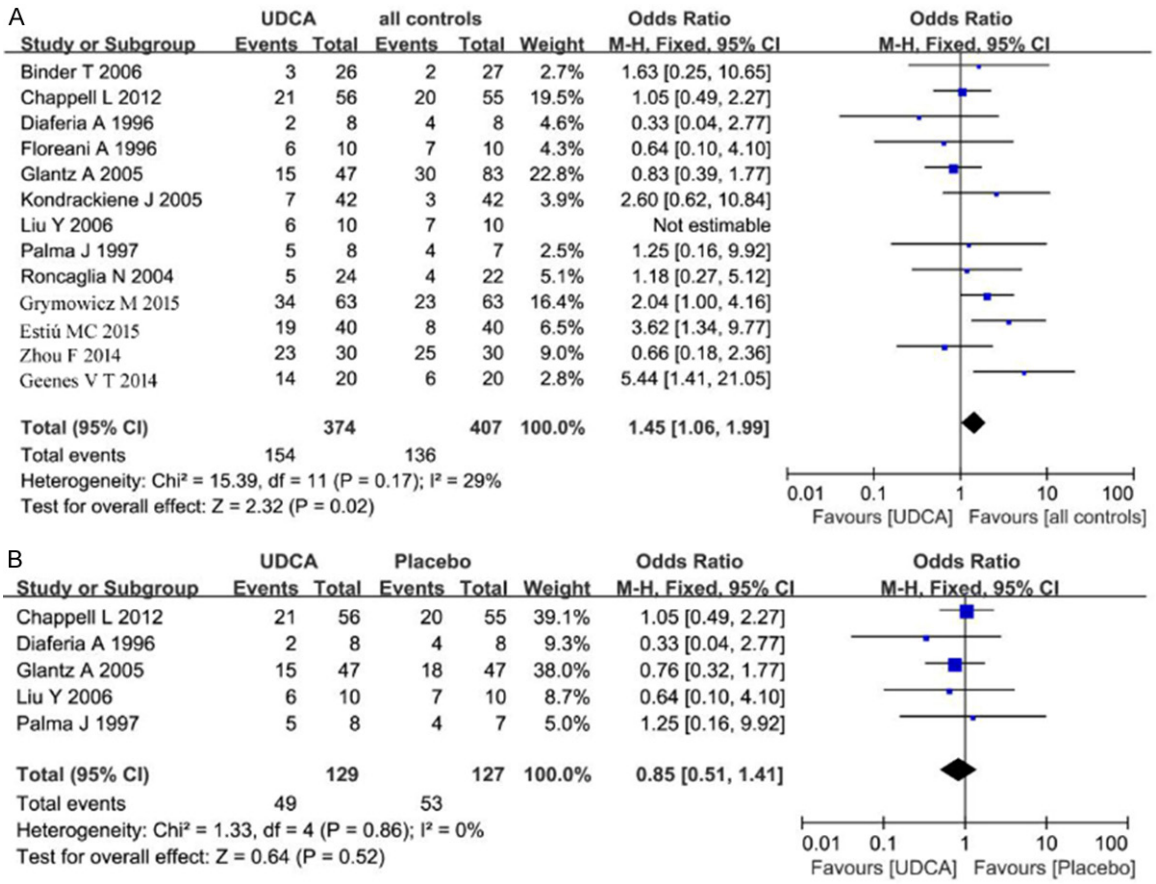

Figure 5. Meta-analysis of cesarean section rate. A. P<0.05 compared to control group; B. P>0.05 compared to placebo group.

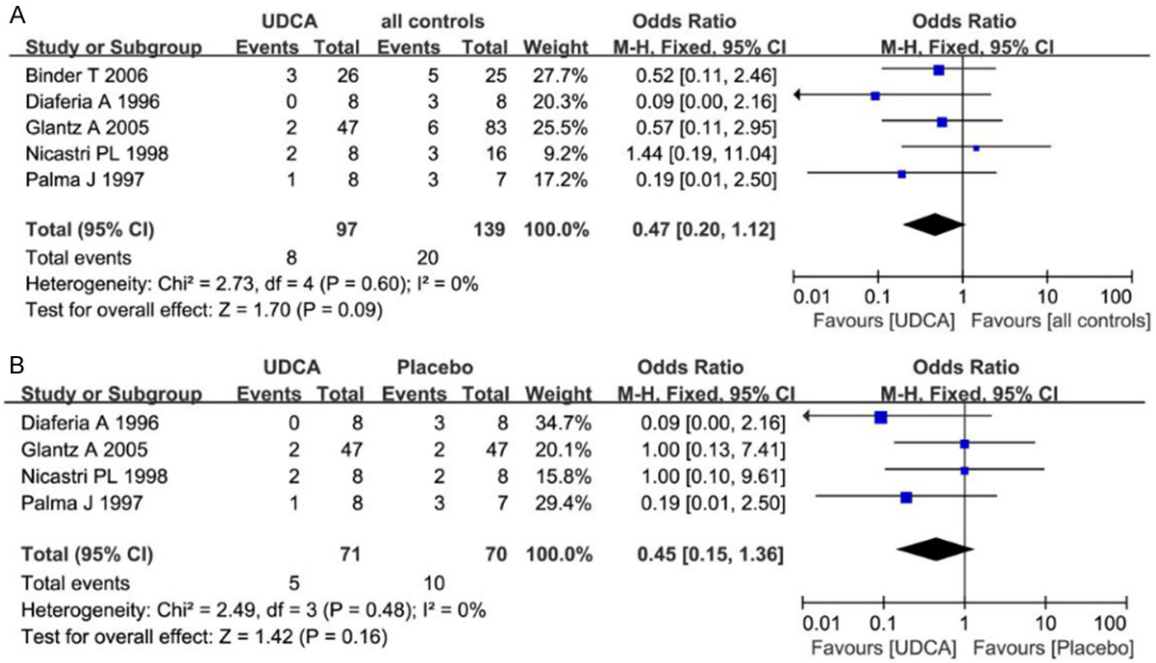

Figure 6. Meta-analysis of in uteri distress rate. A. P>0.05 compared to control group; B. P>0.05 compared to placebo group.

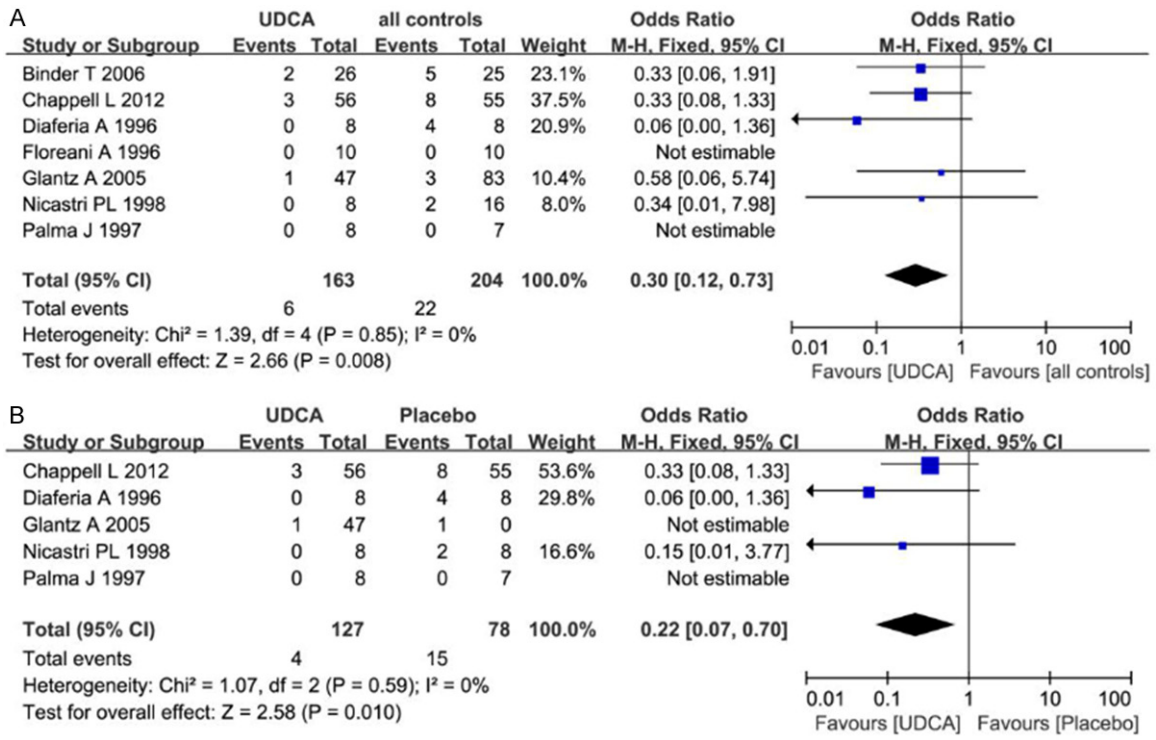

Figure 7. Meta-analysis of apgar score. A. P<0.01 compared to control group; B. P<0.05 compared to placebo group.

improvement of skin itches by UDCA compared to control group (OR = 4.36, 95% CI = 2.158.84, P<0.001). Fixed effect model showed more significant improvement of skin itches by UDCA compared to placebo group (OR = 4.10, 95% CI = 2.008.41, P<0.001, **Figure 3**).

Pregnant outcomes

In a total of 15 studies included [6-20], rate of pre-mature birth were 17.2% (84/488), 24.0% (158/657) and 42.1% (67/159) for UDCA, control and placebo groups, respectively. A random effect model meta-analysis showed more significantly decreased premature birth rate by UDCA compared to control group (OR = 0.51, 95% CI = 0.270.97, P<0.05). Fixed effect model showed more significantly decreased premature birth rate by UDCA compared to placebo group (OR = 0.23, 95% CI = 0.130.39, P<0.001, **Figure 4**).

In a total of 13 studies included [6-10, 12-14, 16, 18, 19, 21, 22] for studying the rate of cesarean section, such rates were 41.2% (154/374), 33.7% (136/407) and 41.7% (53/127) for UDCA, control and placebo groups, respectively. Fixed effect model meta-analysis showed even higher cesarean section rate by UDCA compared to control group (OR = 1.45, 95% CI = 1.061.99, P<0.05) and not significant difference as compared to placebo group (OR = 0.85, 95% CI = 0.511.41, P>0.05, **Figure 5**).

When analyzing the rate of in uteri distress, we analyzed 5 studies [6, 8, 10, 13, 14] and found the rates of in uteri distress were 8.2% (8/97), 14.4% (20/139) and 14.3% (10/70) for UDCA, control and placebo groups, respectively. Fixed effect model meta-analysis showed no significant difference of in uteri distress rate by UDCA compared to control group (OR = 0.47, 95% CI = 0.201.12, P>0.05) or placebo group (OR = 0.45, 95% CI = 0.151.36, P>0.05, **Figure 6**).

We finally studied the neonatal Apgar score in 7 studies [6-9, 11, 12, 14]. The rates of Apgar score less than 7 were 3.7% (6/163), 10.8% (22/204) and 19.2% (15/78) for UDCA, control and placebo groups, respectively. Fixed effect model meta-analysis showed significantly depressed low Apgar score rate by UDCA compared to control group (OR = 0.30, 95% CI = 0.120.73, P<0.01) and placebo group (OR = 0.22, 95% CI = 0.070.70, P<0.05, **Figure 7**).

Discussion

The treatment of IPC using UDCA was firstly reported in 1992 by Palma *et al.*, showing satisfactory efficacy. Current opinions agreed that UDCA can decrease the reabsorption of endogenous bile acid, correct the dysregulation of intestinal-liver cycle of bile salt, and protect hepatocytes in addition to regulate immune functions. Recent clinical trials suggested the satisfactory efficacy of UDCA in treating ICP with less adverse reactions. Whether UDCA can improve the skin itches of ICP, however, is still debated [23, 24]. Previous systematic analysis revealed no significant improvement of serum indexes and skin itches in IPC patients by UDCA. Our meta-analysis, on the contrary, revealed the improvement of serum TBA, ALT and skin itches, lowered pre-mature rate and in uteri distress rate by UDCA when compared to either of control or placebo group. However, UDCA increased the cesarean section rate.

All 17 studies included in this analysis had relatively lower quality of methodology. Although 16 of them mentioned "random" study, only 8 of them described the detailed methods for randomization, suggesting the insufficient randomness of the whole samples. Five studies used blinded study approach, but only 3 of them described the methodology in details, thus may cause selective bias. Due to incomplete information of base line information such as age, severity of ICP, number of fetus, or number of birth, the overall analysis may be affected. Most of these literatures described the treatment efficacy and recordings of UDCA application, but lacked the description of adverse effects; neither did attribution analysis or exclusion analysis.

Overall, this study showed satisfactory treatment efficacy of UDCA in treating ICP by improving serum biochemical indexes, skin itches and pregnant outcomes.

Disclosure of conflict of interest

None.

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