Published online 2016 July 23.

Review Article

Ursodeoxycholic Acid and S-adenosylmethionine for the Treatment of Intrahepatic Cholestasis of Pregnancy: A Meta-analysis

Yang Zhang,^{1,2} Linlin Lu,^{3,4} David W Victor,⁵ Yongning Xin,^{1,2,3,*} and Shiying Xuan^{1,2,3,*}

¹Medical College, Qingdao University, Qingdao, China

²Department of Gastroenterology, Qingdao Municipal Hospital, Qingdao, China

³Digestive Disease Key Laboratory of Qingdao, Qingdao, China

⁴Central Laboratories, Qingdao Municipal Hospital, Qingdao, China

⁵Hepatology and Transplant Medicine, Department of Medicine, Houston Methodist Hospital, Houston, USA

^{*} *Corresponding authors*: Shiying Xuan, Department of Gastroenterology, Qingdao Municipal Hospital, Qingdao, Shandong Province, China. Tel: +86-53288905293, E-mail: xuansydxy@163.com; Yongning Xin, Department of Gastroenterology, Qingdao Municipal Hospital, Qingdao, Shandong Province, China. Tel: +86-53282789463, Fax: +86-53285968434, E-mail: xinyongning@163.com

Received 2016 April 17; Revised 2016 June 22; Accepted 2016 June 28.

Abstract

Context: An optimal therapeutic strategy has not yet been identified for the pharmacological treatment of intrahepatic cholestasis of pregnancy (ICP). The aim of this study was to evaluate the efficacy and safety of ursodeoxycholic acid (UDCA) and S-adenosylmethionine (SAMe) in the treatment of ICP, both individually and in combination.

Evidence Acquisition: A meta-analysis of all randomized controlled trials (RCTs) comparing UDCA, SAMe, and combination therapy was performed. We carried out a literature search using pubmed, embase, the cochrane register of controlled trials, and the science citation index of web of science. The maternal clinical and biochemical responses, including pruritus scores, total bilirubin, total bile acids, alanine aminotransferase, and aspartate transaminase, were evaluated. Safety assessments, including preterm delivery, cesarean section, and meconium-stained amniotic fluid, were also analyzed.

Results: Five RCTs including 311 patients were evaluated. In comparison to SAMe, UDCA significantly reduced the pruritus score (OR = -0.45, 95% confidence interval [CI]: -0.66 to -0.25, P < 0.0001) and improved the levels of total bile acids (TBAs; OR = -0.59, 95% CI: -0.99 to -0.30, P < 0.0001) and alanine aminotransferase (ALT; OR = -0.38, 95% CI: -0.66 to -0.09, P = 0.01). UDCA was associated with significantly lower preterm delivery rates than SAMe (RR = 0.48, 95% CI: 0.32-0.72, P = 0.0004). Interestingly, combination therapy significantly reduced total bilirubin (TB; vs. SAMe, OR = -0.41, 95% CI, -0.74 to -0.08, P = 0.02), aspartate transaminase (AST; vs. UDCA, OR = -0.40, 95% CI, -0.74 to -0.06, P = 0.02), and the rate of preterm delivery (vs. SAMe, OR = 0.62, 95% CI, 0.42 - 0.91, P = 0.02), in comparison with either drug administered alone.

Conclusions: UDCA decreased the pruritus score, TBA, and ALT levels more effectively than SAMe, reducing the rate of preterm delivery for ICP.

Keywords: Ursodeoxycholic Acid, S-Adenosylmethionine, Intrahepatic Cholestasis of Pregnancy

1. Context

Intrahepatic cholestasis of pregnancy (ICP) is a unique hepatic disorder in pregnancy characterized by mild to severe pruritus and disturbed liver function (1-6). ICP is a reversible form of cholestasis occurring mainly in the late second or third trimester of pregnancy, and tends to rapidly resolve after delivery (3, 7, 8). The etiology of ICP is multifactorial and poorly understood; it may be triggered by the cholestatic effects of pregnancy hormones and their metabolites in genetically predisposed women. Multiple factors have been implicated in the pathogenesis of ICP, including environmental influences, nutritional deficiencies, hormonal changes, and genetic variations (9). Although ICP is usually associated with favorable pregnancy outcomes, it may seriously affect the fetus, and it is associated with complications such as premature delivery, meconium-stained amniotic fluid, fetal distress, sudden intrauterine fetal death, stillbirth, and even neonatal death. Thus, women with ICP should be considered high-risk, and the fetus should be carefully monitored during the third trimester. Pharmacological treatment of ICP aims to reduce the maternal symptoms and prevent fetal distress or sudden fetal death (10); however, an optimal therapeutic strategy has not yet been identified. Clinical trials and observational studies conducted over the last 20 years have indicated that ursodeoxycholic acid (UDCA) and S-adenosylmethionine (SAMe) can improve pruritus and serum biochemical abnormalities, further improving perinatal outcomes (11-16). UDCA is a hydrophilic bile acid that detoxifies hydrophobic bile acids, preventing injury to the bile ducts. SAMe is the principal glutathione precur-

Copyright © 2016, Kowsar Corp. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/) which permits copy and redistribute the material just in noncommercial usages, provided the original work is properly cited.

sor and methyl group donor involved in the synthesis of phosphatidylcholine. SAMe not only influences the composition and fluidity of hepatocyte plasma membranes, it also increases the methylation and biliary excretion of hormone metabolites (10). Two previous studies have shown that UDCA and SAMe may have synergistic effects due to their different biochemical mechanisms (17-19). A study by Zhou et al. focused on comparing the effects of UDCA, SAMe, and UDCA + SAMe on the rates of Cesarean section, preterm birth, fetal asphyxia, amniotic fluid pollution, and neonatal weight, but not on the maternal clinical and biochemical responses (20). Therefore, we carried out this meta-analysis to evaluate and compare the efficacy and safety of UDCA and SAMe for the treatment of ICP.

2. Evidence Acquisition

2.1. Identification and Selection of Studies

Relevant studies were identified and selected by searching PubMed (updated to Nov 2015), Embase (1980-November 2015), the cochrane register of controlled trials (Cochrane Library Issue 4, 2015), and the science citation index of web of science (1981-November 2015). The key search terms were "intrahepatic cholestasis of pregnancy," "cholestasis," "pregnancy," "ursodeoxycholic acid," "UDCA," "S-adenosylmethionine," and "SAMe" either alone or in combination with the terms "randomized controlled clinical trials" or "clinical trials". Only English language RCTs were accepted.

The following selection criteria were applied: 1) Study design: randomized or untreated controlled trial; 2) Study population: patients with ICP according to the RCOG green-top guidelines for obstetric cholestasis (21); and 3) Patients received either UDCA, SAMe, or a combination of both throughout the duration of the trial. The decision to include any trial was made by two researchers independently (ZY and YX), and any disagreements were resolved by discussion.

2.2. Study Objective and Definition of End Points

We selected the following eight clinically meaningful parameters to estimate the efficacy and safety of treatment with UDCA, SAMe, or a UDCA + SAMe combination: 1) Pruritus score, 2) Total bile acid (TBA), 3) Total bilirubin (TB), 4) Alanine aminotransferase (ALT), 5) Aspartate transaminase (AST), 6) Preterm delivery, 7) Cesarean section, and 8) Meconium-stained amniotic fluid.

2.3. Quality of Methodology

The methodological quality of the included studies was scored with the Jadad composite scale (Box 1) (22, 23), a five-point quality scale. According to this scale, studies with a score of ≤ 2 are considered low-quality, while those with a score of ≥ 3 are considered high-quality (23, 24). The methodological quality was assessed by two of the authors of the present study (ZY and YX). Each study was given an overall quality score based on the above criteria, then ranked accordingly. Any disagreement was resolved by consensus.

2.4. Statistical Methods

Data was analyzed using the Mantel-Haenszel method (fixed-effect model) or the DerSimonian and Laird method (random-effects model) with the meta-analysis software review manager (RevMan 5.3, Cochrane Collaboration, Oxford, England) (25, 26). The odds ratio (OR) for each clinical event was presented with a 95% confidence interval (CI). Heterogeneity between the trials was tested with χ^2 tests, with a P value of 0.05 indicating significant heterogeneity. The OR for each clinical event was pooled with the fixed-effect model, and if the χ^2 test for heterogeneity was significant, the analysis was also carried out using the random-effects model.

3. Results

3.1. Description of the Selected Studies

A total of 35 studies were identified using our search strategy. Among these studies, we eliminated those that did not fulfill the meta-analysis inclusion criteria, and identified a total of five RCTs comparing UDCA with SAMe (Table 1) (17-19, 27, 28). In one study, a placebo group was used in addition to the UDCA, SAMe, and UDCA + SAMe groups (17). From this study, we included only the data on the UDCA, SAMe, and UDCA + SAMe groups in our analysis. All of the included studies had been published as peerreviewed articles. The main characteristics of these five RCTs are listed in Table 1.

3.2. Maternal Clinical and Biochemical Response

Two studies (17, 19) provided the pruritus scores of the patients; four (17-19, 28) provided the serum TB, TBA, and ALT levels; and three (18, 19, 28) provided the serum AST levels before and after commencement of treatment. The study by Floreani et al. (27), however, did not provide maternal clinical and biochemical response data.

Box 1. Criteria for Grading the Quality of Randomized Controlled Trials: Jadad Score

Study Received a Score of 1 for Each "Yes" Response and 0 for Each "No" Response for Each of the Following Questions:

1. Was the study described as randomized using the words randomly, random, and randomization?

a) An additional point was given if the method of randomization was described and was appropriate (e.g., table of random numbers, computer-generated).

b) A point was deducted if the reported method of randomization was inappropriate (e.g., patients allocated alternately, by birth date, or hospital number).

2. Was the study described as double-blinded?

a) A point was given if the method of blinding was described and was appropriate (e.g., identical placebo).

b) A point was deducted if an inappropriate method of blinding was reported (e.g., comparing placebo tablets with injection).

3. Were the withdrawals and dropouts described?

A maximum of five points could be allocated per study.

Table 1. Characteristics of the Selected Randomized Controlled Trials

Study, y	Country	No. of Patients (UDCA/SAMe/UDCA + SAMe)	UDCA Dose, mg/d	SAMe Dose, mg/d	UDCA + SAMe Dose, mg/d	Planned Treatment Duration	Jadad Quality Score
Floreani (27) 1996	Italy	10/10/Not reported	450	1000	Not reported	Until delivery	3
Nicastri (17) 1998	Italy	8/8/8	600	1000	600 + 1000	20 days	3
Roncaglia (28) 2004	Italy	24/22/Not reported	600	800	Not reported	Until delivery	4
Binder (18) 2006	Czech	26/25/27	750	1000	750 + 1000	Until delivery	3
Zhang (19) 2015	China	41/38/41	1000	1000	1000+1000	14 days	3

3.2.1. Pruritus Score

Inter-trial heterogeneity was found in pruritus scores between UDCA + SAMe vs UDCA and UDCA + SAMe vs. SAMe (UDCA + SAMe vs. UDCA, P = 0.001, I2 = 91%; UDCA + SAMe vs. SAMe, P = 0.009, I2 = 85%), so the random-effects model was used. No heterogeneity was found between the UDCA vs. SAMe treatments (P = 0.40, I2 = 0%); in this case, therefore, a fixed-effects model was used. The meta-analysis demonstrated that the pruritus scores were significantly lower in the UDCA group than in the SAMe group after the treatment (OR = -0.45, 95% CI, -0.66 to -0.25, P < 0.0001). However, the pruritus scores did not differ significantly between the UDCA + SAMe and UDCA treatment groups (OR = 0.32, 95% CI, -0.63 to 1.27, P = 0.51) or the UDCA + SAMe and SAMe groups (OR = -0.07, 95% CI, -0.80 to 0.67, P = 0.86) (Figure 1).

3.2.2. Total Bilirubin

No heterogeneity was found in TB between UDCA and SAMe, UDCA + SAMe and UDCA, and UDCA + SAMe and SAMe (UDCA vs. SAMe, P = 0.88, I2 = 0%; UDCA+SAMe vs UDCA, P = 0.41, I2 = 0%; UDCA+SAMe vs. SAMe, P = 0.19, I2 = 39%); therefore, a fixed-effects model was used. The metaanalysis demonstrated that after the treatment, serum TB levels were significantly lower in the UDCA + SAMe group than in the SAMe group (OR = -0.41, 95% CI, -0.74 to -0.08, P = 0.02). However, serum TB levels did not differ significantly between the UDCA and SAMe groups (OR = -0.25, 95% CI, -0.53 to 0.03, P = 0.08) or the UDCA + SAMe and UDCA groups (OR = -0.19, 95% CI, -0.51 to 0.13, P = 0.25) (Figure 2).

3.2.3. Total Bile Acids

For TBA, inter-trial heterogeneity was found between the UDCA + SAMe and UDCA groups and the UDCA + SAMe and SAMe groups (UDCA + SAMe vs. UDCA, P = 0.02, I2 = 75%) and between the UDCA + SAMe vs. SAMe groups (P = 0.0002, I2 = 88%); therefore, the random-effects model was used. No heterogeneity was found between the UDCA and SAMe groups (P = 0.13, I2 = 47%), and a fixed-effects model was used. The meta-analysis demonstrated that after the treatment, serum TBA levels were significantly lower in the UDCA group than in the SAMe group (OR = -0.52, 95% CI, -0.81 to -0.23, P = 0.0005). However, serum TBA levels did not differ significantly between the UDCA + SAMe and UDCA treatment groups (OR = 0.07, 95% CI, -0.60 to 0.74, P = 0.84) or between the UDCA+SAMe and SAMe treatment groups (OR = -0.44, 95% CI, -1.56 to 0.68, P = 0.44) (Figure 3). Figure 1. Effects of UDCA, SAMe, and UDCA + SAMe on Pruritus Score

A UDCA Mean Difference Mean Difference SAMe Study or Subgroup Mean SD Total Mean SD Total Weight IV, Fixed, 95% CI IV, Fixed, 95% CI Nicastri 1998 -2 0.2645751 8 -1.5 0.2 8 79.5% -0.50 [-0.73, -0.27] -1.12 1.0381233 41 -0.84 1.0114841 38 20.5% -0.28 [-0.73, 0.17] ZHANG 2015 Total (95% Cl) 49 46 100.0% -0.45 [-0.66, -0.25] Heterogeneity: $Chi^2 = 0.72$, df = 1(P = 0.40); $l^2 = 0\%$ -1 -0.5 ò 0.5 1 Test for Overall Effect: Z = 4.35 (P < 0.0001)Favours [Experimental] Favours [Control] В UDCA+SAMe UDCA Mean Difference Mean Difference
 Study or Subgroup
 Mean
 SD
 Total
 Mean

 Nicastri 1998
 -1.2
 0.5
 2
 2.3
 SD Total Weight IV, Random, 95% CI IV, Random, 95% CI -1.2 0.5 8 -2 0.2645751 8 50.3% 0.80 [0.41, 1.19] ZHANG 2015 -1.29 0.9034932 41 -1.12 1.0381233 41 49.7% -0.17 [-0.59, 0.25] Total (95% Cl) 49 49 100.0% 0.32 [-0.63, 1.27] Heterogeneity: Tau²= 0.43, Chi²= 10.92, df = 1 (P = 0.0010); l²= 91% Test for Overall Effect: Z = 0.66 (P = 051) -2 -1 0 Favours [Experimental] Favours [Control] С UDCA+SAMe SAMe Mean Difference Mean Difference Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI IV, Random, 95% CI Nicastri 1998 -1.2 0.5 8 -1.5 0.2 8 50.9% 0.30 [-0.07, 0.67] 41 -0.84 1.0114841 ZHANG 2015 -1.29 0.9034932 38 49.1% -0.45 [-0.87, -0.03] Total (95% Cl) 49 46 100.0% -0.07 [-0.80, 0.67] Heterogeneity: Tau²= 0.24, Chi²= 6.77, df=1 (P = 0.009); l²= 85% 0 2 Test for Overall Effect: Z = 0.18 (P = 0.86)-1 Favours [Experimental] Favours [Control]

A, UDCA and SAMe; B, UDCA + SAMe and UDCA; C, UDCA + SAMe and SAMe.

Figure 2. Effects of UDCA, SAMe, and UDCA + SAMe on total bilirubin

4		LIDCA			SAMe			Std Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV Fixed 95% CI	IV Fixed 95% CI
Binder 2006	-6.9	6 9250054	26	-4.15	6 1 5 3 7 4 9 7	25	76.2%	-0.41 [-0.97 0.14]	
Nicastri 1998	-0.3	0.3230034	20	-4.15	0.1000007.0 0.0	23	20.370	-0.19 [-0.37, 0.14]	
Roncaglia 2004	-0.7	0.4302370	24	-0.5	0.3544362	22	23.9%	-0.10[-1.10, 0.01] -0.31 [-0.89, 0.27]	_
ZHANG 2015	-7 04	12465837	41	-5.1	17 509623	38	41 5%	-0.13[-0.57]0.31]	
2111110 2015	1.04	12.400001	41	0.1	11.505025	00	41.570	0.10[0.01,0.01]	
Total (95% Cl)			99			93	100.0%	-0.25 [-0.53, 0.03]	•
Heterogeneity: Ch	$i^2 = 0.69$	df = 3(P = 0)	1.88).1	$^{2}=0\%$					
Test for Overall Eff	ect: $Z = 1$	1.72 (P = 0.0)	8)	0,0					-2 -1 0 1 2
Test for a relation bit	eeu 2		•)						Favours [Experimental] Favours [Control]
3		UDCA+SA	Me		UDCA		:	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Binder 2006	-9	6.1111292	27	-6.9	6.9250054	26	35.0%	-0.32 [-0.86, 0.22]	
Nicastri 1998	-0.8	0.4	8	-1	0.4582576	8	10.4%	0.44 [-0.56, 1.44]	
ZHANG 2015	-10.78	19.946619	41	-7.04	12.465837	41	54.6%	-0.22 [-0.66, 0.21]	
Total (95% CI)			76			75	100.0%	-0.19 [-0.51, 0.13]	· · · · · · · · · · · · · · · · · · ·
Heterogeneity: Ch	i ² =1.77,	df = 2(P = 0.	.41); l²=	= 0%				-	
Test for Overall Eff	ect: $Z = 1$	1.14 (P = 0.25)	5)						-2 -1 0 1 2
-									ravours [experimental] Favours [control]
-		UDCA+SA	Me		SAMe		5	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Binder 2006	-9	6.1111292	27	-4.15	6.1533487	25	33.8%	-0.78 [-1.34, -0.21]	
Nicastri 1998	-0.8	0.4	8	-0.9	0.6	8	11.2%	0.19 [-0.80, 1.17]	
ZHANG 2015	-10.78	19.946619	41	-5.1	17.509623	38	55.0%	-0.30 [-0.74, 0.14]	
Total (95% Cl)			76			71	100.0 %	-0.41 [-0.74, -0.08]	-
Heterogeneity: Ch	i²= 3.28,	df = 2 (P = 0)	.19); l ²	= 39%				-	
Test for Overall Eff	ect: $Z = 1$	2.42(P=0.0)	02)						Favours [Experimental] Favours [Control]
									ravous [Experimental] ravous [control]

A, UDCA and SAMe; B, UDCA + SAMe and UDCA; C, UDCA + SAMe and SAMe.

A	۱.		UDCA			SAMe			Std. Mean Difference	Std. Mean Difference	
	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI	
	Binder 2006	-39	34.733498	26	-9	29.627016	25	25.2%	-0.91 [-1.49, -0.33]	-#-	
	Nicastri 1998	-14.2	10.709342	8	-19.2	9.3744333	8	8.5%	0.47 [-0.53, 1.47]		
	Roncaglia 2004	-24	18.091487	24	-8.9	34.484018	22	24.2%	-0.55 [-1.14, 0.04]		
	ZHANG 2015	-27.64	43.609333	41	-11.03	22.548508	38	42.1%	-0.47 [-0.92, -0.02]		
	Total (95% Cl)			99			93	100.0 %	-0.52 [-0.81, -0.23]	•	
	Heterogeneity: Chi	² =5.61,	df = 3(P = 0)).13); l²=	= 47%						
_	Test for Overall Effe	ct: Z = 3	.51(P=0.00)	005)						-4 -2 0 2 4 Favours [Experimental] Favours [Control]	
E	3	U	DCA+SAMe			UDCA			Std. Mean Difference	Std. Mean Difference	
_	Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
	Binder 2006	-56	30.810589	27	-39	34.733498	26	34.9%	-0.51 [-1.06, 0.04]		
	Nicastri 1998	-10	8.8605869	8	-39	34.733498	26	26.9%	0.91 [0.09, 1.74]		
	ZHANG 2015	-27.65	39.51506	41	-27.64	43.609333	41	38.2%	-0.00 [-0.43, 0.43]		
	Total (95% Cl)			76			93	100.0%	0.07 [-0.60, 0.74]	-	
	Heterogeneity: Tau	$^{2}=0.26;$	Chi ² =8.00	df = 2	(P = 0.0)	02); l ² =75%			. , .	+ + +	
	Test for Overall Effe	ct: Z = C	0.20(P=0.8)	4)						-4 -2 0 2 Favours [Experimental] Favours [Control]	4
(-					CA1					
	Study or Subgroup	Mean	JCA+SAMe	Total	Mean	SAMe	Total	S Weight	W Pandom 05% CL	W Pandom 05% CI	
-	Binder 1006	Wiean	20.040500	10141	Mean	20.627046	10141	24 GW	1, Kandoni, 95% Ci		
	Nicastri 1008	-50	0.001030	27	10.2	29.02/010	20	34.0%	-1.03 [-2.10, -0.91]		
	ZHANG 2015	-10	20 51 50 5	41	-13.2	3.3744333	20	20.970	0.53 (0.10, 2.00)		
	211/11/0 2015	-27.05	33.31300	41	-11.05	22.340300	50	50.570	-0.01 [-0.00, -0.00]	_	
	Total (95% Cl)			76			71	100.0%	-0.44 [-1.56, 0.68]		
	Heterogeneity: Tau	² = 0.84;	Chi ² =16.97	7, df = 2	2(P = 0.	0002); l ² = 8	38%				
	Test for Overall Effe	ct: Z = 0	0.77 (P = 0.4)	4)						Favours [Experimental] Favours [Control]	-
										ratours [Experimental] Tatours [control]	

Figure 3. Effects of UDCA, SAMe, and UDCA + SAMe on Total Bile Acids

A, UDCA and SAMe; B, UDCA + SAMe and UDCA, C, UDCA + SAMe and SAMe.

3.2.4. Alanine Aminotransferase

For ALT, inter-trial heterogeneity was found between the UDCA + SAMe and SAMe groups (P = 0.01, I2 = 78%), so the random-effects model was used. No heterogeneity was found in the UDCA and SAMe (P = 0.32, I2 = 14%) and UDCA + SAMe and UDCA groups (P = 0.33, I2 = 9%); therefore, a fixed-effects model was used. The meta-analysis demonstrated that after the treatment, serum ALT levels were significantly lower in the UDCA group than in the SAMe group (OR=-0.38, 95% CI, -0.66 to -0.09, P=0.01). However, ALT values did not differ significantly between the UDCA + SAMe and UDCA groups (OR = -0.24, 95% CI, -0.56 to 0.09, P = 0.15) or between the UDCA + SAMe and SAMe treatment groups (OR = -0.48, 95% CI, -1.26 to 0.31, P = 0.23) (Figure 4).

3.2.5. Aspartate Transaminase

For AST, inter-trial heterogeneity was found between the UDCA and SAMe treatment groups (P = 0.002, I2 = 84%) and between the UDCA + SAMe and SAMe treatment groups (P = 0.0002, I2 = 93%); therefore, the random-effects model was used. No heterogeneity was found in AST levels between the UDCA + SAMe and UDCA treatment groups (P = 0.78, I2 = 0%); therefore, the fixed-effects model was used. The meta-analysis demonstrated that after the treatment, serum AST levels were significantly lower in the UDCA + SAMe group than in the UDCA group (OR = -0.40, 95% CI, -0.74 to -0.06, P = 0.02). However, serum AST levels did not differ significantly between the UDCA and SAMe groups (OR = -0.70, 95% CI, -1.49 to 0.09, P = 0.08) or the UDCA + SAMe and SAMe treatment groups (OR = -1.09, 95% CI, -2.55 to 0.36, P = 0.14) (Figure 5).

3.3. Safety Assessment

Of the five studies included in this meta-analysis, four (18, 19, 27, 28) reported the rates of preterm delivery and cesarean section, while three (18, 19, 28) reported the rates of meconium-stained amniotic fluid.

3.3.1. Preterm Delivery

No heterogeneity was found in the rates of preterm delivery between the UDCA and SAMe groups (P = 0.83, I2 = 0%), the UDCA + SAMe and UDCA groups (P = 0.61, I2 = 0%), or the UDCA + SAMe and SAMe groups (P = 0.74, I2 = 0%); therefore, a fixed-effects model was used for the analysis. The meta-analysis showed that after treatment, serum AST levels were significantly lower in the UDCA group than in the SAMe group (OR = 0.48, 95% CI, 0.32-0.72, P = 0.0004), and lower in the UDCA + SAMe group than in the SAMe group

Ire 4. Effects of UDCA, SA	AMe, and								
•									
A		UDCA	T 1 . 1.	SA	Me	C- 4 - 1	147-1-L-C	Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD .	Iotal N	lean	SD .	lotal	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Nicastri 1998	-3	3.3227097	26	-0.82 2.8	340284	25	25.7%	-U.7U [-1.26, -U.13] *	
Roncaglia 2004	-157	183.5027	24	-67 94.	110308	22	23.5%	-0.60 [-1.19, -0.01]	
ZHANG 2015	-127.83	145.90706	41	-107 164	4.46743	38	42.2%	-0.13 [-0.57, 0.31]	
Total (05% Cl)			00			03	100.0%	100.0 33.0 195.0	
Heterogeneity: Chi ²	2 = 3.50. d	f = 3(P = 0.3)	32): $l^2 = 1$	4%		33	100.076	-0.58 [-0.00, -0.05]	
Test for Overall Effe	ct: $Z = 2.5$	6(P=0.01)							-I -0.5 0 0.5 I Favours [Experimental] Favours [Control]
3	TI	DCA+SAMe		П	IDCA			Std Mean Difference	Std Mean Difference
Study or Subgroup	Mean	SD T	fotal M	ean	SD T	otal V	Weight	IV. Fixed. 95% CI	IV. Fixed, 95% CI
Binder 2006	-4.9	3.5993888	27	-3 3.	3227397	26	34.3%	-0.54 [-1.09, 0.01]	•
Nicastri 1998	-36.5	37.7	8	-43.8 25	5.949759	8	10.7%	0.21 [-0.77, 1.20]	
ZHANG 2015	-147.42	144.7621	41 -1	127.83 14	45.90706	41	55.0%	-0.13 [-0.57, 0.30]	
Total (95% Cl)			76			75	100.0%	-0.24 [-0.56, 0.09]	•
Heterogeneity: Chi ²	² = 2.19, df	= 2 (P = 0.3)	3); l²= 9	%					-2 -1 0 1 2
Test for Overall Effe	ct: $Z = 1.4$	4(P=0.15)							Favours [Experimental] Favours [Control]
-	IID)CA+SAMe		SA	Me			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD T	otal M	ean	SD T	otal V	Veight	IV, Random, 95% CI	IV, Random, 95% CI
Binder 2006	-4.9	3.5993888	27	-0.82 2.8	233137	25	35.2%	-1.24 [-1.83, -0.64]	
Nicastri 1998	-36.5	37.7	8	-43.9 25.	340284	8	26.1%	0.22 [-0.77, 1.20]	
2114103 2015	-147.42	144.7621	41	-107 164	4.40/43	38	38.1%	-0.26 [-0.70, 0.18]	270
Total (95% Cl)			76			71	100.0%	-0.48 [-1.26, 0.31]	
Hotopogopoitry Tau?									
Test for Overall Effe	² = 0.36; C ect: Z = 1.19 + SAMe an	$hi^2 = 9.01, d$ P = 0.23)	If= 2 (P = UDCA + S)	= 0.01); l ² : SAMe and	= 78%				-2 -1 0 1 2 Favours [Experimental] Favours [Control]
Test for Overall Effe	² = 0.36; C ct: Z = 1.19 + SAMe an	Chi ² = 9.01, d (P= 0.23)	If= 2 (P =	= 0.01); l ² :	= 78%				-2 -1 0 1 2 Favours [Experimental] Favours [Control]
Test for Overall Effect	² = 0.36; C ct: Z = 1.19 + SAMe an AMe, and U	.hi²=9.01, d) (P=0.23) d UDCA, C, 1 JDCA + SAM	UDCA+:	= 0.01); l ² : SAMe and Partate Tra SAM	= 78% SAMe. Insamina Me	se		td. Mean Difference	-2 -1 0 1 2 Favours [Experimental] Favours [Control]
reterogenery: Idu Test for Overall Effect ICA and SAMe, B, UDCA	² = 0.36; C ct: Z = 1.19 + SAMe an AMe, and T	Li ² = 9.01, d (P= 0.23) JDCA, C, 1 JDCA + SAM	UDCA + : e on Asp	= 0.01); I ² - SAMe and Partate Tra SAM	SAMe.	se otal V	S Weight	td. Mean Difference IV, Random, 95% CI	-2 -1 0 1 2 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Random, 95% CI
reterogenery: Idu Test for Overall Effect CA and SAMe, B, UDCA re 5. Effects of UDCA, S/ Study or Subgroup Binder 2006 Nicastri 1998	⁴ = 0.36; C ct: Z = 1.19 + SAMe arr AMe, and I U <u>Mean</u> -2.52 1	Li ² = 9.01, d (P= 0.23) Id UDCA, C, 1 JDCA + SAMA JDCA <u>SD T</u> .5977171	$\frac{1}{2}$	= 0.01); I ² - SAMe and Partate Tra SAM ean 0.08 1460 4 74	= 78% SAMe. Insamina Me <u>SD T</u> 1.78 26322	se fotal N 25	S Weight 32.0%	td. Mean Difference IV, Random, 95% CI -1.42 [-2.04, -0.80] -0.67 [-1.27 - 0.07]	-2 -1 0 1 2 Favours [Experimental] Favours [Control]
CA and SAMe, B, UDCA CA and SAMe, B, UDCA re 5. Effects of UDCA, S/ Study or Subgroup Binder 2006 Nicastri 1998 ZHANG 2015	⁴ = 0.36; C ct: Z = 1.19 + SAMe arr AMe, and I <u>Mean</u> -2.52 1 -271 1 -81.41 9	hi²=9.01, d (P= 0.23) id UDCA, C, 1 JDCA + SAM JDCA <u>SD T</u> 5977171 54.20441 1.157094	UDCA + : e on Asp otal M 26 24 41 - 7	= 0.01); I ² - SAMe and partate Tra SAM ean 0.08 -160 171 4.39 124	= 78% SAMe. Insamina Me <u>SD T</u> J.78 .36333 .61966	se otal V 25 22 38	S Weight 32.0% 32.5%	td. Mean Difference IV, Random, 95% CI -1.42 [-2.04, -0.80] -0.67 [-1.27, -0.07] -0.06 [-0.51, 0.38]	-2 -1 0 1 2 Favours [Experimental] Favours [Control]
CA and SAMe, B, UDCA CA and SAMe, B, UDCA re 5. Effects of UDCA, S/ Study or Subgroup Binder 2006 Nicastri 1998 ZHANG 2015	² = 0.36; C ct: Z = 1.19 + SAMe ar AMe, and I Mean -2.52 1 -271 1 -81.41 9	hi²= 9.01, d) (P= 0.23) id UDCA, C, 1 JDCA + SAM JDCA <u>SD T</u> 5977171 54.20441 1.157094	UDCA + 1 e on Asp otal M 26 - 24 41 - 7	= 0.01); I ² - SAMe and bartate Tra bartate Tra SAM ean 0.08 -160 171 4.39 124	= 78% ISAMe. Insamina Me SD T 1.78 .36333 .61966	se otal V 25 22 38	S <u>Weight</u> 32.0% 32.5% 35.5%	td. Mean Difference IV, Random, 95% Cl -1.42 [-2.04, -0.80] -0.67 [-1.27, -0.07] -0.06 [-0.51, 0.38]	-2 -1 0 1 2 Favours [Experimental] Favours [Control]
CA and SAMe, B, UDCA CA and SAMe, B, UDCA re 5. Effects of UDCA, S/ Study or Subgroup Binder 2006 Nicastri 1998 ZHANG 2015 Total (95% Cl)	² = 0.36; C ct: Z = 1.19 + SAMe ar AMe, and I <u>Mean</u> -2.52 1 -271 1 -81.41 9	Li ² = 9.01, d (P= 0.23) Lid UDCA, C, 1 UDCA + SAMA JDCA <u>SD T</u> .5977171 54.20441 1.157094 bi ² = 12.42	UDCA + 1 e on Asp otal M 26 - 24 41 - 7 91	= 0.01); I ² - SAMe and bartate Tra bartate Tra SAM can 0.08 -160 171 4.39 124 P = 0.002	= 78% SAMe. Insamina Me SD T 1.78 .36333 .61966	se 25 22 38 85	S Weight 32.0% 32.5% 35.5% 100.0 %	td. Mean Difference IV, Random, 95% Cl -1.42 [-2.04, -0.80] -0.67 [-1.27, -0.07] -0.06 [-0.51, 0.38] - 0.70 [-1.49, 0.09]	-2 -1 0 1 2 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Random, 95% CI
CA and SAMe, B, UDCA CA and SAMe, B, UDCA e 5. Effects of UDCA, S/ Study or Subgroup Binder 2006 Nicastri 1998 ZHANG 2015 Total (95% Cl) Heterogeneity: Tau ² Test for Overall Effec	$f^2 = 0.36$; C ct: Z = 1.19 + SAMe an AMe, and U -2.52 1 -271 1 -81.41 9 $f^2 = 0.41$; C ct: Z = 1.73	hi ² = 9.01, d (P = 0.23) hd UDCA, C, UDCA + SAM JDCA 5977171 54.20441 11.157094 hi ² = 12.42, (P = 0.08)	$\frac{1}{1} = 2 (P = 1)^{1}$	= 0.01); I ² - SAMe and bartate Tra 0.08 1-60 171 4.39 124 P = 0.002	= 78% SAMe. Insamina SD T 1.78 .36333 .61966	se 25 22 38 85	S Weight 32.0% 32.5% 35.5% 100.0 %	td. Mean Difference IV, Random, 95% Cl -1.42 [-2.04, -0.80] -0.67 [-1.27, -0.07] -0.06 [-0.51, 0.38] - 0.70 [-1.49, 0.09]	-2 -1 0 1 2 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Random, 95% CI
CA and SAMe, B, UDCA CA and SAMe, B, UDCA e 5. Effects of UDCA, S/ Study or Subgroup Binder 2006 Nicastri 1998 ZHANG 2015 Total (95% Cl) Heterogeneity: Tau ² Test for Overall Effect	2 = 0.36; C ct: Z = 1.19 + SAMe and U AMe, and U -2.52 1 -271 1 -271 1 -81.41 9 2 = 0.41; C ct: Z = 1.73	hi ² = 9.01, d (P= 0.23) hd UDCA, C, UDCA + SAM JDCA 5977171 54.20441 11.157094 hi ² = 12.42, ; (P = 0.08)	$\frac{1}{1} = 2 (P = 1)^{1}$	= 0.01); I ² - SAMe and Partate Tra 0.08 -160 171 4.39 124 P = 0.002	SAMe. Isamina Me <u>SD T</u> 1.78 .36333 .61966 (); l ² = 84%	se otal V 25 22 38 85 6	S Weight 32.0% 32.5% 35.5% 100.0 %	td. Mean Difference IV, Random, 95% Cl -1.42 [-2.04, -0.80] -0.67 [-1.27, -0.07] -0.06 [-0.51, 0.38] - 0.70 [-1.49, 0.09]	Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control]
CA and SAMe, B, UDCA CA and SAMe, B, UDCA re 5. Effects of UDCA, S/ Study or Subgroup Binder 2006 Nicastri 1998 ZHANG 2015 Total (95% Cl) Heterogeneity: Tau ² Test for Overall Effect Study or Subgroup	² = 0.36; C ct: Z = 1.19 + SAMe and U AMe, and U -2.52 1 -271 1 -21.17 2 = 0.41; C ct: Z = 1.73 UD0 Mean	Lini2 = 9.01, d (P = 0.23) Linu UDCA, C, (UDCA + SAMA JDCA 5977171 54.20441 11.157094 Chi2 = 12.42, (P = 0.08) CA+SAMe SD T	$\frac{\text{ODCA} + 1}{26}$ e on Asp $\frac{\text{OTA} M}{26}$ $\frac{24}{41} - 7$ 91 $df = 2 (1)$ $\frac{1}{2}$	= 0.01); I ² - SAMe and Partate Tra 0.08 -160 171 4.39 124 P = 0.002 UD ean	SAMe. Insamina Me <u>SD T</u> 1.78 .36333 .61966 (); l ² = 849 DCA SD T	se otal V 25 22 38 85 4 5 5	S Weight 32.0% 32.5% 35.5% 100.0 % Weight	td. Mean Difference IV, Random, 95% Cl -1.42 [-2.04, -0.80] -0.67 [-1.27, -0.07] -0.06 [-0.51, 0.38] -0.70 [-1.49, 0.09] Std. Mean Difference IV, Fixed 95% Cl	Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Favours [Control] Std. Mean Difference IV Fixed 95% CI
CA and SAMe, B, UDCA CA and SAMe, B, UDCA re 5. Effects of UDCA, S/ Study or Subgroup Binder 2006 Nicastri 1998 ZHANG 2015 Total (95% Cl) Heterogeneity: Tau ² Test for Overall Effect Study or Subgroup Binder 2006	² = 0.36; C ct: Z = 1.19 + SAMe and U AMe, and U -2.52 1 -271 1 -271 1 -81.41 9 ² = 0.41; C ct: Z = 1.73 UD0 Mean -3.27 1	Lini2 = 9.01, d (P = 0.23) Linu UDCA, C, (UDCA + SAMe JDCA SD T 5977171 54.20441 11.157094 Chi2 = 12.42, (P = 0.08) CA+SAMe SD T .6030908	$\frac{1}{1} = 2 (P = 1)$ $\frac{1}{2} = 2 (P = 1)$ $\frac{1}{2} = 1$	= 0.01); I ² - SAMe and bartate Tra 0.08 -160 171 4.39 124 P = 0.002 0.00 0.02 0.	 SAMe. SAMe. Insamina SD T 1.78 .36333 .61966 .20 T .21 P .26 A .20 T .27 T .27 T 	se 25 22 38 85 6 0tal V 26	S Weight 32.0% 32.5% 35.5% 100.0 % Weight 39.0%	td. Mean Difference IV, Random, 95% Cl -1.42 [-2.04, -0.80] -0.67 [-1.27, -0.07] -0.06 [-0.51, 0.38] -0.70 [-1.49, 0.09] -0.70 [-1.49, 0.09] Std. Mean Difference IV, Fixed, 95% Cl -0.46 [-1.01, 0.08]	Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Fixed, 95% CI
CA and SAMe, B, UDCA CA and SAMe, B, UDCA re 5. Effects of UDCA, S/ Study or Subgroup Binder 2006 Nicastri 1998 ZHANG 2015 Total (95% Cl) Heterogeneity: Tau ² Test for Overall Effect Study or Subgroup Binder 2006 ZHANG 2015	² = 0.36; C ct: Z = 1.19 + SAMe and U AMe, and U -2.52 1 -271 1 -21.1 2 -21.1 2 -21.2 2 -21.1 2 -21.2 2 -21.1 2 -21.2 2 -21.	hi²= 9.01, d 0 (P= 0.23) nd UDCA, C, (UDCA + SAMu JDCA 5977171 54.20441 11.157094 Chi² = 12.42, 5 (P = 0.08) CA+SAMe SD T .6030908 10.09797	$\frac{\text{UDCA} + 2}{\text{e on Asp}}$ $\frac{\text{otal } M}{26} - \frac{24}{41} - 7$ 91 $df = 2 (1)$ $\frac{\text{otal } M}{27} - \frac{41}{41} - 8$	E 0.01); I ²⁻ SAMe and Partate Tra 0.08 -160 171 4.39 124 P = 0.002 UD ean 2.52 1.55 1.41 91.1	SAMe. ISAMe. Insamina Me SD T 1.78 .36333 .61966 (); l ² = 849 DCA SD T 977171 157094	se 25 22 38 85 6 0tal V 26 41	S Weight 32.0% 32.5% 35.5% 100.0% <u>Weight</u> 39.0% 61.0%	td. Mean Difference IV, Random, 95% Cl -1.42 [-2.04, -0.80] -0.67 [-1.27, -0.07] -0.06 [-0.51, 0.38] -0.70 [-1.49, 0.09] -0.70 [-1.49, 0.09] -0.46 [-1.01, 0.08] -0.36 [-0.80, 0.08]	Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Fixed, 95% CI
CA and SAMe, B, UDCA CA and SAMe, B, UDCA re 5. Effects of UDCA, S <i>i</i> Study or Subgroup Binder 2006 Nicastri 1998 ZHANG 2015 Total (95% Cl) Heterogeneity: Tau ² Test for Overall Effect Study or Subgroup Binder 2006 ZHANG 2015 Total (95% Cl)	² = 0.36; C ct: Z = 1.19 + SAMe and U AMe, and U -2.52 1 -271 1 -21.17 2 = 0.41; C ct: Z = 1.73 UD0 Mean -3.27 1 -118.2 1	hi²= 9.01, d 0 (P= 0.23) nd UDCA, C, UDCA + SAMu JDCA 5977171 54.20441 11.157094 Chi² = 12.42, ; (P = 0.08) CA+SAMe SD T .6030908 10.09797	$\frac{\text{O} \text{C} \text{C} \text{C} \text{C} \text{C} \text{C} \text{C} C$	E 0.01); I ²⁻ SAMe and Partate Tra 0.08 -160 171 4.39 124 P = 0.002 UD ean 2.52 1.55 1.41 91.1	= 78% SAMe. Insamina SD T 1.78 .36333 .61966 (2); l ² = 84% DCA SD T 377171 157094	se <u>otal V</u> 25 22 38 85 6 0tal V 26 41 67	S Weight 32.0% 32.5% 35.5% 100.0% Meight 39.0% 61.0%	td. Mean Difference IV, Random, 95% Cl -1.42 [-2.04, -0.80] -0.67 [-1.27, -0.07] -0.06 [-0.51, 0.38] -0.70 [-1.49, 0.09] -0.70 [-1.49, 0.09] -0.46 [-1.01, 0.08] -0.36 [-0.80, 0.08] -0.40 [-0.74, -0.05]	Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Fixed, 95% CI
CA and SAMe, B, UDCA CA and SAMe, B, UDCA re 5. Effects of UDCA, S/ Study or Subgroup Binder 2006 Nicastri 1998 ZHANG 2015 Total (95% Cl) Heterogeneity: Tau ² Test for Overall Effect Study or Subgroup Binder 2006 ZHANG 2015 Total (95% Cl) Heterogeneity: Chi ²	² = 0.36; C ct: Z = 1.19 + SAMe and U AMe, and U -2.52 1 -271 1 -271 1 -81.41 9 ² = 0.41; C ct: Z = 1.73 UD0 Mean -3.27 1 -118.2 1 -22 0, 8, d	hi ² = 9.01, d (P = 0.23) hd UDCA, C, UDCA + SAM JDCA <u>5977171</u> 54.20441 11.157094 :hi ² = 12.42, ; (P = 0.08) CA+SAMe <u>50 T</u> .6039008 10.09797 f = 1 (P = 0.7)	$\frac{1}{1} = 2 (P = 1)$ $\frac{1}{2} = 2 (P = 1)$	= 0.01); I ² - SAMe and bartate Tra Construction SAMe and bartate Tra Construction Constructi	= 78% SAMe. Insamina Me SD T 1.78 .36333 .61966 20); l ² = 84% DCA SD T 977171 157094	se <u>otal V</u> 25 22 38 85 6 0tal V 26 41 67	S Weight 32.0% 32.5% 35.5% 100.0% <u>Weight</u> 39.0% 61.0% 100.0 %	td. Mean Difference IV, Random, 95% Cl -1.42 [-2.04, -0.80] -0.67 [-1.27, -0.07] -0.06 [-0.51, 0.38] -0.70 [-1.49, 0.09] -0.70 [-1.49, 0.09] -0.36 [-0.80, 0.08] -0.46 [-1.01, 0.08] -0.40 [-0.74, -0.06]	Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Fixed, 95% CI
CA and SAMe, B, UDCA CA and SAMe, B, UDCA re 5. Effects of UDCA, S/ Study or Subgroup Binder 2006 Nicastri 1998 ZHANG 2015 Total (95% Cl) Heterogeneity: Tau ² Test for Overall Effect Study or Subgroup Binder 2006 ZHANG 2015 Total (95% Cl) Heterogeneity: Chi ² Total (95% Cl) Heterogeneity: Chi ² Total (95% Cl)	² = 0.36; C ct: Z = 1.19 + SAMe and U AMe, and U -2.52 1 -271 1 -217 1 -81.41 9 ² = 0.41; C ct: Z = 1.73 UD0 Mean -3.27 1 -118.2 1 -218.2 1	hi ² = 9.01, d (P = 0.23) hd UDCA, C, UDCA + SAMe SD T .5977171 54.20441 11.157094 CA+SAMe SD T .6030908 10.09797 f = 1 (P = 0.72) C (P = 0.02)	$\frac{1}{1} = 2 (P = 1)^{1}$ $\frac{1}{2} = 0$	= 0.01); I ² - SAMe and hartate Tra 0.08 -160 171 4.39 124 P = 0.002 UD ean 2.52 1.55 1.41 91.1 0%	= 78% SAMe. Insamina Me SD T 1.78 .36333 .61966 .36333 .61966 .350 T 977171 157094	se <u>otal V</u> 25 22 38 85 6 0tal V 26 41 67	S Weight 32.0% 32.5% 35.5% 100.0% <u>Weight</u> 39.0% 61.0% 100.0 %	td. Mean Difference IV, Random, 95% Cl -1.42 [-2.04, -0.80] -0.67 [-1.27, -0.07] -0.06 [-0.51, 0.38] -0.70 [-1.49, 0.09] -0.70 [-1.49, 0.09] -0.40 [-1.01, 0.08] -0.36 [-0.80, 0.08] -0.40 [-0.74, -0.06]	Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Fixed, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control]
CA and SAMe, B, UDCA CA and SAMe, B, UDCA Study or Subgroup Binder 2006 CHANG 2015 Total (95% Cl) Heterogeneity: Chi ² Total (95% Cl) Heterogeneity: Chi ² Total (95% Cl) Heterogeneity: Chi ² Total (95% Cl) Heterogeneity: Chi ² Total (95% Cl)	² = 0.36; C ct: Z = 1.19 + SAMe and U AMe, and U -2.52 1 -271 1 -21.17 2 = 0.41; C ct: Z = 1.73 UDD Mean -3.27 1 -118.2 1 -21.08, d ct: Z = 2.34	hi ² = 9.01, d (P = 0.23) hd UDCA, C, UDCA + SAMA JDCA 5977171 54.20441 11.157094 Chi ² = 12.42, (P = 0.08) CA+SAMe <u>SD T</u> .6030908 10.09797 f = 1 (P = 0.7) (P = 0.02)	$\frac{1}{1} = 2 (P = 1)^{1}$ $\frac{1}{2} = 0 + 1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 +$	= 0.01); I ² - SAMe and hartate Tra 0.08 -160 171 4.39 124 P = 0.002 UD ean 2.52 1.55 1.41 91.1 0%	SAMe. Insamina Me <u>SD T</u> 1.78 .36333 .61966 (); l ² = 849 DCA <u>SD T</u> 977171 157094	se 25 22 38 85 6 0tal V 26 41 67	S Weight 32.0% 32.5% 35.5% 100.0% Meight 39.0% 61.0% 100.0%	td. Mean Difference IV, Random, 95% Cl -1.42 [-2.04, -0.80] -0.67 [-1.27, -0.07] -0.06 [-0.51, 0.38] -0.70 [-1.49, 0.09] -0.70 [-1.49, 0.09] -0.46 [-1.01, 0.08] -0.46 [-1.01, 0.08] -0.40 [-0.74, -0.06]	Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Fixed, 95% CI -4 -2 0 -2 4 Favours [Experimental] Favours [Control]
CA and SAMe, B, UDCA CA and SAMe, B, UDCA CA and SAMe, B, UDCA Te 5. Effects of UDCA, S/ Study or Subgroup Binder 2006 Nicastri 1998 ZHANG 2015 Total (95% Cl) Heterogeneity: Tau ² Test for Overall Effect Study or Subgroup Binder 2006 ZHANG 2015 Total (95% Cl) Heterogeneity: Chi ² Total (95% Cl)	² = 0.36; C ct: Z = 1.19 + SAMe and U AMe, and U -2.52 1 -271 1 -21.17 2 = 0.41; C ct: Z = 1.73 UD0 Mean -3.27 1 -118.2 1 2 = 0.08, d ct: Z = 2.30 UDC Mean	hi ² =9.01, d (P=0.23) hd UDCA, C, UDCA + SAMe SD T 5977171 54.20441 11.157094 Chi ² =12.42, (P=0.08) CA+SAMe SD T .6030908 10.09797 f=1(P=0.7) C(P=0.02) CA+SAMe	$\frac{1}{1} = 2 (P = 1)^{1}$ $\frac{1}{2} = 2 (P = 1)^{1}$ $\frac{1}{2} = 0$ $\frac{1}{2} = 0$ $\frac{1}{2} = 1$ $\frac{1}{2} = 0$	= 0.01); I ² - SAMe and Partate Tra 0.08 -160 171 4.39 124 P = 0.002 UD ean 2.52 1.55 1.41 91.1 0% SAM	Ae SAMe. Insamina Me SD T 1.78 .36333 .61966 .36333 .61966 .36333 .61966 .36333 .61966 .377171 157094 Me SD T .377171	se <u>otal V</u> 25 22 38 85 6 0tal V 26 41 67	S Weight 32.0% 32.5% 35.5% 100.0% 100.0% 100.0% S Veight	td. Mean Difference IV, Random, 95% Cl -1.42 [-2.04, -0.80] -0.67 [-1.27, -0.07] -0.06 [-0.51, 0.38] -0.70 [-1.49, 0.09] -0.70 [-1.49, 0.09] -0.46 [-1.01, 0.08] -0.36 [-0.80, 0.08] -0.40 [-0.74, -0.06] -0.40 [-0.74, -0.06]	Std. Mean Difference IV, Random, 95% CI Favours [Experimental] Favours [Control] Std. Mean Difference IV, Fixed, 95% CI
CA and SAMe, B, UDCA CA and SAMe, B, UDCA CA and SAMe, B, UDCA Test, Effects of UDCA, S/ Study or Subgroup Binder 2006 Nicastri 1998 ZHANG 2015 Total (95% Cl) Heterogeneity: Tau ² Test for Overall Effect Study or Subgroup Binder 2006 ZHANG 2015 Total (95% Cl) Heterogeneity: Chi ² Total (95% Cl) Heterogeneity: Chi ² Total (95% Cl) Heterogeneity: Chi ² Total (95% Cl) Heterogeneity: Chi ² Study or Subgroup Binder 2006	² = 0.36; C ct: Z = 1.19 + SAMe and U AMe, and U -2.52 1 -271 1 -271 1 -81.41 9 ² = 0.41; C ct: Z = 1.73 UD0 Mean -3.27 1 -118.2 1 -2.33 UD0 Mean -3.27 2	hi ² = 9.01, d (P = 0.23) hd UDCA, C, UDCA + SAMe SD T 5977171 54.20441 11.157094 CA+SAMe SD T .6030908 10.09797 f = 1 (P = 0.72) CA+SAMe SD T .6030908 10.09797 f = 1 (P = 0.72) CA+SAMe SD T .6020000	$\frac{1}{1} = 2 (P = 1)^{1}$ $\frac{1}{2} = 2 (P = 1)^{1}$ $\frac{1}{2} = 0 + 1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 +$	= 0.01); I ² - SAMe and hartate Tra SAM ean 2.52 1.55 1.41 91.1 0% SAM ean	Ae SAMe. (SAMe. (ISAMe. SD T 1.78 .36333 .61966 SD T SD T SD T 157094 Ae SD T 1 7094	se <u>otal V</u> 25 22 38 85 6 0tal V 67 0tal V 25 22 38 22 38 85 6 7 10 10 10 10 10 10 10 10 10 10	S Weight 32.0% 32.5% 35.5% 100.0% Meight 39.0% 61.0% 100.0% S Veight	td. Mean Difference IV, Random, 95% CI -1.42 [-2.04, -0.80] -0.67 [-1.27, -0.07] -0.06 [-0.51, 0.38] -0.70 [-1.49, 0.09] -0.46 [-1.01, 0.08] -0.46 [-1.01, 0.08] -0.46 [-0.74, -0.06] -0.40 [-0.74, -0.06] -0.40 [-0.74, -0.06] -0.40 [-0.74, -0.06] -0.40 [-0.74, -0.06]	Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Fixed, 95% CI -4 -2 0 5 0 0.5 1 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Fixed, 95% CI -1 -0.5 0 0.5 1 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Random, 95% CI
CA and SAMe, B, UDCA Test for Overall Effect DCA and SAMe, B, UDCA re 5. Effects of UDCA, S/ Study or Subgroup Binder 2006 Nicastri 1998 ZHANG 2015 Total (95% Cl) Heterogeneity: Tau ² Test for Overall Effect Study or Subgroup Binder 2006 ZHANG 2015 Total (95% Cl) Heterogeneity: Chi ² Test for Overall Effect Study or Subgroup Binder 2006 ZHANG 2015	² = 0.36; C ct: Z = 1.19 + SAMe and U AMe, and U -2.52 1 -271 1 -211 2 -271 1 -81.41 9 ² = 0.41; C ct: Z = 1.73 UDU Mean -3.27 1 -118.2 1 -3.27 1 -118.2 1	hi ² = 9.01, d (P= 0.23) hd UDCA, C, UDCA + SAMe S0 T 5977171 54.20441 11.157094 Chi ² = 12.42, (P= 0.08) CA+SAMe SD T .6030908 10.09797 f = 1 (P = 0.7) C (P = 0.02) CA+SAMe SD T .6030908 10.09797	$\frac{\text{otal } M}{26} = 2 \text{ (P} = \frac{1}{2} \text{ (P} = \frac{1}{2}$	= 0.01); I ² - SAMe and Partate Tra 0.08 -160 171 4.39 124 P = 0.002 UD ean 2.52 1.55 1.41 91.1 0% SAM ean 0.08 4.39 124	Ae SD T SAMe. SD T 1.78 .36333 .61966 .0; J ² = 849 DCA <u>SD T</u> 157094 <u>SD T</u> 4.78 .61966	se otal V 25 22 38 85 6 0tal V 26 41 67 0tal V 25 38 38 38 38 38 38 38 38 38 38	S Weight 32.0% 32.5% 35.5% 100.0% 100.0% 100.0% S Veight 48.6% 51.4%	td. Mean Difference IV, Random, 95% CI -1.42 [-2.04, -0.80] -0.67 [-1.27, -0.07] -0.06 [-0.51, 0.38] -0.70 [-1.49, 0.09] -0.36 [-0.80, 0.08] -0.46 [-1.01, 0.08] -0.36 [-0.80, 0.08] -0.40 [-0.74, -0.06] -0.40 [-0.74, -0.06] -0.37 [-0.82, 0.08]	Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Fixed, 95% CI -4 -2 0 5 0 0.5 1 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Fixed, 95% CI -1 -0.5 0 0.5 1 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Random, 95% CI
CA and SAMe, B, UDCA CA and SAMe, B, UDCA CA and SAMe, B, UDCA Te 5. Effects of UDCA, S/ Study or Subgroup Binder 2006 Nicastri 1998 ZHANG 2015 Total (95% Cl) Heterogeneity: Tau ² Test for Overall Effect Study or Subgroup Binder 2006 ZHANG 2015 Total (95% Cl) Heterogeneity: Chi ² Total (95% Cl) Heterogeneity:	² = 0.36; C ct: Z = 1.19 + SAMe and U AMe, and U -2.52 1 -271 1 -211; C ct: Z = 1.73 UD0 Mean -3.27 1 -118.2 1 -3.27 1 -118.2 1	hi ² = 9.01, d (P= 0.23) hd UDCA, C, JDCA SD T .5977171 54.20441 11.157094 CA+SAMe SD T .6030908 10.09797 f = 1 (P = 0.7) 0 (P = 0.02) CA+SAMe SD T .6030908 10.09797	$\frac{1}{1} = 2 (P = 1)^{1}$ $\frac{1}{2} = 2 (P = 1)^{1}$ $\frac{1}{2} = 0 + 1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 +$	= 0.01); I ² - SAMe and hartate Tra SAM ean 2.52 1.55 1.41 91.1 0% SAM ean 0.08 4.39 124	Ae SD T SAMe. (SAMe. (SAMe. SD T 1.78 .36333 .61966 .01966 .0177171 157094 .0178 .01966	se otal V 25 22 38 85 6 0tal V 26 41 67 0tal V 25 22 38 85 6 0tal V 26 38 85 6 7 0tal V 26 27 38 85 6 7 7 7 85 85 6 7 7 7 85 85 85 85 85 85 85 85 85 85	S Weight 32.0% 32.5% 35.5% 100.0% 100.0% 100.0% S Veight 48.6% 51.4%	td. Mean Difference IV, Random, 95% CI -1.42 [-2.04, -0.80] -0.67 [-1.27, -0.07] -0.06 [-0.51, 0.38] -0.70 [-1.49, 0.09] -0.40 [-1.01, 0.08] -0.40 [-1.01, 0.08] -0.40 [-0.74, -0.06] -0.40 [-0.74, -0.06] -0.40 [-0.74, -0.06] -0.40 [-0.74, -0.06] -0.37 [-0.82, 0.08] -0.37 [-0.82, 0.08]	Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Fixed, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Fixed, 95% CI -4 -2 0 0,5 1 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Random, 95% CI
CA and SAMe, B, UDCA CA and SAMe, B, UDCA re 5. Effects of UDCA, S/ Study or Subgroup Binder 2006 Nicastri 1998 ZHANG 2015 Total (95% Cl) Heterogeneity: Tau ² Test for Overall Effect Study or Subgroup Binder 2006 ZHANG 2015 Total (95% Cl) Heterogeneity: Chi ² Test for Overall Effect Study or Subgroup Binder 2006 ZHANG 2015 Total (95% Cl) Heterogeneity: Chi ² Total (95% Cl) Heterogeneity: Chi ² Total (95% Cl) Binder 2006 ZHANG 2015	2 = 0.36; C ct: Z = 1.19 + SAMe and U AMe, and U -2.52 1 -271 1 -271 1 -81.41 9 2 = 0.41; C ct: Z = 1.73 UDD Mean -3.27 1 -118.2 1 -218.2 1 -218.2 1	hi ² = 9.01, d (P= 0.23) hd UDCA, C, JDCA SD T 5977171 54.20441 11.157094 CA+SAMe SD T .6030908 10.09797 f = 1 (P = 0.7) 0 (P = 0.02) CA+SAMe SD T .6030908 10.09797 hi ² = 10.75	$\frac{1}{1} = 2 (P = 1)^{1}$ $\frac{1}{2} = 2 (P = 1)^{1}$ $\frac{1}{2} = 0 + 1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 +$	= 0.01); I ² - SAMe and bartate Tra ean 0.08 -160 171 4.39 124 P = 0.002 ean 2.52 1.55 1.41 91.1 0% SAM ean 0.08 4.39 124 0.08	Ae SD T SAMe. (SAMe. (Insamina Me SD T 1.78 .36333 .61966 .025 T SD T 1.7794 Me SD T 1.78 .61966 .1.78 .61966	se <u>otal V</u> 25 22 38 85 6 6 67 0 0 0 1 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	S Weight 32.0% 32.5% 35.5% 100.0% ^W eight 39.0% 61.0% 100.0% S Veight 48.6% 51.4% 100.0%	td. Mean Difference IV, Random, 95% CI -1.42 [-2.04, -0.80] -0.67 [-1.27, -0.07] -0.06 [-0.51, 0.38] -0.70 [-1.49, 0.09] -0.46 [-1.01, 0.08] -0.46 [-1.01, 0.08] -0.46 [-1.01, 0.08] -0.46 [-0.74, -0.06] -0.40 [-0.74, -0.08] -0.40 [-	Std. Mean Difference IV, Random, 95% CI -4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Fixed, 95% CI -4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Fixed, 95% CI -4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Random, 95% CI -4 -4 -4 -4 -4 -4 -4 -4 -4 -4
CA and SAMe, B, UDCA CA and SAMe, B, UDCA CA and SAMe, B, UDCA Test, Effects of UDCA, S/ Study or Subgroup Binder 2006 Nicastri 1998 ZHANG 2015 Total (95% Cl) Heterogeneity: Tau ² Test for Overall Effect Study or Subgroup Binder 2006 ZHANG 2015 Total (95% Cl) Heterogeneity: Chi ² Test for Overall Effect Study or Subgroup Binder 2006 ZHANG 2015 Total (95% Cl) Heterogeneity: Tau ² Total (95% Cl) Heterogeneity: Tau ² Total (95% Cl) Heterogeneity: Tau ² Study or Subgroup Binder 2006 ZHANG 2015	2 = 0.36; C ct: Z = 1.19 + SAMe and U AMe, and U -2.52 1 -271 1 -271 1 -81.41 9 2 = 0.41; C ct: Z = 1.73 UDU Mean -3.27 1 -118.2 1 -3.27 1 -118.2 1 -3.27 1 -118.2 1 -3.27 1 -118.2 1	hi ² = 9.01, d (P = 0.23) hd UDCA, C, $(P = 0.23)$ UDCA + SAM JDCA SD T 54.20441 11.157094 CA+SAMe SD T .6030908 10.09797 f = 1 (P = 0.7) 0 (P = 0.02) CA+SAMe SD T .6030908 10.09797 hi ² = 13.47, d 7 (P = 0.14)	$\frac{1}{1} = 2 (P = 1)^{1}$ $\frac{1}{2} = 2 (P = 1)^{1}$ $\frac{1}{2} = 0 + 1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 + 1 +$	$= 0.01); I^{2}$ SAMe and eartate Tra SAM ean 0.08 160 171 4.39 124 P = 0.002 ean 2.52 1.41 91.1 0% SAM ean 0.08 4.39 124 P = 0.0002 P = 0.002 P	Ae SD T SAMe. SD T 1.78 .36333 .61966 DCA SD T SD T 977171 157094 Ae SD T 1.78 .61966 1.78 .61966 2); l ² = 93	se <u>otal V</u> 25 22 38 85 6 6 67 67 0 0 0 1 0 0 1 0 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	S Weight 32.0% 32.5% 35.5% 100.0% 100.0% 51.0% 51.4% 100.0%	td. Mean Difference IV, Random, 95% CI -1.42 [-2.04, -0.80] -0.67 [-1.27, -0.07] -0.06 [-0.51, 0.38] -0.70 [-1.49, 0.09] -0.36 [-0.30, 0.09] -0.46 [-1.01, 0.08] -0.36 [-0.80, 0.08] -0.40 [-0.74, -0.06] -0.40 [-0.74, -0.06] -0.37 [-0.82, 0.08] -1.09 [-2.55, 0.36] -0.95% CI	Std. Mean Difference IV, Random, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Fixed, 95% CI -4 -2 0 2 4 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Fixed, 95% CI -4 -2 0 0 0.5 1 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Random, 95% CI -4 -2 0 0 0.5 1 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Random, 95% CI -4 -2 0 0 0.5 1 Favours [Experimental] Favours [Control] Std. Mean Difference IV, Random, 95% CI -4 -2 0 0 0.5 1 Favours [Experimental] Favours [Control]

A, UDCA and SAMe; B, UDCA+SAMe and UDCA; C, UDCA + SAMe and SAMe.

(OR = 0.62, 95% CI, 0.42-0.91, P = 0.02). However, rates of preterm delivery did not differ significantly between the UDCA + SAMe and UDCA groups (OR = 1.28, 95% CI, 0.76-2.16, P = 0.35) (Figure 6).

3.3.2. Cesarean Section

No heterogeneity was found in the rates of cesarean section between the UDCA and SAMe groups (P = 0.90, I2 = 0%), the UDCA + SAMe and UDCA groups (P = 0.54, I2 = 0%), or the UDCA + SAMe and SAMe groups (P = 0.23, I2 = 30%); therefore, a fixed-effects model was used. The meta-analysis demonstrated that after the treatment, there were no significant differences in the rates of cesarean section between the UDCA and SAMe groups (OR = 0.84, 95% CI, 0.63-1.10, P = 0.20), the UDCA + SAMe and UDCA groups (OR = 1.03, 95% CI, 0.75-1.42, P = 0.85), or the UDCA + SAMe and SAMe groups (OR = 0.82, 95% CI, 0.61-1.09, P = 0.17) (Figure 7).

3.3.3. Meconium-Stained Amniotic Fluid

There was no heterogeneity in the rates of meconiumstained amniotic fluid between the UDCA and SAMe treatment groups (P = 0.36, I2 = 1%), the UDCA + SAMe and UDCA groups (P = 0.45, I2 = 0%), or the UDCA + SAMe and SAMe groups (P = 0.93, I2 = 30%); therefore, a fixedeffects model was used. According to the meta-analysis, there were no significant differences between the UDCA and SAMe groups (OR = 0.77, 95% CI, 0.40 - 1.46, P = 0.42), the UDCA + SAMe and UDCA groups (OR = 0.82, 95% CI, 0.38 - 1.78, P = 0.62), or the UDCA + SAMe and SAMe groups (OR = 0.77, 95% CI, 0.36 - 1.66, P = 0.51) after treatment (Figure 8).

4. Conclusions

ICP is an uncommon occurrence in pregnancy, but is associated with adverse perinatal outcomes. As its pathogenesis is still not fully understood, the appropriate pharmacological treatment of ICP remains controversial. According to the latest EASL clinical practice guidelines for the management of cholestatic liver diseases (29), the goal of ICP treatment is not only to decrease itching and improve liver function, but also to improve pregnancy outcomes without any side effects for either the mother or the fetus. UDCA and SAMe have been used to treat ICP for decades (30). UDCA is a naturally-occurring hydrophilic bile salt that may increase the hydrophilic properties of the bile acid pool, thereby preventing damage to membranes by hydrophobic bile salts (31). SAMe influences methylation reactions, increasing the flow of bile and biliary lipid metabolism, which is impaired by the estrogen load produced by the placenta in patients with ICP (32).

To better explore the optimal treatment for ICP, we performed a meta-analysis to evaluate the efficacy and safety of UDCA and SAMe on maternal clinical and biochemical parameters, as well as fetal outcomes. To our knowledge, this is the first meta-analysis to comparatively analyze the use of UDCA and SAMe for ICP. Our analysis echoes previous reports showing that both drugs are effective and safe. One of the RCTs included in the present meta-analysis reported that UDCA and SAMe are both effective and safe in the treatment of ICP(19). UDCA has virtually no side effects, except for mild diarrhea in some cases. Because the start of treatment with UDCA is usually delayed until the third trimester, the risk of teratogenicity is further minimized (33).

The present meta-analysis included a total of eight clinical parameters (pruritus score, TBA, total bilirubin, ALT, AST, preterm delivery, cesarean section, and meconiumstained amniotic fluid) in order to assess the efficacy of UDCA and/or SAMe on ICP. Early onset of pruritus and high serum TBA levels were included as predictors of preterm delivery in ICP (1). Moreover, TB, ALT, and AST were also included, as they have been weakly correlated to preterm delivery (1).

Our results revealed that UDCA improves pruritus, TBA, and ALT more effectively than SAMe. Additionally, UDCA reduced the rate of preterm delivery more effectively than SAMe. Therefore, our analysis favors the use of UDCA as first-line therapy for ICP. Randomized trials have suggested that UDCA is a more effective therapy than SAMe for ICP (17-19, 27, 28). Roncaglia et al. reported that UDCA improved serum bile acid levels and other liver function tests more effectively than SAMe (28). However, UDCA and SAMe were equally effective at reducing pruritus. In contrast, Floreani et al. reported that UDCA and SAMe equally effectively controlled pruritus and TBA levels (27). In no study was UDCA inferior to SAMe.

As mentioned previously, these drugs have different modes of action and thus have the potential to be used synergistically. However, data regarding the concomitant use of these therapies is limited. Additionally, only a few studies have compared treatment of ICP with UDCA and SAMe. Binder et al. reported that while UDCA effectively treated ICP, combining it with SAMe produced a synergistic effect on the biochemical parameters. Although UDCA+SAMe was more effective than UDCA or SAMe alone, its effect on the fetal prognosis is unclear (18). Nicastri et al. also found that the combination of UDCA + SAMe was more effective than either drug used alone, and reported that UDCA + SAMe reduced pruritus and TB levels more effectively than UDCA alone (17), although levels of bile salts, alkaline phosphatase, and serum glutamic pyruvic transaminase did not differ significantly between the UDCA and UDCA

L	UDCA		SAMe			Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Binder 2006	4	26	7	25	15.4%	0.55 [0.18, 1.65]	4		
Floreani 1996	3	10	4	10	8.6%	0.75 [0.22, 2.52]	•	•	
Roncaglia 2004	3	24	8	22	18.0%	0.34 [0.10, 1.13]	•		
ZHANG 2015	13	41	26	38	58.1%	0.46 [0.28, 0.76]			
Total (95% Cl)		101		95	100.0%	0.48 [0.32, 0.72]	-		
Total Events	23		45						
Heterogeneity: Chi ² = 0	.90, df = 3	(P = 0.8)	3); l ² = 0%						
Test for Overall Effect: Z	2 = 3.56(P=	= 0.000	4)					0.5 0.7 1 1.5 2 Favours [Experimental] Favours [Control]	
6	UDCA	A+SAMe	UDO	CA		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Binder 2006	4	27	4	26	23.9%	0.96 [0.27, 3.45]		• <u>• •</u>	
ZHANG 2015	18	41	13	41	76.1%	1.38 [0.79, 2.44]			
Total (95% Cl)		68		67	100.0%	1.28 [0.76, 2.16]		•	
Total Events	22		17						
Heterogeneity: Chi ² = 0	.26, df = 1	(P = 0.6)	1); l²= 0%				1		10.0
Test for Overall Effect: Z	2 = 0.94(P = 0.94)	= 0.35)					0.01	Favours [Experimental] Favours [Control]	100
	UDCA	+SAMe	SAN	1e		Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI	
Binder 2006	4	27	7	25	21.2%	0.53 [0.18, 1.59]			
ZHANG 2015	18	41	26	38	78.8%	0.64 [0.43, 0.96]			
Total (95% Cl)		68		63	100.0%	0.62 [0.42, 0.91]		•	
Total Events	22		33						
Heterogeneity: Chi ² = 0	.11, df = 1 (l	P = 0.74); l²= 0%				1		100
Test for Overall Effect: Z	L = 2.41(P =	0.02)					0.01	U.I I IU	100
								ravours [caperimental] ravours [Control]	

+ SAMe groups. Furthermore, UDCA + SAMe could reduce bile salts and alkaline phosphatase more efficiently than SAMe alone. Zhang et al. indicated that UDCA monotherapy should be used as first-line therapy for ICP because it is more efficacious, cost-effective, and convenient (19). Our

analysis echoes this recommendation.

Figure 6. Effects of UDCA, SAMe, and UDCA + SAMe on rate of preterm deliveries

The different efficacies of these two therapies may be attributed to their different pharmacological effects. Further studies should examine how both of these drugs influence ICP, as well as the differences in the mechanisms by which these therapies improve symptoms in ICP patients.

Interestingly, the results of this meta-analysis showed that while UDCA and SAMe alone had the aforementioned effects, they did not affect TB and AST levels. However, combination therapy significantly decreased these levels. We found that when applied together, these drugs may exert a synergistic effect in the treatment of ICP. Further studies should be carried out to study this effect.

In conclusion, this meta-analysis indicated that although both drugs are safe and relatively efficacious, UDCA monotherapy should be the first choice for the treatment of ICP, given that it was more effective than SAMe in reducing TBA, pruritus, and preterm delivery. Although both UDCA and SAMe have been used to treat ICP for several years, relatively few RCTs have compared the effects of these two drugs or a combination thereof. Our analysis suggested that compared with either drug administered alone, when used in combination, these drugs are more effective only in reducing AST (vs. UDCA), total bilirubin (vs. SAMe), and the rate of preterm delivery (vs. SAMe), and no evidence showed the combination to be better than either drug for the other parameters. It is not clear whether this synergistic relationship should be adopted for all cases of ICP or if SAMe can be added if biochemical or clinical parameters are not met after initiation of UDCA. Future studies should focus on optimized regimens of UDCA and SAMe, including the dosage and course, and whether they should be administered independently or in tandem.

Figure 7. . Effects of UDCA, SAMe, and UDCA + SAMe on Rate of Cesarean Sections

Α	UDCA	`	SAM	e		Risk Ratio			Risk	Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fix	ed, 95	% CI		
Binder 2006	3	26	5	25	11.0%	0.58 [0.15, 2.16]	4-			+			
Floreani 1996	6	10	7	10	15.1%	0.86 [0.45, 1.64]	•		•	-			_
Roncaglia 2004	5	24	4	22	9.0%	1.15 [0.35, 3.73]	•		_	-	•		
ZHANG 2015	26	41	29	38	64.9%	0.83 [0.62, 1.11]							
Total (95% Cl)		101		95	100.0%	0.84 [0.63, 1.10]				-			
Total Events	40		45										
Heterogeneity: Chi ² =	0.58, df = 3	(P = 0.9)	90); l²= 0%					+		<u>+</u>	+	+	
Test for Overall Effect	: Z = 1.28(P=	= 0.20)						0.7	0.85	1	1.2	1.5	
								Favours [Exp	erimentaij	Favou	irs [Control		
B	UDCA	A+SAMe	UD	CA		Risk Ratio			Risk	Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI			M-H, Fix	ed, 95	% CI		
Binder 2006	2	27	· 3	26	10.5%	0.64 [0.12, 3.54]							
ZHANG 2015	28	41	26	41	89.5%	1.08 [0.79, 1.47]							
Total (95% Cl)		68	1	67	100.0 %	1.03 [0.75, 1.42]			•	•			
Total Events	30		29										
Heterogeneity: Chi ² =	0.37, df = 1	(P=0.5	(4); $l^2 = 0\%$				0.01	0.1		1	10		100
Test for Overall Effect	: Z = 0.19 (P	= 0.85)						Favours [Exp	erimental]	Favou	ırs [Control		
С													
Study on Submoun	UDCA	+SAMe	SAN	le Total	Waight	KISK RATIO			KISK	Ratio	CI		
study of subgroup	Events	IOLA	Events	IOLAI	weight	M-H, FIXED, 95% CI	4		M-FI, FIX	-u, 95/	5 CI		
Binder 2006	2	21	5	25	14.7%	0.37 [0.08, 1.74]			_				
ZHANG 2015	28	41	29	38	85.3%	0.89 [0.68, 1.18]							
Total (95% Cl)		68	:	63	100.0%	0.82 [0.61, 1.09]			-				
Total Events	30		34										
Heterogeneity: Chi ² =	1.42, df = 1	P = 0.2	3); l ² = 30%				0.1	0.2	0.5	1	2	5	10
Test for Overall Effect	: Z = 1.37(P=	0.17)						Eavours (Exr	erimentall	Favor	- irs [Control	ı j	
lest for overall Energy		0/)						ravours [EX]	ermentalj	ravot	us (controi	I	

A, UDCA and SAMe; B, UDCA + SAMe and UDCA; C, UDCA + SAMe and SAMe.

Figure 8. Effects of UDCA, SAMe, and UDCA + SAMe on Rate of Meconium-Stained Amniotic Fluid



A, UDCA and SAMe; B, UDCA + SAMe and UDCA; C, UDCA + SAMe and SAMe.

Footnotes

Authors' Contribution: Study concept and design: Yang Zhang, Linlin Lu, and Yongning Xin; acquisition of data: Yang Zhang, Linlin Lu, and Yongning Xin; analysis and interpretation of data: Yang Zhang and Yongning Xin; drafting of the manuscript: Yang Zhang, Linlin Lu, and Yongning Xin; critical revision of the manuscript for important intellectual content: David W. Victor and Shiying Xuan; statistical analysis: Yang Zhang; administrative, technical, and material support: David W. Victor and Yongning Xin; study supervision: Shiying Xuan.

Funding/Support: This study was supported by the Qingdao livelihood, science and technology project, China (Grant No.14-2-3-17-nsh) and the Qingdao key health discipline development fund.

References

- Kondrackiene J, Kupcinskas L. Intrahepatic cholestasis of pregnancycurrent achievements and unsolved problems. World J Gastroenterol. 2008;14(38):5781-8. [PubMed: 18855975].
- Arrese M, Reyes H. Intrahepatic cholestasis of pregnancy: a past and present riddle. Ann Hepatol. 2006;5(3):202-5. [PubMed: 17060884].
- Lee NM, Brady CW. Liver disease in pregnancy. World J Gastroenterol. 2009;15(8):897-906. [PubMed: 19248187].
- Ahmed KT, Almashhrawi AA, Rahman RN, Hammoud GM, Ibdah JA. Liver diseases in pregnancy: diseases unique to pregnancy. World J Gastroenterol. 2013;19(43):7639–46. doi: 10.3748/wjg.v19.i43.7639. [PubMed: 24282353].
- 5. Williamson C, Geenes V. Intrahepatic cholestasis of pregnancy. *Obstet Gynecol.* 2014;**124**(1):120–33. doi: 10.1097/AOG.0000000000346. [PubMed: 24901263].
- Gabzdyl EM, Schlaeger JM. Intrahepatic cholestasis of pregnancy: a critical clinical review. J Perinat Neonatal Nurs. 2015;29(1):41–50. doi: 10.1097/JPN.000000000000077. [PubMed: 25633399].
- Diken Z, Usta IM, Nassar AH. A clinical approach to intrahepatic cholestasis of pregnancy. *Am J Perinatol.* 2014;**31**(1):1–8. doi: 10.1055/s-0033-1333673. [PubMed: 23359238].
- 8. Tan LK. Obstetric cholestasis: current opinions and management. *Ann Acad Med Singapore*. 2003;**32**(3):294–8. [PubMed: 12854371].
- Pathak B, Sheibani L, Lee RH. Cholestasis of pregnancy. Obstet Gynecol Clin North Am. 2010;37(2):269–82. doi: 10.1016/j.ogc.2010.02.011. [PubMed: 20685553].
- Ozkan S, Ceylan Y, Ozkan OV, Yildirim S. Review of a challenging clinical issue: Intrahepatic cholestasis of pregnancy. World J Gastroenterol. 2015;21(23):7134–41. doi: 10.3748/wjg.v21.i23.7134. [PubMed: 26109799].
- Palma J, Reyes H, Ribalta J, Hernandez I, Sandoval L, Almuna R, et al. Ursodeoxycholic acid in the treatment of cholestasis of pregnancy: a randomized, double-blind study controlled with placebo. *J Hepatol.* 1997;**27**(6):1022-8. [PubMed: 9453428].
- Liu Y, Qiao F, Liu H, Liu D. Ursodeoxycholic acid in the treatment of intraheptic cholestasis of pregnancy. J Huazhong Univ Sci Technolog Med Sci. 2006;26(3):350-2. [PubMed: 16961291].
- Zapata R, Sandoval L, Palma J, Hernandez I, Ribalta J, Reyes H, et al. Ursodeoxycholic acid in the treatment of intrahepatic cholestasis of pregnancy. A 12-year experience. *Liver Int.* 2005;25(3):548–54. doi: 10.1111/j.1478-3231.2004.0996.x. [PubMed: 15910492].
- 14. Glantz A, Marschall HU, Lammert F, Mattsson LA. Intrahepatic cholestasis of pregnancy: a randomized controlled trial com-

paring dexamethasone and ursodeoxycholic acid. *Hepatology*. 2005;**42**(6):1399-405. doi: 10.1002/hep.20952. [PubMed: 16317669].

- Kondrackiene J, Beuers U, Kupcinskas L. Efficacy and safety of ursodeoxycholic acid versus cholestyramine in intrahepatic cholestasis of pregnancy. *Gastroenterology*. 2005;**129**(3):894–901. doi: 10.1053/j.gastro.2005.06.019. [PubMed: 16143129].
- Frezza M, Centini G, Cammareri G, Le Grazie C, Di Padova C. Sadenosylmethionine for the treatment of intrahepatic cholestasis of pregnancy. Results of a controlled clinical trial. *Hepatogastroenterol*ogy. 1990;**37 Suppl 2**:122–5. [PubMed: 2083923].
- Nicastri PL, Diaferia A, Tartagni M, Loizzi P, Fanelli M. A randomised placebo-controlled trial of ursodeoxycholic acid and Sadenosylmethionine in the treatment of intrahepatic cholestasis of pregnancy. *Br J Obstet Gynaecol.* 1998;**105**(11):1205-7. [PubMed: 9853771].
- Binder T, Salaj P, Zima T, Vitek L. Randomized prospective comparative study of ursodeoxycholic acid and S-adenosyl-L-methionine in the treatment of intrahepatic cholestasis of pregnancy. J Perinat Med. 2006;34(5):383-91. doi: 10.1515/JPM.2006.077. [PubMed: 16965225].
- Zhang L, Liu XH, Qi HB, Li Z, Fu XD, Chen L, et al. Ursodeoxycholic acid and S-adenosylmethionine in the treatment of intrahepatic cholestasis of pregnancy: a multi-centered randomized controlled trial. *Eur Rev Med Pharmacol Sci.* 2015;19(19):3770–6. [PubMed: 26502869].
- Zhou F, Gao B, Wang X, Li J. Meta-analysis of ursodeoxycholic acid and S-adenosylmethionine for improving the outcomes of intrahepatic cholestasis of pregnancy [in Chinese]. *Zhonghua Gan Zang Bing Za Zhi*. 2014;22(4):299–304. doi: 10.3760/cma.j.issn.1007-3418.2014.04.013. [PubMed: 25173231].
- 21. Kenyon AP, Girling JC. Obstetrics Cholestasis. London: Royal College of Obstetricians and Gynaecologist; 2011.
- Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Control Clin Trials*. 1996;17(1):1–12. [PubMed: 8721797].
- Kjaergard LL, Villumsen J, Gluud C. Reported methodologic quality and discrepancies between large and small randomized trials in meta-analyses. *Ann Intern Med.* 2001;135(11):982–9. [PubMed: 11730399].
- Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, et al. Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses?. *Lancet.* 1998;**352**(9128):609–13. doi: 10.1016/S0140-6736(98)01085-X. [PubMed: 9746022].
- DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177–88. [PubMed: 3802833].
- Shadish WR, Haddock CK. Combining estimates of effects size. In: Cooper H, Hedges LV,ed. The handbook of research synthesis. New York: Russel Sage Foundation; 1994. pp. 261–81.
- Floreani A, Paternoster D, Melis A, Grella PV. S-adenosylmethionine versus ursodeoxycholic acid in the treatment of intrahepatic cholestasis of pregnancy: preliminary results of a controlled trial. *Eur J Obstet Gynecol Reprod Biol.* 1996;67(2):109–13. [PubMed: 8841797].
- Roncaglia N, Locatelli A, Arreghini A, Assi F, Cameroni I, Pezzullo JC, et al. A randomised controlled trial of ursodeoxycholic acid and Sadenosyl-l-methionine in the treatment of gestational cholestasis. *BJOG.* 2004;111(1):17-21. [PubMed: 14687046].
- European Association for the Study of the Liver . EASL Clinical Practice Guidelines: management of cholestatic liver diseases. J Hepatol. 2009;51(2):237–67. doi: 10.1016/j.jhep.2009.04.009. [PubMed: 19501929].
- Azzaroli F, Turco L, Lisotti A, Calvanese C, Mazzella G. The pharmacological management of intrahepatic cholestasis of pregnancy. *Curr Clin Pharmacol.* 2011;6(1):12–7. [PubMed: 21352094].
- Beuers U. Drug insight: Mechanisms and sites of action of ursodeoxycholic acid in cholestasis. Nat Clin Pract Gastroenterol Hepatol. 2006;3(6):318–28. doi: 10.1038/ncpgasthep0521. [PubMed: 16741551].

- Almasio P, Bortolini M, Pagliaro L, Coltorti M. Role of S-adenosyl-L-methionine in the treatment of intrahepatic cholestasis. *Drugs*. 1990;40 Suppl 3:111–23. [PubMed: 2081476].
- Lammert F, Marschall HU, Glantz A, Matern S. Intrahepatic cholestasis of pregnancy: molecular pathogenesis, diagnosis and management. *J Hepatol.* 2000;33(6):1012–21. [PubMed: 11131439].