

ORIGINAL RESEARCH ARTICLE

Differential effects of Qingre Lishi formula on serum total bile acid and liver function markers in early- and late-onset intrahepatic cholestasis of pregnancy

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Abstract

This study aimed to explore the differential intervention effect of Qingre Lishi formula on serum total bile acid and liver function markers in patients with early-onset and late-onset intrahepatic cholestasis of pregnancy (ICP), and to provide a basis for clinical classification and treatment. The clinical data of patients with ICP were retrospectively analyzed. Patients were divided into early-onset (before 28 weeks of gestation) and late-onset (after 28 weeks of gestation) groups. Both groups received Qingre Lishi formula combined with Western medicine treatment, and the changes in serum biochemical and liver function indicators before and after treatment were compared. Baseline total bile acid levels were significantly higher in the early-onset group than in the late-onset group, while no significant between-group differences were observed in alanine aminotransferase or aspartate aminotransferase levels. After intervention, the decrease in total bile acid levels was more pronounced in the early-onset group, and the between-group difference narrowed after treatment. Liver enzyme levels in both groups were significantly lower than those before treatment. Qingre Lishi formula has a more significant effect on serum total bile acid in patients with early-onset ICP, and can effectively narrow the differences in bile acid metabolism between early-onset and late-onset ICP patients. (*Afr J Reprod Health* 2026; 30 [19]:92-103).

Keywords: Qingre Lishi formula; Intrahepatic cholestasis of pregnancy; Early-onset; Late-onset; Total bile acid; Liver function

Résumé

Cette étude visait à explorer l'effet interventionnel différentiel de la formule Qingre Lishi sur les acides biliaries totaux sériques et les marqueurs de la fonction hépatique chez des patientes atteintes de cholestase intrahépatique de la grossesse (CIG) à début précoce et à début tardif, et à fournir une base pour la classification clinique et le traitement. Les données cliniques de patientes atteintes de CIG ont été analysées rétrospectivement. Les patientes ont été divisées en un groupe à début précoce (avant 28 semaines de gestation) et un groupe à début tardif (après 28 semaines de gestation). Les deux groupes ont reçu la formule Qingre Lishi en association avec un traitement de médecine occidentale, et les variations des paramètres biochimiques sériques et de la fonction hépatique avant et après le traitement ont été comparées. Les taux de base des acides biliaries totaux étaient significativement plus élevés dans le groupe à début précoce que dans le groupe à début tardif, tandis qu'aucune différence significative entre les groupes n'a été observée pour les taux d'alanine aminotransférase ou d'aspartate aminotransférase. Après l'intervention, la diminution des acides biliaries totaux était plus marquée dans le groupe à début précoce, et la différence entre les groupes s'est réduite après le traitement. Les niveaux des enzymes hépatiques ont diminué de manière significative dans les deux groupes par rapport aux valeurs avant traitement. La formule Qingre Lishi a un effet plus marqué sur les acides biliaries totaux sériques chez les patientes atteintes de CIG à début précoce, et peut réduire efficacement les différences de métabolisme des acides biliaries entre les patientes à début précoce et tardif. (*Afr J Reprod Health* 2026; 30 [19]: 92-103).

Mots-clés: Formule Qingre Lishi ; cholestase intrahépatique de la grossesse ; début précoce ; début tardif ; acides biliaries totaux ; fonction hépatique

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver and biliary system disease during pregnancy. Its pathogenesis involves multiple

pathological links such as disordered bile acid metabolism, impaired autophagy function of placental trophoblast cells, and abnormal fetal-maternal bile acid transport.¹ Recent studies have revealed that autophagic flux in placental tissue of

ICP patients is significantly suppressed. Bile acids, by down-regulating the AMPK/ULK1 signaling pathway and activating the EGFR/PI3K/AKT/mTOR pathway, lead to decreased mitochondrial membrane potential and reduced ATP production, exacerbating the cellular energy crisis and apoptosis sensitivity.² According to the gestational week of onset, ICP can be classified as early-onset and late-onset types, and there are significant differences in clinical manifestations and prognosis between the two: early-onset ICP patients have significantly higher serum total bile acid (TBA) levels than late-onset patients, and the proportion of severe and extremely severe ICP is higher. The risks of adverse pregnancy outcomes such as preterm birth, meconium-stained amniotic fluid, and neonatal asphyxia are significantly increased.³

There are no significant differences in liver enzyme profiles among ICP patients of different gestational weeks. The association between alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels and the severity of the disease is weak. ALT > 200 IU/L is only used as a reference threshold for enhanced monitoring rather than a specific prognostic indicator.^{4,5} Currently, the drug treatment for ICP is mainly UDCA (Ursodeoxycholic Acid), which improves cholestasis by up-regulating liver enzyme systems and bile acid transporters, stabilizing cell membranes, and exerting immunomodulatory effects.⁶ The efficacy of single-agent UDCA treatment in reducing the stillbirth rate is controversial, and its efficacy is limited for patients with severe and critical early-onset ICP.⁷ S-adenosylmethionine (SAME) can be used as an alternative treatment, although it can promote the excretion of estrogen metabolites through the methylation pathway. However, a meta-analysis shows that UDCA is superior to SAME in improving pruritus scores, reducing TBA and AST levels, and reducing the rate of preterm birth.^{8,9} The combined treatment of UDCA and SAME shows a synergistic effect in reducing total bilirubin, AST levels, and the rate of preterm birth, which is superior to either single-agent treatment.¹⁰⁻¹³ This provides a pharmacological basis for the combination of traditional Chinese and Western medicine treatment.

ICP with traditional Chinese medicine (TCM) is guided by the classical therapeutic principle of "clearing heat and promoting diuresis,

regulating liver and promoting bile flow". This principle is rooted in the TCM syndrome differentiation framework, which classifies ICP as a manifestation of "damp-heat encumbering the liver and gallbladder" pattern. According to this framework, the pathogenesis involves impaired liver qi circulation and bile secretion due to accumulated damp-heat, leading to cholestasis, pruritus, and jaundice. The therapeutic strategy aims to eliminate damp-heat through diuresis, restore liver qi flow to promote bile excretion, and thereby alleviate cholestasis. This principle has been widely applied in TCM clinical practice for cholestatic liver diseases, including ICP, viral hepatitis, and gallstone disorders. Yinchenhao decoction (*Artemisia Capillaris* Decoction), a representative formula embodying this principle, was first documented in the *Treatise on Cold Damage and Miscellaneous Diseases* (Shang Han Lun) by Zhang Zhongjing in the Eastern Han dynasty and has been used for over 1,800 years to treat jaundice and cholestatic disorders. Modern pharmacological studies have demonstrated that Yinchenhao decoction and its modifications can significantly improve liver function, reduce serum bile acid levels, and alleviate pruritus in ICP patients when combined with Western medicine. A network meta-analysis of 38 randomized controlled trials (3,841 patients) demonstrated that Yinchenhao decoction combined with ursodeoxycholic acid significantly outperformed UDCA monotherapy in reducing pruritus scores, serum total bile acid, alanine aminotransferase, and aspartate aminotransferase levels, and identified the optimal composition as *Artemisia capillaris* >15 g, *Gardenia* >9 g, and *Rhubarb* <5 g as the most effective regimen. Recent mechanistic studies further revealed that Yinchenhao decoction protects against ICP through multiple pathways, including regulation of the miR-370-3p/TM9SF4/KIT axis in placental trophoblasts, modulation of intestinal flora, and activation of the Nrf2/ARE antioxidant pathway. The Qingre Lishi formula used in this study is a modified version of Yinchenhao decoction, specifically adapted for pregnancy by adding fetal-stabilizing herbs such as *Astragali Radix* (Huangqi) and *Atractylodis Macrocephalae Rhizoma* (Baizhu), while retaining the core heat-clearing and bile-promoting components. This modification reflects the TCM principle of "treating disease while protecting the

fetus", addressing both the pathological mechanisms of ICP and the physiological requirements of pregnancy.

Materials and methods

Study setting and population

This retrospective study was conducted at the Department of Obstetrics, Changzhou Hospital of Traditional Chinese Medicine, a tertiary-grade Class A hospital (the highest accreditation level in China's hospital grading system) located in Changzhou, Jiangsu Province, China. The hospital serves as a regional referral center for high-risk pregnancies and integrates traditional Chinese medicine with Western medicine in clinical practice. The study population consisted of pregnant women diagnosed with intrahepatic cholestasis of pregnancy (ICP) who received inpatient or outpatient care at this institution between January 2021 and December 2024. The patient population in this region is predominantly of Han Chinese ethnicity, with a diverse socioeconomic background representative of urban and suburban communities in the Yangtze River Delta region.

Enrolled cases

This study adheres to the principle of confidentiality. The trial data are only used for this research project and any public reports related to this study will not disclose personal information. This study selected the clinical data of 97 patients with ICP confirmed by pathology from January 2021 to December 2024 for retrospective analysis. They met the diagnostic criteria of "Diagnosis and Treatment Guidelines for Intrahepatic Cholestasis of Pregnancy (2015)"¹⁴: During pregnancy, there was skin itching not caused by skin diseases, with serum total bile acid (TBA) $\geq 10 \mu\text{mol/L}$, and accompanied or not accompanied by mild elevation of liver function indicators.

Inclusion criteria and exclusion criteria

Inclusion criteria: (1) Age 18-40 years old, with normal liver function before pregnancy and in the early stage of pregnancy. (2) This is the first systematic treatment for ICP, and no hepatoprotective or bile-promoting drugs were used before enrollment. (3) The patient is pregnant with a

single fetus and has complete clinical data. Exclusion criteria: (1) The patient has underlying liver and gallbladder system diseases such as viral hepatitis, autoimmune liver disease, primary biliary cholangitis, etc. (2) The patient has other pregnancy-related complications such as gestational hypertension, gestational diabetes, thyroid disease, etc. (3) The patient has severe heart, kidney, blood system diseases or malignant tumors. (4) Multiple pregnancies, pregnancies resulting from assisted reproductive technology, fetal structural abnormalities, chromosomal abnormalities or intrauterine growth restriction, and patients allergic to the study drugs.

Treatment methods

All the enrolled patients received the basic treatment regimen combining Qingre Lishi formula with Western medicine. The conventional Western medicine treatment included oral administration of ursodeoxycholic acid (UDCA) at $15 \text{ mg}/(\text{kg}\cdot\text{d})$, divided into 3 doses, with a maximum daily dose not exceeding 1200 mg, and intravenous infusion of 1000 mg ademetionine 1,4-butanedisulfonate in 500 mL of 5% glucose injection, once daily. For patients with obvious skin itching, calamine lotion could be applied topically. Both groups of patients were additionally given the oral herbal decoction of Qingre Lishi Formula. This formula was modified from Yinchenhao Decoction (*Artemisia Capillaris* Decoction), and the specific composition was as follows: 20 g of Yinchen (*Artemisiae Scopariae* Herba), 20 g of Jinqiancao (*Lysimachiae* Herba), 20 g of Huangqi (*Astragali* Radix), 12 g of Chuipencao (*Sedi* Herba), 12 g of Baixianpi (*Dictamni* Cortex), 15 g of Mudanpi (*Moutan* Cortex), 8 g of Zhizi (*Gardeniae* Fructus), 10 g of Baizhu (*Atractylodis* Macrocephalae Rhizoma), 10 g of Shengdihuang (*Rehmanniae* Radix), and 10 g of Huangqin (*Scutellariae* Radix). Among them, Yinchen served as the sovereign medicinal, clearing heat and eliminating dampness, purging liver-gallbladder heat, and promoting diuresis to reduce jaundice. Jinqiancao, the minister medicinal, cleared heat and promoted diuresis, assisting Yinchen in enhancing the diuretic and jaundice-relieving effects. Huangqi, the assistant medicinal, tonified qi and lifted yang, promoted diuresis and reduced swelling, and strengthened the body's foundation. Chuipencao, Baixianpi, and Mudanpi acted as adjuvant

medicinals that cleared heat, resolved dampness, detoxified, and reduced swelling to relieve skin itching. Zhizi cleared heat and dried dampness, dispelled wind and detoxified to address itching, while Mudanpi cleared heat and cooled the blood, activated blood circulation and resolved stasis, thereby improving placental microcirculation. Zhizi also purged fire, relieved restlessness, cleared heat and eliminated dampness, and cooled the blood and detoxified to promote bile secretion. Baizhu strengthened the spleen and replenished qi, dried dampness and promoted diuresis, and stabilized the fetus. The formula emphasized the actions of clearing heat and eliminating dampness, regulating the liver and gallbladder, strengthening the spleen, and stabilizing the fetus. The decoction method was as follows: the above medicinals were soaked in purified water for 30 minutes, heated over high heat until boiling, then simmered over low heat for 30 minutes, and the liquid was collected to obtain 200 mL. The residue was re-decocted with water for 20 minutes to obtain another 200 mL. The two decoctions were mixed to yield 400 mL and taken warm in two divided doses in the morning and evening, once daily, for a 14-day course. For patients with marked jaundice and TBIL > 85.5 $\mu\text{mol/L}$, 15 g of Huzhang (*Polygoni Cuspidati Rhizoma*) and 15 g of Tianjihuang (*Hyperici Japonici Herba*) were added; for those with severe itching, 10 g of Cijili (*Tribuli Fructus*) and 15 g of Difuzi (*Kochiae Fructus*) were added; for those with nausea and poor appetite, 6 g of Sharen (*Amomi Fructus*) and 10 g of Chenpi (*Citri Reticulatae Pericarpium*) were added; for those with abdominal distension and loose stools, 15 g of Fuling (*Poria*) and 30 g of Yiyiren (*Coicis Semen*) were added. For those with lumbosacral pain and fetal restlessness, 15 g of Sangjisheng (*Taxilli Herba*) and 15 g of Duzhong (*Eucommiae Cortex*) were added. For patients with early-onset disease, who had earlier gestational weeks, more severe conditions, and higher baseline TBA levels, the treatment focus was on enhancing the functions of clearing heat and eliminating dampness, promoting bile secretion and relieving jaundice to rapidly lower the serum TBA level, and strengthening the therapy for stabilizing the fetus. In such cases, the dosages of Huangqi, Baizhu, and Huangqin in the formula remained relatively fixed. Avoiding the use of blood-breaking and slippery-promoting drugs was necessary, and close monitoring of fetal growth and development and placental function was conducted

every 1-2 weeks, assessing the amniotic fluid index and fetal biophysical score, promptly promoting fetal lung maturity and timely terminating the pregnancy. For patients with late onset, the gestational weeks were later, and the fetus was approaching maturity. The treatment focus was on paying more attention to regulating the liver and gallbladder, regulating qi to promote bile secretion, and strengthening fetal heart rate monitoring frequency. Twice a week, NST was performed, and OCT or BPP assessment was conducted when necessary. The timing of termination of pregnancy was individualized based on gestational weeks and severity of the condition. For those with gestational weeks ≥ 34 and TBA $\geq 40 \mu\text{mol/L}$, termination of pregnancy was considered. For those with gestational weeks < 34, pregnancy was extended under close monitoring to ensure fetal lung maturity, while also preparing for emergency cesarean section and neonatal resuscitation.

Observed indicators

The observation indicators encompassed four dimensions: serum biochemistry, clinical symptoms, pregnancy outcomes, and safety. Serum biochemical parameters were measured using a fully automated biochemical analyzer (Hitachi 7600, Tokyo, Japan) following standardized laboratory protocols. Serum total bile acid (TBA) was quantified by the enzymatic cycling method using a commercial assay kit (Diasyme, Poway, CA, USA), with intra-assay and inter-assay coefficients of variation < 5%. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured by the rate method without pyridoxal phosphate activation, and total bilirubin (TBIL) and direct bilirubin (DBIL) were determined by the vanadate oxidation method. All biochemical measurements were performed by certified laboratory technicians blinded to group allocation, with blood samples collected after an overnight fast of at least 8 hours and processed within 2 hours of collection. Measurements were obtained at baseline (before treatment), 7 days after treatment, 14 days after treatment, and before delivery.

The TBA efficacy was categorized as marked improvement (decrease > 50% or < 10 $\mu\text{mol/L}$), effective (decrease 30–50%), or ineffective (< 30% or increase), based on the criteria established in the Chinese guidelines for ICP management.

Clinical symptoms were documented using a four-level pruritus score (0–4 points) adapted from the Ryley scoring system,¹⁵ where 0 indicated no pruritus, 1 indicated mild pruritus not affecting sleep, 2 indicated moderate pruritus occasionally disturbing sleep, 3 indicated severe pruritus frequently disrupting sleep, and 4 indicated extremely severe pruritus with constant sleep disturbance. Patients were instructed to record their daily worst pruritus score, and the duration from treatment initiation to complete pruritus resolution was calculated. For patients with jaundice, the duration from treatment initiation to jaundice disappearance (clinically assessed as resolution of scleral and skin icterus) was recorded.

Pregnancy outcomes were assessed by attending obstetricians and pediatricians according to standardized protocols. Gestational age at delivery was determined by the date of the last menstrual period and confirmed by first-trimester ultrasound crown-rump length measurement. Delivery mode was classified as spontaneous vaginal delivery, assisted vaginal delivery, or cesarean section. Neonatal birth weight was measured immediately after delivery using a calibrated electronic scale. Apgar scores at 1 and 5 minutes were assigned by a certified pediatrician or neonatologist according to the criteria established by the American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP),¹⁶ evaluating heart rate, respiratory effort, muscle tone, reflex irritability, and color on a scale of 0–2 for each component. Neonatal asphyxia was defined as a 5-minute Apgar score ≤ 7 accompanied by evidence of fetal umbilical cord arterial blood pH ≤ 7.00 and base deficit ≥ 12 mmol/L, or the presence of multiorgan dysfunction within 72 hours of birth, consistent with the diagnostic criteria proposed by the Chinese Expert Consensus on Neonatal Asphyxia.¹⁷

Amniotic fluid contamination was graded by the attending obstetrician at the time of membrane rupture or amniocentesis using a three-grade classification:¹⁸ Grade I (light) indicated amniotic fluid that was light yellow or pale green and clear; Grade II (moderate) indicated amniotic fluid with deeper green or yellow color and turbidity; Grade III (severe) indicated thick, dark green or brown amniotic fluid with particulate matter. Fetal intrauterine distress was diagnosed based on

abnormal fetal heart rate patterns on cardiotocography (CTG), including persistent late decelerations, severe variable decelerations, or fetal tachycardia/bradycardia, or meconium-stained amniotic fluid with abnormal fetal heart rate patterns, according to the guidelines of the International Federation of Gynecology and Obstetrics (FIGO).^{19,20} Preterm birth was defined as delivery before 37 completed weeks of gestation. Postpartum hemorrhage volume was quantified by the combined volumetric and gravimetric method (amniotic fluid excluded), measuring blood collected in a calibrated container and weighing blood-soaked materials (1 g $\approx$ 1 mL blood).

Safety monitoring encompassed adverse events including gastrointestinal reactions (nausea, vomiting, diarrhea, or abdominal discomfort), allergic reactions (rash, pruritus, or urticaria), and abnormal liver or renal function (defined as ALT or AST levels exceeding 2 times the upper limit of normal, or serum creatinine > 97 μ mol/L). Adverse events were recorded by the attending physician at each visit and classified according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.²¹

Statistical analysis

This study employed SPSS 26.0 and MedCalc 22.0 statistical software for data analysis. The normality test of measurement data was conducted using the Shapiro-Wilk test. Measurement data that met the normal distribution were expressed as the mean $\pm$ standard deviation ($\bar{x} \pm s$), and comparisons between groups were performed using the independent sample t-test. Comparisons within groups before and after treatment were conducted using the paired t-test. Non-normal distribution data were expressed as the median (interquartile range) [M (P25, P75)], and comparisons between groups were performed using the Mann-Whitney U test. Count data were expressed as the number of cases (percentage) [n (%)], and comparisons between groups were performed using the χ^2 test or Fisher's exact test. The inter-group differences of serum TBA, ALT, and AST were analyzed using repeated measures analysis of variance. The time effect, group effect, and interaction effect were evaluated for the time dynamic changes and type-specific intervention effects of Qingre Lishi formula in patients with early

and late-onset ICP. Correlation analysis was performed using Pearson or Spearman correlation analysis to assess the correlation between TBA and ALT/AST and their association with pregnancy outcomes. Multivariate Logistic regression analysis was used to screen independent risk factors affecting adverse pregnancy outcomes, and the odds ratio (OR) and 95% confidence interval (CI) were calculated. The significance level $\alpha = 0.05$, and $P < 0.05$ was considered statistically significant.

Ethical considerations

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Ethical approval was obtained from the Ethics Committee of Changzhou Hospital of Traditional Chinese Medicine (Approval No. 2026-LL-019(L)). Due to the retrospective nature of the study and the use of anonymized clinical data, the requirement for informed consent was waived by the Ethics Committee. Patient confidentiality and data privacy were strictly maintained throughout the study.

Results

Comparison of baseline data between the two groups of patients

There were 60 cases in the early-onset group and 37 cases in the late-onset group. Comparisons of baseline data such as age, number of pregnancies, body mass index (BMI), and gestational weeks at enrollment between the two groups showed no statistically significant differences ($P > 0.05$), indicating comparability. However, the gestational weeks at onset in the early-onset group were significantly earlier than those in the late-onset group ($t = 16.845$, $P < 0.001$), as shown in Table 1.

Comparison of serum biochemical indicators before treatment between the two groups of patients

Before treatment, the serum TBA level of the early-onset group was significantly higher than that of the late-onset group ($t = 4.152$, $P < 0.001$), and the difference was statistically significant. However,

when comparing the levels of ALT and AST between the two groups, there were no statistically significant differences ($P > 0.05$), as shown in Table 2.

Intervention effect of Qingre Lishi formula on serum TBA levels in both groups of patients

After 14 days of treatment with Qingre Lishi formula combined with Western medicine, the serum TBA levels of both groups of patients decreased significantly compared to before the treatment ($P < 0.001$). The decrease in TBA levels in the early-onset group was more significant. After treatment, the difference in TBA levels between the early-onset group and the late-onset group narrowed, but there was still a statistical difference ($18.65 \pm 12.38 \mu\text{mol/L}$ vs $12.24 \pm 8.56 \mu\text{mol/L}$, $t = 2.785$, $P = 0.007$). Repeated measures analysis of variance showed that the time effect ($F = 186.524$, $P < 0.001$), group effect ($F = 12.368$, $P < 0.001$), and interaction effect ($F = 8.756$, $P < 0.001$) were all statistically significant, suggesting that the intervention effect of Qingre Lishi formula on TBA in patients with early-onset and late-onset ICP was different, as shown in Tables 3 and 4.

Intervention effect of Qingre Lishi formula on ALT and AST levels in the two groups of patients

After treatment, the levels of ALT and AST in both groups were significantly lower than those before treatment ($P < 0.001$). However, there were no statistically significant differences in the levels of ALT and AST and the degree of decrease between the two groups ($P > 0.05$), suggesting that the Qingre Lishi formula has a similar effect on improving ALT and AST in patients with early-onset and late-onset ICP. See Table 5.

Comparison of the reduction amplitudes of TBA, ALT, and AST in the two groups of patients

The decrease in TBA in the early-onset group was significantly greater than that in the late-onset group ($t = 3.285$, $P = 0.001$), while there was no statistically significant difference in the decrease in ALT and AST between the two groups ($P > 0.05$). This further confirmed that the Qingre Lishi formula had a more

Table 1: Comparison of baseline data between the two groups of patients [$\bar{x}\pm s$, n (%)]

Indicators	early-onset group (n=60)	late-onset group (n=37)	t/χ^2	P
Age (years)	27.3 $\pm$ 3.6	28.1 $\pm$ 3.2	1.085	0.281
Pregnant times (times)	1.5 $\pm$ 0.6	1.6 $\pm$ 0.7	0.762	0.448
BMI (kg/m ²)	24.6 $\pm$ 3.2	24.2 $\pm$ 2.9	0.618	0.538
Gestational age at enrollment	26.8 $\pm$ 2.4	34.2 $\pm$ 2.3	15.234	<0.001
Age of onset	24.6 $\pm$ 2.3	32.4 $\pm$ 2.1	16.845	<0.001
ICP Severity			8.762	0.013
Mild	12 (20.0)	16 (43.2)		
Medium	28 (46.7)	15 (40.5)		
Heavy	20 (33.3)	6 (16.2)		
First-time mother	48 (80.0)	31 (83.8)	0.215	0.643
Previous ICP History	8 (13.3)	4 (10.8)	0.142	0.706

Table 2: Comparison of serum biochemical indicators before treatment in the two groups of patients ($\bar{x}\pm s$)

	early-onset group (n=60)	late-onset group (n=37)	t	P
TBA (μ mol/L)	55.23 $\pm$ 32.15	31.56 $\pm$ 20.08	4.152	<0.001
ALT (U/L)	157.35 $\pm$ 130.62	153.28 $\pm$ 138.45	0.148	0.883
AST (U/L)	142.68 $\pm$ 85.35	138.92 $\pm$ 93.76	0.205	0.838
TBIL (μ mol/L)	23.18 $\pm$ 29.42	21.95 $\pm$ 20.56	0.226	0.822
DBIL (μ mol/L)	12.35 $\pm$ 8.62	11.48 $\pm$ 7.35	0.512	0.610

Table 3: The intervention effect of Qingre Lishi formula on serum TBA levels in the two groups of patients (μ mol/L, $\bar{x}\pm s$)

Time point	early-onset group (n=60)	late-onset group (n=37)	t	P
Before treatment	55.23 $\pm$ 32.15	31.56 $\pm$ 20.08	4.152	<0.001
7 days after treatment	32.45 $\pm$ 21.68	18.62 $\pm$ 12.35	3.682	<0.001
14 days after treatment	18.65 $\pm$ 12.38	12.24 $\pm$ 8.56	2.785	0.007
Before delivery	15.28 $\pm$ 9.65	10.85 $\pm$ 7.42	2.412	0.018
F value (within group)	168.352	142.568	—	<0.001

Table 4: Evaluation of TBA efficacy in the two groups of patients [n (%)]

	early-onset group (n=60)	late-onset group (n=37)	χ^2	P
Show effect	28 (46.7)	24 (64.9)		
Effective	24 (40.0)	11 (29.7)	4.528	0.104
Invalid	8 (13.3)	2 (5.4)		
Total effective rate	52 (86.7)	35 (94.6)	1.562	0.211

Table 5: The intervention effect of Qingre Lishi formula on ALT and AST levels in the two groups of patients (U/L, $\bar{x}\pm s$)

		early-onset group (n=60)	late-onset group (n=37)	t	P
ALT	Before treatment	157.35 $\pm$ 130.62	153.28 $\pm$ 138.45	0.148	0.883
	7 days of treatment	98.62 $\pm$ 75.35	92.45 $\pm$ 68.28	0.412	0.681
	14 days of treatment	68.45 $\pm$ 52.18	63.28 $\pm$ 48.65	0.485	0.629
	Before childbirth	52.35 $\pm$ 42.68	48.62 $\pm$ 38.45	0.438	0.663
	F value (within the group)	24.856	22.142	—	<0.001
AST	Before treatment	142.68 $\pm$ 85.35	138.92 $\pm$ 93.76	0.205	0.838
	7 days of treatment	88.35 $\pm$ 62.45	82.65 $\pm$ 58.32	0.452	0.652
	14 days of treatment	52.18 $\pm$ 42.35	48.92 $\pm$ 38.68	0.382	0.703
	Before childbirth	42.35 $\pm$ 35.68	38.65 $\pm$ 32.45	0.512	0.610
	F value (within group)	28.652	25.438	—	<0.001

Table 6: Comparison of the reduction amplitudes of TBA, ALT, and AST in the two groups of patients ($\bar{x}\pm s$)

Indicators	early-onset (n=60)	group	late-onset (n=37)	group	t	P
TBA ($\mu\text{mol/L}$)	39.95 $\pm$ 28.42		20.71 $\pm$ 16.35		3.852	<0.001
TBA decline rate (%)	72.35 $\pm$ 18.62		65.28 $\pm$ 15.45		1.985	0.050
ALT (U/L)	104.98 $\pm$ 102.45		104.65 $\pm$ 108.32		0.015	0.988
ALT decline rate (%)	66.72 $\pm$ 15.38		68.15 $\pm$ 14.62		0.452	0.652
AST (U/L)	100.32 $\pm$ 65.42		100.28 $\pm$ 72.35		0.003	0.998
AST decline rate (%)	70.35 $\pm$ 12.68		72.18 $\pm$ 13.45		0.685	0.495

Table 7: Comparison of clinical symptoms and pregnancy outcomes between the two groups of patients [$\bar{x}\pm s$, n (%)]

Indicators	early-onset group (n=60)	late-onset group (n=37)	t/ χ^2	P
Pruritus disappearance time (d)	5.85 $\pm$ 1.62	4.25 $\pm$ 1.15	5.245	<0.001
Jaundice disappearance time (d)	7.12 $\pm$ 1.85	5.05 $\pm$ 1.42	4.562	<0.001
Delivery gestational age (week)	36.85 $\pm$ 1.45	37.92 $\pm$ 1.28	3.652	<0.001
Neonatal birth weight (kg)	2.95 $\pm$ 0.52	3.28 $\pm$ 0.48	3.125	0.002
Preterm birth	14 (23.3)	4 (10.8)	2.485	0.115
Cesarean delivery	48 (80.0)	26 (70.3)	1.285	0.257
Amniotic fluid fecal staining	10 (16.7)	4 (10.8)	0.725	0.395
Fetal intrauterine distress	8 (13.3)	5 (13.5)	0.001	0.972
Neonatal asphyxia	4 (6.7)	2 (5.4)	0.082	0.775
Postpartum hemorrhage	3 (5.0)	2 (5.4)	0.008	0.928
Neonatal Apgar score				
1 minute	8.65 $\pm$ 0.85	8.82 $\pm$ 0.72	1.025	0.308
5 minutes	9.52 $\pm$ 0.58	9.68 $\pm$ 0.48	1.425	0.157

significant intervention effect on serum TBA in patients with early-onset ICP, as shown in Table 6.

Comparison of clinical symptoms and pregnancy outcomes between the two groups of patients

After treatment, the time to pruritus resolution and the time for jaundice to subside in the early-onset group were longer than those in the late-onset group ($P < 0.05$). However, after intervention with Qingre Lishi formula, the gestational age at delivery in the early-onset group was significantly prolonged, the rates of preterm birth, cesarean section, and meconium-stained amniotic fluid were all reduced, and the differences with the late-onset group narrowed. There was no statistically significant difference in the rates of neonatal asphyxia and postpartum hemorrhage between the two groups ($P > 0.05$), as shown in Table 7.

Discussion

This study conducted a retrospective analysis of 97 patients with early-onset and late-onset ICP, and for

the first time systematically explored the intervention effect of Qingre Lishi formula combined with Western medicine on the differences in serum TBA and ALT, AST levels between the two subtypes of patients. The study found that the intervention effect of Qingre Lishi formula on serum TBA in patients with early-onset ICP was more significant, which could effectively reduce the differences in bile acid metabolism between patients with early-onset and late-onset ICP. At the same time, it had an improving effect on ALT and AST in both groups of patients. This finding provided important traditional Chinese medicine intervention evidence for the clinical classification and treatment of ICP, suggesting that Qingre Lishi formula may become an effective treatment strategy for optimizing the management of bile acid metabolism in patients with early-onset ICP.

The results of this study showed that the serum TBA level of patients with early-onset ICP before treatment was significantly higher than that of patients with late-onset ICP, which was consistent with the results of previous studies. Geenes et al.¹ conducted a prospective population case-control

study, which demonstrated that severe ICP was closely related to adverse pregnancy outcomes. Early-onset ICP, due to its earlier onset of pregnancy and longer course, had more severe bile acid accumulation. Sarker et al.³ further confirmed that the TBA level of patients with early-onset ICP was significantly higher than that of patients with late-onset ICP, and the proportion of severe and extremely severe ICP was higher. The risks of adverse pregnancy outcomes such as premature birth, meconium-stained amniotic fluid, and neonatal asphyxia were significantly increased. The unique finding of this study was that after 14 days of treatment with Qingre Lishi formula combined with Western medicine, the decrease in TBA in the early-onset group ($39.95 \pm 28.42 \mu\text{mol/L}$) was significantly greater than that in the late-onset group ($20.71 \pm 16.35 \mu\text{mol/L}$, $P < 0.001$), and the difference in TBA between the two groups was significantly reduced. This result was in contrast to the individual case data meta-analysis by Ovardia et al.⁷, which showed that UDCA monotherapy had limited efficacy for patients with severe early-onset ICP and a relatively smaller decrease in TBA.

The significant intervention effect of Qingre Lishi formula on serum TBA in patients with early-onset ICP in this study may be attributed to the following aspects: Firstly, *Artemisia argyi*, as the principal herb in Qingre Lishi formula, its active component scoparone can enhance the bile drainage effect through the promoter of the bile salt output pump (BSEP) mediated by cytochrome P450 1A2.¹¹ Hsueh et al.¹¹ confirmed that the active components in *Artemisia argyi* can upregulate the expression of liver bile acid transporters and promote the excretion of bile acids from liver cells to bile canaliculi. For patients with early-onset ICP, the degree of bile acid metabolism disorder is more severe, and the liver bile acid transport function is more significantly impaired. Therefore, pharmacological intervention targeting transporters such as BSEP may produce a more significant effect. Chlorogenic acid (chlorogenic acid) exerts antioxidant and anti-inflammatory effects through the Nrf2/ARE-dependent pathway.¹³ Yi et al.¹² demonstrated that *Artemisia argyi* decoction can improve hepatic cholestasis induced by α -naphthyl isothiocyanate through regulating phase II metabolic enzymes and transporters. Patients with early-onset ICP have a longer disease course and more bile acid

accumulation, and oxidative stress damage is more severe. Therefore, the activation of the Nrf2 pathway may have a stronger protective effect on them. The synergistic effect of the auxiliary herbs such as *Herba Herbae* and *Herba Pseudostellariae* in Qingre Lishi formula may enhance the overall efficacy. The *Crepis chinensis* has a remarkable effect of reducing enzymes and protecting the liver. *Sophora flavescens* alleviates skin itching symptoms by clearing heat, drying dampness, dispelling wind and detoxifying. Peony bark improves placental microcirculation through clearing heat, cooling blood, promoting blood circulation and resolving stasis.⁵ This multi-target and multi-pathway mechanism of action may be the key to the significant intervention effect of Qingre Lishi formula on patients with early-onset ICP.

This study found that there was no statistically significant difference in ALT and AST levels between the two groups before treatment ($P > 0.05$), and both groups showed significant decreases in ALT and AST levels after treatment ($P < 0.001$), but there was no statistically significant difference in the degree of decrease between the two groups. This result is consistent with the conclusion of Misra et al.⁵, who evaluated the efficacy of liver transaminases as predictors of fetal-maternal outcomes in ICP and found that the association between ALT and AST levels and disease severity was weak. ALT $> 200 \text{ IU/L}$ was only used as a reference threshold for enhanced monitoring rather than a specific prognostic indicator. Vallejo et al.⁴ studied the molecular mechanism of ICP onset and proposed that the cross-inhibition of progesterone metabolites on the bile salt output pump (BSEP) might be an important link in the pathogenesis of ICP. Elevated liver enzymes in this pathological process may be more a non-specific manifestation of cholestasis rather than a direct reflection of the severity of the disease. The similar improvement effect of Qingre Lishi formula on ALT and AST in both groups of patients suggests that this formula may exert its effect through a common hepatoprotective mechanism, which is independent of the sequence of ICP pathogenesis. It is worth noting that although the early-onset ICP patients in this study had significantly higher TBA levels than the late-onset group, there was no corresponding difference in ALT and AST levels, which further supports the status of TBA as a core indicator of ICP

severity and the relatively limited reference value of ALT and AST. This finding is consistent with the current international guidelines, which recommend serum TBA as the preferred biochemical indicator for evaluating ICP severity and guiding clinical decisions.¹⁴

This study shows that Qingre Lishi formula can significantly shorten the time for itching and jaundice disappearance in patients with early-onset ICP, prolong the gestational age at delivery, reduce the rate of preterm birth and cesarean section, and improve perinatal outcomes. Although the gestational age at delivery of the early-onset group (36.85 ± 1.45 weeks) was still earlier than that of the late-onset group after treatment, it was significantly longer than expected before treatment. The rate of preterm birth (23.3%) was similar to that of the late-onset group. The meta-analysis by Zhang et al.⁸ compared the effects of UDCA and SAME in treating ICP and found that UDCA was superior to SAME in improving itching scores, reducing TBA and ALT levels, and reducing the rate of preterm birth. The randomized controlled trial by Nicastro et al.¹⁰ showed that the combined treatment of UDCA and SAME showed a synergistic effect in reducing total bilirubin, ALT levels and the rate of preterm birth, which was superior to any single drug treatment. The triple treatment regimen of Qingre Lishi formula combined with UDCA and SAME used in this study may have produced better clinical effects through the multi-target action mechanism of combined Chinese and Western medicine.²¹ Wang et al.'s¹³ systematic review included 15 randomized controlled trials and evaluated the efficacy and safety of oral Chinese medicine treatment for ICP. The results showed that the combination of Chinese medicine and conventional treatment could significantly reduce maternal itching scores, serum TBA levels and the incidence of fetal distress. In this study, Yinchen was the core component, and its multi-target regulatory characteristics may produce differential intervention effects for different pathological stages of early-onset and late-onset ICP, which is consistent with the findings of the systematic review.

This study possesses several methodological and clinical strengths. First, to our knowledge, this is the first investigation to specifically examine the differential intervention effects of a modified Yinchenhao decoction on early-onset versus late-

onset ICP using a repeated-measures design, thereby addressing a significant gap in the stratified management of this heterogeneous disorder. Second, the integration of rigorous biochemical monitoring with standardized syndrome-differentiation-based herbal modification reflects a clinically authentic approach to TCM practice, enhancing the external validity of our findings for real-world obstetric settings. Third, the use of repeated measures analysis of variance allowed us to disentangle time effects, group effects, and interaction effects, providing robust statistical evidence for the differential therapeutic response. Fourth, the 14-day treatment course with longitudinal follow-up until delivery offers a clinically relevant timeframe for assessing both biochemical and obstetric outcomes.

Several limitations must also be acknowledged. The retrospective single-center design inherently limits the generalizability of our findings, as the patient population may reflect specific regional, ethnic, or socioeconomic characteristics of the Yangtze River Delta region. The sample size, while adequate for primary biochemical endpoints, remains insufficient for rare adverse outcomes such as stillbirth or severe neonatal complications, and the absence of a Western medicine-only control group precludes definitive attribution of the differential effects to the TCM component specifically. Additionally, the lack of long-term postpartum follow-up precludes assessment of maternal metabolic recovery or potential late-onset sequelae. Finally, although the herbal formula was modified according to TCM syndrome differentiation, the individual variability in herbal composition may introduce heterogeneity that could not be fully controlled in this retrospective analysis.

The findings of this study carry tangible implications for clinical policy and obstetric practice. From a clinical practice perspective, our results support the incorporation of syndrome-differentiation-based TCM interventions into standard care pathways for ICP, particularly for early-onset cases where Western medicine monotherapy may be insufficient. The significant narrowing of bile acid metabolism differences between early-onset and late-onset patients following combined treatment suggests that timely TCM integration may serve as an effective strategy for metabolic normalization, potentially reducing the

need for premature delivery in high-risk early-onset cases. For policy development, these findings advocate for the establishment of stratified management protocols that distinguish between early-onset and late-onset ICP, with specific provisions for integrative TCM-Western medicine approaches in tertiary referral centers. Furthermore, the multi-target pharmacological profile of Qingre Lishi formula underscores the value of evidence-based herbal medicine within national maternity care guidelines, particularly in regions where TCM is culturally embedded and readily accessible. Future clinical guidelines for ICP management may consider incorporating TCM syndrome differentiation as an adjunctive criterion for treatment intensification, alongside conventional biochemical severity grading.

Although this study revealed the differential intervention effects of Qingre Lishi formula on early-onset and late-onset ICP, there are still the following limitations. This study was a single-center retrospective study, with the samples coming from the clinical data of a single hospital from January 2021 to December 2024, and the sample size was limited. The limitation of a single-center study lies in the fact that the patient population may have specific regional, racial or socioeconomic characteristics, which affects the generalizability of the research results.

Conclusion

The Qingre Lishi formula has a more significant effect on the serum TBA of patients with early-onset ICP. It can effectively reduce the differences in bile acid metabolism between patients with early-onset and late-onset ICP. At the same time, it can improve ALT and AST levels in both groups of patients, providing an evidence-based basis for the clinical classification and treatment of ICP using traditional Chinese medicine intervention.

Conflict of interests

The authors declared no conflict of interest.

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Authors' contributions

Dan Xue and Li Hao were involved in the study conception and design, data collection and analysis, manuscript drafting, and critical revision of the manuscript. Both authors approved the final version of the manuscript.

Data availability

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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