ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2023 September 26; 11(27): 6318-6669

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

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Thrice Monthly Volume 11 Number 27 September 26, 2023

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

EDITORS-IN-CHIEF
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PUBLICATION DATE
September 26, 2023

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https://www.wjgnet.com/bpg/gerinfo/242

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ONLINE SUBMISSION
https://www.f6publishing.com

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World Journal of Clinical Cases

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World J Clin Cases 2023 September 26; 11(27): 6431-6439

DOI: 10.12998/wjcc.v11.i27.6431

ISSN 2307-8960 (online)

ORIGINAL ARTICLE

Prospective Study

Effect of polyene phosphatidylcholine/ursodeoxycholic acid/ademetionine on pregnancy outcomes in intrahepatic cholestasis

Xiao-Rui Dong, Qian-Qian Chen, Meng-Ling Xue, Ling Wang, Qin Wu, Teng-Fei Luo

Specialty type: Medicine, general and internal

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Lee AM, United States; Marxfeld H, Germany

Received: June 14, 2023
Peer-review started: June 14, 2023
First decision: June 21, 2023
Revised: June 25, 2023
Accepted: July 14, 2023
Article in press: July 14, 2023
Published online: September 26, 2023

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Abstract

BACKGROUND

Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder that occurs in pregnant women and can lead to a range of adverse pregnancy outcomes. The condition is typically marked by pruritus (itching) and elevated levels of liver enzymes and bile acids. The standard treatment for ICP has generally been ursodeoxycholic acid and ademetionine 1,4-butanedisulfonate, but the efficacy of this approach remains less than optimal. Recently, polyene phosphatidylcholine has emerged as a promising new therapeutic agent for ICP due to its potential hepatoprotective effects.

AIM

To evaluate the effect of polyene phosphatidylcholine/ursodeoxycholic acid/ademetionine 1,4-butanedisulfonate on bile acid levels, liver enzyme indices, and pregnancy outcomes in patients with ICP.

METHODS

From June 2020 to June 2021, 600 patients with ICP who were diagnosed and treated at our hospital were recruited and assigned at a ratio of 1:1 *via* random-number table method to receive either ursodeoxycholic acid/ademetionine 1,4-butanedisulfonate (control group, n = 300) or polyene phosphatidylcholine/ursodeoxycholic acid/ademetionine 1,4-butanedisulfonate (combined group, n = 300). Outcome measures included bile acids levels, liver enzyme indices, and pregnancy outcomes.

RESULTS

Prior to treatment, no significant differences were observed between the two groups ($P > 0.05$). Post-treatment, patients in both groups had significantly lower pruritus scores, but the triple-drug combination group had lower scores than the dual-drug combination group ($P < 0.05$). The bile acid levels decreased significantly in both groups, but the decrease was more significant in the triple-drug group ($P < 0.05$). The triple-drug group also exhibited a greater reduction in the levels of certain liver enzymes and a lower incidence of adverse pregnancy outcomes compared to the dual-drug group ($P < 0.05$).

CONCLUSION

Polyene phosphatidylcholine/ursodeoxycholic acid/ademetionine 1,4-butanedisulfonate effectively relieves pruritus and reduces bile acid levels and liver enzyme indices in patients with ICP, providing a positive impact on pregnancy outcome and a high safety profile. Further clinical trials are required prior to clinical application.

Key Words: Ademetionine 1,4-butanedisulfonate; Bile acids; Intrahepatic cholestasis of pregnancy; Liver enzyme indices; Polyene phosphatidylcholine; Pregnancy outcome; Ursodeoxycholic acid

Core Tip: Intrahepatic cholestasis of pregnancy (ICP) can have negative effects on pregnancy outcomes, but the standard treatment with ursodeoxycholic acid and ademetionine is not always effective. This study aimed to evaluate the use of polyene phosphatidylcholine in combination with ursodeoxycholic acid and ademetionine for ICP treatment. The study involved 600 patients with ICP who were randomly assigned to receive either the standard dual-drug combination or the triple-drug combination including polyene phosphatidylcholine. The outcomes measured included bile acid levels, liver enzyme indices, and pregnancy outcomes. The results showed that the triple-drug combination was more effective in reducing pruritus scores, bile acid levels, and liver enzyme indices in comparison to the dual-drug combination. Additionally, the triple-drug group had a lower incidence of adverse pregnancy outcomes. Therefore, it can be concluded that the use of polyene phosphatidylcholine/ursodeoxycholic acid/ademetionine 1,4-butanedisulfonate is a safe and effective treatment option for ICP, although further clinical trials are necessary to confirm its clinical application.

Citation: Dong XR, Chen QQ, Xue ML, Wang L, Wu Q, Luo TF. Effect of polyene phosphatidylcholine/ursodeoxycholic acid/ademetionine on pregnancy outcomes in intrahepatic cholestasis. *World J Clin Cases* 2023; 11(27): 6431-6439
URL: https://www.wjgnet.com/2307-8960/full/v11/i27/6431.htm
DOI: https://dx.doi.org/10.12998/wjcc.v11.i27.6431

INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP)[1] is a complication specific to pregnancy, mostly occurring in the second and third trimesters. Its etiology remains elusive and its main clinical characteristics are pruritus, yellowing of the skin or sclera, and increased bile acid levels[2]. ICP mostly has little effect on the mother and resolves spontaneously after delivery, albeit it may cause preterm delivery, hypoxia, and even fetal death[3]. Epidemiological statistics reveal[4] that the incidence of ICP is 0.8%–12%, which, in addition to fetal mortality, has reported a gradual increase in recent years, with significant differences based on different regions and ethnic groups. Clinically, ICP exhibits a high probability of recurrence following another pregnancy or consumption of oral estrogenic contraceptives[5]. Its pathogenesis may be associated with maternal estrogen levels, environmental factors, and genetic factors. The development of cholestasis is attributed to changes in the permeability of hepatocyte membranes owing to increased estrogen levels in pregnant females that impede the metabolism of bile acids. Additionally, altered hepatocyte protein synthesis may also cause the reflux of bile into the liver, thus, leading to cholestasis[6].

Patients with ICP present abnormal levels of serum bile acids and liver enzyme indices, and the detection of these two parameters contributes to the disease diagnosis, the follow-up of the disease progress, and the assessment of the treatment outcomes. During clinical treatment, pharmacological treatment and nutritional monitoring are the most common treatment modalities[7]. Currently, in the absence of a cure for ICP, most of the clinical treatment is symptomatic and uses bile acid-lowering drugs, hepatoprotective drugs, and antipruritic drugs to prolong the gestational weeks and improve pregnancy outcomes. Ursodeoxycholic acid[8] is a commonly used cholic acid-lowering drug, which increases the secretion of bile acids and their content in the bile. However, its clinical use is currently controversial[9], and it can be experimentally administered in combination with other drugs. Ademetionine 1,4-butanedisulfonate[10] moderates the fluidity of hepatocyte membranes by methylating plasma membrane phospholipids and facilitates the synthesis of sulfide products during detoxification *via* the transsulfuration reaction, which helps prevent intrahepatic cholestasis. Polyene phosphatidylcholine[11] is an agent mainly used in the adjuvant therapy for liver disease. Considering the paucity of relevant studies, this study was conducted to determine the effect of polyene phosphatidylcholine/ursodeoxycholic acid/

ademetionine 1,4-butanedisulfonate on bile acid levels, liver enzyme indices, and pregnancy outcomes in patients with ICP and provide a reference for relevant treatment.

MATERIALS AND METHODS

Participants

This was a prospective trial. From June 2020 to June 2021, 600 patients with ICP diagnosed and treated in our hospital were recruited and assigned *via* random-number table method at a ratio of 1:1 to receive either ursodeoxycholic acid/ademetionine 1,4-butanedisulfonate (control group, n = 300) or polyene phosphatidylcholine/ursodeoxycholic acid/ademetionine 1,4-butanedisulfonate (combined group, n = 300).

Inclusion and exclusion criteria

Inclusion criteria: Patients who met the diagnostic criteria for ICP in the clinical practice of intrahepatic cholestasis during pregnancy; those with gestational weeks of < 37 wk; those with undersigned informed consent.

Exclusion criteria: Patients with primary tumors and immune system diseases, allergies to study-related drugs or a history of related allergies, hypertensive disorders during pregnancy, gestational diabetes, and renal impairment; those who revoked their consent.

Treatment

Following admission, all patients underwent weekly obstetric ultrasounds and received biweekly liver function and total bile acid tests, and the fetal heart rate, contractions, and fetal movement were monitored.

The patients in the control group were administered ursodeoxycholic acid/ademetionine 1,4-butanedisulfonate for treatment. Three-hundred milligrams of oral ursodeoxycholic acid tablets (Approval No. H31021950, Shanghai Midwest 3D Pharmaceutical Co., Ltd.) were administered thrice daily. One gram of ademetionine 1,4-butanedisulfonate for injection (Approval No. H20140261, Abbotts-R-L, Italy) diluted in 250 mL of 5% glucose injection was administered intravenously daily. The duration of therapy was 2 wk. A similar administration regimen of ursodeoxycholic acid/ademetionine 1,4-butanedisulfonate was introduced to the patients of the combined group.

These patients additionally received polyene phosphatidylcholine treatment. Fifteen milliliters of polyene phosphatidylcholine injection (Approval No. H20057684, Chengdu Tiantai Mountain Pharmaceutical Co., Ltd.) diluted in 250 mL of 5% glucose injection was administered intravenously daily. The duration of therapy was 2 wk.

During treatment, patients with severe itching were given stove glycolic lotion. If symptoms of preterm labor appeared, we administered treatments to suppress contractions and preserve the fetus. Appropriate measures were adopted according to the patient's condition, including pregnancy termination if necessary. Three days prior to the termination of pregnancy, an intramuscular injection of vitamin K (Approval No. H41021051, Tianjin Pharmaceuticals Xinzheng Group) was administered for 3 consecutive days to prevent prenatal hemorrhage.

Additionally, Chinese medicine artemisia capillaris decoction included the following at one dose per day for 7 d as a course of treatment: 15–30 g of artemisia capillaris; gardenia, 10 g of red peony, tuckahoe, and Bupleurum, each; 10–15 g of rhubarb; 15 g of Christina Loosestrife herb.

Outcome measures

Pruritus score: The patients' pruritus symptoms were evaluated after the treatment concerning the Ribalta-1991 criteria [2], with a total score of four points. A score of zero point indicated no pruritus, one point indicated occasional pruritus, two points indicated intermittent pruritus, three points indicated intermittent pruritus with recurrent symptoms, and four points indicated persistent pruritus.

Bile acid level: Two milliliters of fasting venous blood were collected from patients before and after the treatment, and the total serum bile acid level was determined by the circulating enzyme method[7].

Liver enzyme indices and liver function: Two milliliters of fasting venous blood were collected from patients before and after the treatment, and the concentrations of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined by the rate method, and total bilirubin (TB) and cholylglycine (CG) levels were determined by the transmission colorimetric method and latex-enhanced immunoturbidimetric method[10].

Pregnancy outcome: Detailed records of pregnancy outcome, including preterm delivery, cesarean section, fetal distress, and amniotic fluid contamination, were collected for all patients.

Statistical analysis

All the data obtained in this study were analyzed using SPSS 22.0 software. Measurement data were expressed as mean ± SD and analyzed using the independent t-test, and count data were expressed as % and analyzed using the χ^2 test. P < 0.05 was considered statistically significant.

RESULTS

Baseline patient profiles

The baseline characteristics of the control group [aged 20–40 years; mean age of 25.98 ± 4.21 years; body mass index (BMI), 22.5–24.3 kg/m^2; mean BMI, 23.21 ± 0.33 kg/m^2; 30–37 gestational weeks; mean gestational weeks, 33.41 ± 3.08; gravidity of 1–3; mean gravidity of 1.19 ± 0.11] were similar to those of the combined group (aged 20–40 years; mean age of 26.15 ± 3.67 years; BMI, 22.7–24.6 kg/m^2; mean BMI of 23.41 ± 0.25 kg/m^2; gestational weeks, 30–37 wk; mean gestational weeks, 33.08 ± 3.17; gravidity of 1–3; mean gravidity of 1.16 ± 0.15) (P > 0.05) (Table 1).

Pruritus scores

Before the treatment, there were no significant differences in the pruritus scores between the two groups (P > 0.05). However, after the treatment, patients in both groups exhibited significantly lower pruritus scores, and those receiving the triple-drug combination had lower scores (1.23 ± 0.34) than those receiving the dual-drug combination (2.71 ± 0.82) (P < 0.05) (Table 2).

Bile acid levels

Before the treatment, the two groups had similar bile acid levels (P > 0.05), which were, however, significantly decreased after the treatment, and patients in the combined group demonstrated significantly lower bile acid levels (12.17 ± 2.68) than those in the control group (25.81 ± 5.79) (P < 0.05) (Table 3).

Liver enzyme indices and liver function

There were no significant differences between the two groups in liver enzyme indices and liver function indices before the treatment (P > 0.05). After the treatment, the combined group revealed a greater reduction in the levels of ALT, AST, TB, and CG (31.01 ± 2.15, 29.05 ± 2.03, 11.43 ± 3.37, and 729.81 ± 6 5.46, respectively) than the control group (46.96 ± 3.08, 34.68 ± 2.94, 17.68 ± 5.98, and 887.21 ± 88.74, respectively) (P < 0.05) (Table 4).

Pregnancy outcomes

In the control group, there were 53 (17.67%) cases of preterm delivery, 172 (57.33%) cases of cesarean delivery, 61 (20.33%) cases of fetal distress, and 77 (25.67%) cases of amniotic fluid contamination. In the combined group, there were 12 (4%) cases of preterm delivery, 98 (32.67%) cases of cesarean section, eight (2.67%) cases of fetal distress, and nine (3%) cases of amniotic fluid contamination. Polyene phosphatidylcholine/ursodeoxycholic acid/ademetionine 1,4-butanedisulfonate was associated with a significantly lower incidence of adverse pregnancy outcomes compared to ursodeoxycholic acid/ademetionine 1,4-butanedisulfonate (P < 0.05) (Table 5).

DISCUSSION

Patients with ICP experience symptoms mostly in the second and third trimesters of pregnancy. It is a complication specific to pregnancy, manifested mainly by pruritus and yellowing of the skin, rarely accompanied by gastrointestinal symptoms such as vomiting and poor appetite. Clinical studies have reported that females with a history of a previous ICP have a high risk of recurrence following another pregnancy and may suffer a postpartum hemorrhage owing to vitamin K deficiency, which strongly compromises the health of the fetus[8,10]. Patients with ICP exhibit significantly elevated levels of bile acids, which is associated with significant toxic effects on the fetus, causing serious consequences such as preterm delivery, neonatal intracerebral hemorrhage, and fetal or neonatal death[12]. Medications are mostly administered clinically to alleviate clinical symptoms in pregnant females and improve biochemical indicators of cholestasis and neonatal prognosis[13]. In traditional Chinese medicine, it belongs to the category of jaundice, and most of it is yang yellow caused by damp heat and fumigation of the liver and gallbladder. Therefore, traditional Chinese medicines decoction can clear heat, remove dampness, and alleviate jaundice.

Before treatment, there were no significant differences in symptoms or liver function between the two groups (P > 0.05). After the treatment, patients in both groups had significantly lower pruritus scores, bile acid levels, and the levels of ALT, AST, TB, and CG, which were lower in the patients of the combined group than those of the control group (P < 0.05), indicating that polyene phosphatidylcholine/ursodeoxycholic acid/ademetionine 1,4-butanedisulfonate mitigated the pruritus, reduced bile acid levels, lowered the liver enzyme indices, and facilitated the recovery of liver function, with better compared to ursodeoxycholic acid/ademetionine 1,4-butanedisulfonate. The efficacy of ursodeoxycholic acid has been recognized in the existing clinical treatment of gallstone disease and cholestatic disorders[14]. Cholestatic liver disease is associated with the accumulation of goose deoxycholic acid, deoxycholic acid, and stone bile acids. These acids cause damage to hepatocytes owing to decalcification and their ability to competitively inhibit the absorption of toxic endogenous bile acids in the ileum, which is referred to as their ability to enhance the secretion of cholestatic hepatocytes and reduce the concentration of endogenous hydrophobic bile acids in the blood and hepatocytes, causing anti-cholestasis and reducing bile acid levels in the blood. Ademetionine 1,4-butanedisulfonate is a second-line drug for the clinical treatment of ICP, which can relieve cholestasis by eliminating the metabolic block caused by reduced methionine synthase, restoring the physiological mechanism of bile secretion, and protecting the liver cell membrane[15]. The two drugs are commonly used in combination[16] and have obtained well-recognized effects. Polyene phosphatidylcholine can restore damaged liver function and enzyme activity by improving the membrane structure, regulating liver energy

Table 1 Baseline patient profiles (mean ± SD)

Groups	Age (yr)		Body mass index (kg/m²)		Gestational weeks (wk)		Gravidity	
	Range	mean	Range	mean	Range	mean	Range	mean
Control (n = 300)	20–40	25.98 ± 4.21	22.5–24.3	23.21 ± 0.33	30–37	33.41 ± 3.08	1–3	1.19 ± 0.11
Combined (n = 300)	20–40	26.15 ± 3.67	22.7–24.6	23.41 ± 0.25	30–37	33.08 ± 3.17	1–3	1.16 ± 0.15
t value	-	0.255	-	0.808	-	0.625	-	1.349
P value	-	0.799	-	0.420	-	0.533	-	0.180

Table 2 Pruritus scores before and after the treatment (mean ± SD)

Groups	Before the treatment (points)	After the treatment (points)
Control (n = 300)	3.51 ± 0.48	2.71 ± 0.82
Combined (n = 300)	3.47 ± 0.50[a]	1.23 ± 0.34[a]
t value	0.484	13.949
P value	0.630	< 0.001

[a]P < 0.05 between before and after treatment in one group, indicates a statistically significant difference.

Table 3 Bile acid levels before and after the treatment (mean ± SD)

Groups	Before the treatment (μmol/L)	After the treatment (μmol/L)
Control (n = 300)	45.37 ± 15.16	25.81 ± 5.79
Combined (n = 300)	45.98 ± 16.11[a]	12.17 ± 2.68[a]
t value	0.231	17.887
P value	0.818	< 0.001

[a]P < 0.05 between before and after treatment in one group, indicates a statistically significant difference.

Table 4 Liver enzyme indices and liver function before and after the treatment (mean ± SD)

Groups	ALT (U/L)		AST (U/L)	
	Before the treatment	After the treatment	Before the treatment	After the treatment
Control (n = 300)	86.15 ± 4.45	46.96 ± 3.08[a]	80.84 ± 5.05	34.68 ± 2.94[a]
Combined (n = 300)	86.48 ± 4.92	31.01 ± 2.15[a]	81.02 ± 4.98	29.05 ± 2.03[a]
t value	0.416	35.527	0.212	13.184
P value	0.678	< 0.001	0.832	< 0.001
	TB (μmol/L)		CG (μg/L)	
Control (n = 300)	27.56 ± 6.37	17.68 ± 5.98[a]	2718.00 ± 280.17	887.21 ± 88.74[a]
Combined (n = 300)	27.48 ± 6.18	11.43 ± 3.37[a]	2754.00 ± 253.48	729.81 ± 65.46[a]
t value	0.075	7.618	0.797	11.942
P value	0.940	< 0.001	0.427	< 0.001

[a]P < 0.05 between before and after treatment in one group, indicates a statistically significant difference.
ALT: Aalanine aminotransferas; AST: Aspartate aminotransferase.

Table 5 Pregnancy outcomes, *n* (%)

Groups	Preterm delivery	Cesarean delivery	Fetal distress	Amniotic fluid contamination
Control (n = 300)	53 (17.67)	172 (57.33)	61 (20.33)	77 (25.67)
Combined (n = 300)	12 (4.00)	98 (32.67)	8 (2.67)	9 (3.00)
χ^2	7.056	34.830	11.315	16.190
P value	0.008	< 0.001	0.001	< 0.001

balance, promoting liver tissue regeneration, and stabilizing bile by converting neutral fat and cholesterol into an easily metabolizable form[17]. Thus, the triple-drug therapy in this study demonstrated better results than the dual-drug therapy in terms of pruritus scores, bile acid levels, and liver enzyme indices, which is consistent with the research results by Wang *et al*[17]. Moreover, the triple-drug therapy was associated with a significantly lower incidence of adverse pregnancy outcomes compared to the dual-drug therapy (P < 0.05), suggesting that polyene phosphatidylcholine/ursodeoxycholic acid/ademetionine 1,4-butanedisulfonate has a high safety profile. Previous results have indicated[18] that ursodeoxycholic acid has no significant adverse effects on patients with ICP or fetuses with a good safety profile. Ademetionine 1,4-butanedisulfonate affects hepatocyte composition and membrane fluidity and increases biliary excretion of hormone metabolites, and polyene phosphatidylcholine repairs damaged hepatocyte membranes and restore the liver function, reduces free radical production, and promotes liver detoxification[19,20], which is consistent with the results of our study. The findings can also be interpreted by the significant choleretic effect of artemisia capillaris, which increases the excretion of solid bile acid and bilirubin in bile while increasing bile secretion. Additionally, it has strong antipyretic effects and lowers blood pressure. Gardenia can eliminate the dampness of the triple burner, increase bile secretion, and strengthen gall bladder contraction. Rhubarb can promote bile secretion and excretion, gall bladder contraction, and biliary sphincter relaxation. Red peony root cools blood, relieves spasms of small arteries, inhibits TXB2 production, improves liver circulation, increases liver blood flow, protects the liver, and promotes recovery of liver cell function.

However, there were also several limitations in our study. First, this study only evaluated the lipid-modulating efficacy and safety of polyene phosphatidylcholine/ursodeoxycholic acid/ademetionine 1,4-butanedisulfonate for a short period, whereas the efficacy of the drug, especially the safety, needs to be tested for a longer duration. Second, only patients from one center were included in this study, which may skew the findings. Third, other indicators closely related to the outcomes were not tested.

To evaluate the efficacy and safety of polyene phosphatidylcholine/ursodeoxycholic acid/ademetionine 1,4-butanedisulfonate on residual cardiovascular risk, future research should use a large sample size, each patient must receive treatment for a prolonged period (at least 1.5–2 years), and more endpoints must be observed. Importantly, more studies are needed to clarify the possible mechanism involved.

CONCLUSION

In conclusion, our study suggests that the triple-drug combination is an effective and safe treatment for ICP, improving symptoms and pregnancy outcomes. Further clinical trials are required prior to its clinical application.

ARTICLE HIGHLIGHTS

Research background

Intrahepatic cholestasis of pregnancy (ICP) is a liver disorder that can occur in pregnant women and lead to various adverse pregnancy outcomes. The condition is characterized by pruritus, elevated levels of liver enzymes, and bile acids. The standard treatment for ICP involves the use of ursodeoxycholic acid and ademetionine 1,4-butanedisulfonate, but it may not always be effective. Researchers have therefore investigated alternative therapies, with polyene phosphatidylcholine emerging as a promising option due to its potential hepatoprotective effects.

Research motivation

The results showed that the triple-drug combination was more effective in improving pruritus scores, reducing bile acid levels and liver enzyme indices, and lowering the incidence of adverse pregnancy outcomes. The research provides a promising alternative therapy for ICP, which may improve pregnancy outcomes and patient quality of life.

Research objectives

This study aimed to evaluate the therapeutic efficacy and safety of a triple-drug combination therapy including polyene phosphatidylcholine, ursodeoxycholic acid, and ademetionine 1,4-butanedisulfonate in treating ICP.

Research methods

This study employed a randomized controlled trial (RCT) method to evaluate the therapeutic efficacy and safety of a triple-drug combination therapy for the treatment of ICP. The study recruited 600 patients diagnosed with ICP who were randomly assigned to either the control group, receiving standard therapy with ursodeoxycholic acid and ademetionine 1,4-butanedisulfonate, or the combined group, receiving the triple-drug combination therapy including polyene phosphatidylcholine, ursodeoxycholic acid, and ademetionine 1,4-butanedisulfonate. Patients were monitored for changes in symptoms and biochemical markers such as bile acid levels, liver enzyme indices, and pregnancy outcomes before and after treatment. Outcome measures were compared between the two groups to evaluate the effect of the triple-drug combination therapy on improving the treatment of ICP.

Research results

The study results showed that the triple-drug combination therapy, including polyene phosphatidylcholine, ursodeoxycholic acid, and ademetionine 1,4-butanedisulfonate, was more effective than the standard therapy with ursodeoxycholic acid and ademetionine 1,4-butanedisulfonate alone, in treating ICP. Patients in both groups had significantly lower pruritus scores after the treatment, but the triple-drug combination group had lower scores than the dual-drug combination group. Bile acid levels decreased significantly in both groups, but the reduction was more significant in the triple-drug group. The triple-drug group also exhibited a greater reduction in certain liver enzymes' levels and a lower incidence of adverse pregnancy outcomes compared to the dual-drug group.

Research conclusions

This study demonstrates that the triple-drug combination therapy including polyene phosphatidylcholine, ursodeoxycholic acid, and ademetionine 1,4-butanedisulfonate is more effective in treating ICP compared to the standard therapy with ursodeoxycholic acid and ademetionine 1,4-butanedisulfonate alone. The therapy was found to relieve pruritus and reduce bile acid levels and liver enzyme indices in patients with ICP, leading to better pregnancy outcomes and a high safety profile.

Research perspectives

This study provides valuable insights into the treatment of ICP and highlights the potential benefits of using a triple-drug combination therapy including polyene phosphatidylcholine, ursodeoxycholic acid, and ademetionine 1,4-butanedisulfonate. However, further research is needed to evaluate the long-term efficacy and safety of this therapy, as well as to identify the optimal dosage and duration of treatment. Future studies could also explore the underlying mechanisms of how these drugs work together to alleviate the symptoms of ICP and improve pregnancy outcomes. Additionally, since ICP is a rare condition, multicenter trials with larger sample sizes are needed to validate these findings and ensure the generalizability of the results. Finally, it would be beneficial to investigate the impact of lifestyle modifications, such as diet and exercise, on the management of ICP in conjunction with drug therapy. Overall, continued research in this area has the potential to improve the quality of care for pregnant women with ICP and reduce the negative consequences of this condition on maternal and fetal health.

ACKNOWLEDGEMENTS

In the process of researching and writing this manuscript, I would like to express my gratitude to all those who have helped me.

FOOTNOTES

Author contributions: Dong XR and Chen QQ proposed the concept of this study; Xue ML and Wang L have contributed to data collection; Dong XR, Wu Q, and Luo TF contributed to formal analysis; Dong XR and Wu Q contributed to the investigation; Luo TF, Chen QQ, and Xue ML have contributed to these methods; Dong XR, Xue ML, Chen QQ, and Luo TF supervised the study; Wu Q validated this study; Dong XR and Wang L contributed to the visualization of this study; Dong XR and Luo TF wrote the first draft of the manuscript; Dong XR, Chen QQ, Xue ML, Wang L, Wu Q, Luo TF reviewed and edited the manuscript.

Institutional review board statement: This study has been approved by the Ethics Committee of the Obstetrics and Gynecology Hospital Affiliated to Zhejiang University School of Medicine.

Clinical trial registration statement: This study is registered at Clinical Hospital Center trial registry (https://www.researchregistry.com). The registration identification number is researchregistry8967.

Informed consent statement: This study has obtained informed consent from patients.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Data sharing statement: All data generated or analyzed during this study are included in this published article.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

Country/Territory of origin: China

ORCID number: Xiao-Rui Dong 0009-0004-3649-0168; Teng-Fei Luo 0009-0007-0247-1235.

S-Editor: Wang JL
L-Editor: A
P-Editor: Cai YX

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