SYSTEMATIC REVIEW

Intrahepatic cholestasis of pregnancy and maternal dyslipidemia: a systematic review and meta-analysis

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Abstract

Introduction: The association between intrahepatic cholestasis of pregnancy (ICP) and maternal lipid metabolism remains unknown. This systematic review and meta-analysis aimed to evaluate the association between ICP and maternal lipid metabolism.

Material and methods: We systematically searched Medline, Embase and the Cochrane Library (up to December 11, 2021) to identify relevant studies that investigated ICP and maternal plasma lipid concentrations. The weighted mean difference (WMD) and 95% confidence intervals (CI) were calculated using random-effects models. A subgroup analysis was conducted to identify the potential sources of heterogeneity. Potential publication bias was tested using funnel plots and the Egger’s and Begg’s tests. This meta-analysis was registered with PROSPERO (CRD42021293783).

Results: Eleven studies were included in this qualitative analysis. A random-effects meta-analysis of data from the final included nine studies (n = 786 participants) showed a significant association between ICP and maternal dyslipidemia, with elevated levels of triglycerides (WMD, 0.67 mmol/L; 95% CI 0.39–0.95; P < 0.001), total cholesterol (WMD, 1.08 mmol/L; 95% CI 0.58–1.58; P < 0.001), low-density lipoprotein cholesterol (WMD, 1.08 mmol/L; 95% CI 0.53–1.64; P < 0.001), and reduced high-density lipoprotein cholesterol level (WMD, −0.38 mmol/L; 95% CI −0.53 to −0.23; P < 0.001) vs normal pregnancies.

Conclusions: The present study’s findings support an association between ICP and maternal dyslipidemia. ICP pregnancies have dysregulated lipid metabolism vs normal pregnancies.

KEYWORDS
cholesterol, dyslipidemia, intrahepatic cholestasis of pregnancy, lipid, triglycerides

Abbreviations: BA, bile acid; CI, confidence intervals; FXR, farnesoid X receptor; GDM, gestational diabetes mellitus; HDL, high-density lipoprotein; ICP, intrahepatic cholestasis of pregnancy; LDL, low-density lipoprotein; NOS, Newcastle–Ottawa Scale; TC, total cholesterol; TG, triglycerides; UDCA, ursodeoxycholic acid; WMD, weighted mean difference.

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1  |  INTRODUCTION

Intrahepatic cholestasis of pregnancy (ICP) is a pregnancy-related disease characterized by pruritus and elevated levels of total bile acids (BA) in the second and late trimesters with a wide incidence of 0.2%–25% that varies among populations and regions.\(^1,2\) ICP is considered a benign disease in pregnant women but is associated with adverse perinatal outcomes, stillbirth being the most severe.\(^3\) Ursodeoxycholic acid (UDCA) is a first-line treatment for ICP. Recent randomized control studies and evidence-based studies revealed that treatment with UDCA probably results in a small improvement in pruritus and reductions in maternal serum total BA and alanine aminotransferase levels. However, UDCA treatment may not be able to reduce adverse perinatal outcomes in ICP women.\(^4,6\)

The etiology and pathogenesis of ICP are complex and unclear and may be attributed to genetic, hormonal and environmental factors.\(^2\) Recent studies examined the relation between ICP and metabolism, hypothesizing that ICP may be part of a metabolic disorder. Increasing evidence supports the hypothesis that farnesoid X receptor (FXR), the primary BA receptor, may influence lipid and glucose metabolism and homeostasis.\(^7,8\) It is reasonable to believe that elevated BA levels can influence lipid and glucose metabolism in women with ICP. A recent meta-analysis revealed that women with ICP were more likely to have gestational diabetes mellitus (GDM).\(^9\) However, study findings of ICP and maternal dyslipidemia have been inconsistent. As early as 1973, a cross-sectional study reported an association between ICP and dysregulated lipid profiles.\(^10\) In contrast, some studies reported negative conclusions that ICP was not related to dyslipidemia.\(^11\) This study aimed to investigate the potential association between ICP and maternal lipid metabolism to understand further the etiology and pathophysiology of ICP.

2  |  MATERIAL AND METHODS

2.1  |  Search strategy

This study was designed in accordance with the guidelines of the 2009 Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.\(^12\) This meta-analysis was registered with PROSPERO (CRD42021293783, www.crd.york.ac.uk/PROSPERO). Related literature published before December 11, 2021 was systematically searched in the Medline, Embase and Cochrane Library databases without limitations on publication year or language. The search strategy was based on a combination of the following terms: cholestasis, intrahepatic; pregnancy; dyslipidemia; dyslipoproteinemia; triglycerides; total cholesterol; high-density lipoprotein; and low-density lipoprotein. The systematic search strategy is presented in Appendix S1. References from the included studies were manually crosschecked for additional relevant studies that were missed in the database search.

2.2  |  Study selection

Studies were included if they met the following inclusion criteria: (i) randomized controlled trials, prospective or retrospective cohort studies, and case–control studies published in English and Chinese, hopefully providing a more comprehensive presentation of the topic; (ii) pregnant women diagnosed with ICP and healthy pregnant controls; (iii) diagnosis of ICP based on the presence of pruritus and elevated total BA levels; and (iv) availability of information on maternal lipid concentrations, including triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol. Studies were excluded if: (i) a case series with no more than five patients; (ii) lacking gestational data for maternal lipid concentrations (only pre- or postpartum data available); (iii) inclusion of only one study group without a comparison group; and (iv) poor baseline information comparability, such as different body mass index between groups and the existence of pregestational metabolic disorders.

Two reviewers (YZ and TX) independently reviewed the retrieved titles and abstracts for eligible studies that met the inclusion criteria. When a decision could be made, full-text screening was performed to make the final decision. When agreement could not be reached, a third independent reviewer (XW) was consulted until consensus was reached.

2.3  |  Data extraction

Two independent reviewers (YZ and TX) performed the data extraction carefully according to the study criteria. The relevant information was extracted from the eligible studies as follows: last name of the first author, publication year, study region, group sample sizes, diagnosis criteria for ICP, and maternal lipid levels (TG, TC, HDL cholesterol, LDL cholesterol). Data are shown as mean±standard deviation when the data were available. Units of all maternal lipid factors, including TG, TC, HDL cholesterol and LDL cholesterol, are shown as millimoles per liter. Multipliers of 0.026 and 0.011 were used to convert cholesterol (TC, HDL cholesterol and LDL cholesterol) and TG units from milligrams per deciliter to millimoles per liter, respectively. Authors were contacted if important information was missing. A third reviewer (XW) extracted the data independently for consensus when a discrepancy existed.

2.4  |  Quality assessment

Study quality was assessed independently by two reviewers (YZ and TX) according to the modified Newcastle–Ottawa Scale (NOS).\(^13\)
according to the following parameters: selection (0–4 stars), comparability (0–2 stars) and outcome (0–3 stars). The total quality score of each study was 0–9 stars. Studies with seven or more total stars were of high quality, those with six stars were of moderate quality, and those with fewer than six stars were of low quality. Disagreements were resolved through consultation with a third reviewer (XW).

2.5 Statistical analysis

All statistical analyses were performed using STATA 14.0 (Stata Corp, College Station, TX, USA). A meta-analysis of maternal lipid concentrations was performed using a random-effects model instead of a fixed-effects model because of the heterogeneity of studies in terms of test methods or machines used to determine lipid concentrations, gestational age at the time of the test, influence of ICP treatment and fasting state, and demographic characteristics of individual trials (maternal age, population, maternal body mass index, etc.). The weighted mean difference (WMD) was used as a summary statistic in the meta-analysis of maternal lipid concentrations and is expressed as WMD and 95% confidence interval (95% CI). I² was calculated to test statistical heterogeneity among studies. An I² >50% indicated substantial heterogeneity. A subgroup analysis by study quality was conducted to assess potential sources of heterogeneity. To evaluate the influence of each study on the overall estimated effect size, sensitivity analysis of individual studies was conducted by iterative removal of each study and repeat of the analysis. Potential publication bias was tested using a funnel plot, Egger’s test and Begg’s test. Statistical significance was set at P < 0.05.

3 RESULTS

3.1 General study characteristics

The initial literature search revealed 351 relevant references for ICP and maternal lipid concentration. After duplicates were removed, the titles and/or abstracts of the 278 references were carefully screened. After that assessment, 11 studies met the inclusion criteria and were included in the qualitative analysis. Finally, nine studies were included in the final meta-analysis, with all nine reporting TG, TC and HDL cholesterol data and eight reporting LDL cholesterol data (Figure 1).

The characteristics of the studies included in this systematic review and meta-analysis are shown in Tables 1 and 2. A total of 786 pregnant women were included; of them, 427 were diagnosed with ICP and 359 were healthy controls. A total of 41–108 participants were included in each study, the publication years of which were 1996–2021. Among these 11 studies, four were conducted in China,20,22 two in Poland,23 two in Turkey,26,27 one in the UK,16 and one in the USA.19

Among the 11 included studies, one was a prospective case–control study17 and 10 were cohort studies, including seven prospective cohort studies.34,16,18–22 Study quality was assessed using the modified NOS. The median NOS quality score of the included studies was 7 (mean, 6.55 ± 0.82; range, 5–8). Except for one study that obtained 5 stars in the quality assessment,18 all were of moderate to high quality according to the modified NOS score.

3.2 Synthesis of results

A random-effects model meta-analysis showed a significant association between ICP and maternal lipid concentration. Women with ICP had significantly higher plasma levels of TG (WMD, 0.67 mmol/L; 95% CI 0.39–0.95; P < 0.001), TC (WMD, 1.08 mmol/L; 95% CI 0.58–1.58; P < 0.001) and LDL cholesterol (WMD, 1.08 mmol/L; 95% CI 0.53–1.64; P < 0.001) compared with healthy pregnant women. In contrast, the mean HDL cholesterol level was significantly lower in the ICP vs healthy controls (WMD, −0.38 mmol/L; 95% CI −0.53 to −0.23; P < 0.001) (Figure 2).

The heterogeneity among the retrieved studies was significant. The I² values of the meta-analysis of TG, TC, HDL cholesterol and LDL cholesterol were 72.8% (P < 0.001), 90.8% (P < 0.001), 93.9% (P < 0.001) and 88.3% (P < 0.001), respectively. Therefore, a subgroup analysis was performed to assess potential sources of heterogeneity. The included studies were divided into high-quality and not high-quality groups based on whether the NOS score was 7 or higher. Figure 2 shows the subgroup analysis for each meta-analysis; the association between ICP and maternal lipid concentrations was still significant and consistent in the high-quality and not high-quality groups. Meanwhile, the I² of the high-quality group meta-analysis reduced remarkably to 45.3% (P = 0.140), 31.5% (P = 0.223),
| Author          | Ref.       | Country     | Study design | Maternal age (years)          | BMI (kg/m²) | Gestational age at testing (weeks) | Testing performed before ICP treatment | Tests were fasting or not | NOS scores |
|-----------------|------------|-------------|--------------|------------------------------|-------------|-----------------------------------|----------------------------------------|----------------------------|-------------|
| Nikkila         | 14         | Finland     | Pro CS       | ICP: 30.1 ± 5.29; Control: 30.7 ± 3.25 | NA           | Once before delivery              | NA                                    | 10-h overnight fast       | 7           |
| Dai             | 11         | China       | CS           | ICP: 28.0 ± 4.0; Control: 27.0 ± 3.0 | NA           | Third trimester                   | NA                                    | Fast                       | 6           |
| Wojcicka        | 15         | Poland      | CS           | ICP: 27.0 ± 3.0; Control: 28.0 ± 4.0 | ICP: 26.97 ± 5.75; Control: 27.68 ± 5.65 | NA                                    | Yes                       | 12-h fast | 6           |
| Dann            | 16         | UK          | Pro CS       | ICP: 31.0 ± 5.0; Control: 31.0 ± 5.0 | NA           | Four-week interval during gestation | Yes                                    | Not                        | 8           |
| Kebapciar       | 17         | Turkey      | Pro CCS      | ICP: 27.1 ± 5.4; Control: 27.6 ± 5.1 | ICP: 31.6 ± 4.6; Control: 32.0 ± 2.5 | NA                                    | NA                       | Overnight fast | 6           |
| Zhang           | 18         | China       | Pro CS       | ICP: 27.30 ± 4.89; Control: 26.50 ± 4.30 | NA           | NA                                | NA                                    | NA                        | 5           |
| Martineau       | 19         | UK and the US| Pro CS       | ICP: 30.5 ± 1.1; Control: 31.1 ± 1.0 | ICP: 25.5 ± 1.0; Control: 32.0 ± 2.5 | NA                                    | NA                       | Overnight fast | 7           |
| Hao             | 20         | China       | Pro CS       | ICP: 28.80 ± 3.62; Control: 29.00 ± 4.14 | ICP: 23.47 ± 3.32; Control: 24.27 ± 3.56 | 28, 32, 36, 38 | NA                       | Fast                    | 7           |
| Basaranoglu     | 21         | Turkey      | Pro CS       | ICP: 29.2 ± 5.9; Control: 30.4 ± 4.8 | ICP: 28.2 ± 4.8; Control: 27.5 ± 4.9 | NA                                    | NA                       | NA                        | 6           |
| Xu              | 22         | China       | Pro CS       | ICP: 31.17 ± 1.03; Control: 31.5 ± 0.69 | NA           | Before cesarean section           | Not                                    | Fast                       | 7           |
| Kukta           | 23         | Poland      | CS           | ICP: 32.0 ± 4.26; Control: 26.0 ± 6.67 | ICP: 28.4 ± 4.33; Control: 22.1 ± 5.10 | At the time of diagnosis              | Yes                                    | Fast                       | 7           |

Abbreviations: BMI, body mass index; CCS, case–control study; CS, cohort study; ICP, intrahepatic cholestasis of pregnancy; NA, not available; NOS, Newcastle–Ottawa Scale.
## TABLE 2  Lipid profiles of the included studies

| Author Ref (year) | Group size | ICP | Control | TG (mmol/L) | TC (mmol/L) | HDL cholesterol (mmol/L) | LDL cholesterol (mmol/L) |
|-------------------|------------|-----|---------|-------------|-------------|--------------------------|--------------------------|
| Nikkila14 (1996)  | 28 13      | ICP: 3.86±1.43; Control: 2.50±1.37 | ICP: 8.02±1.85; Control: 6.96±1.59 | ICP: 1.07±0.32; Control: 1.74±0.43 | NA |
| Dai11 (1997)      | 35 33      | ICP: 3.1±1.2; Control: 3.1±1.1 | ICP: 6.8±1.4; Control: 6.9±0.9 | ICP: 1.2±0.5; Control: 1.6±0.4 | ICP: 4.1±1.2; Control: 3.3±0.7 |
| Wojicka15 (2005)  | 58 42      | ICP: 3.31±1.20; Control: 2.39±0.74 | ICP: 8.11±1.31; Control: 6.94±1.00 | ICP: 1.04±0.41; Control: 1.75±0.51 | ICP: 5.17±1.39; Control: 2.35±0.86 |
| Dann16 (2006)     | 63 26      | NA | 18 (6 to 32)<sup>a</sup> | -0.4 (-0.6 to 0.3)<sup>b</sup> | 64 (37 to 96)<sup>b</sup> |
| Kebapcilar17 (2009)| 32 32     | ICP: 2.79±0.99; Control: 1.88±0.35 | ICP: 7.20±1.63; Control: 4.04±0.47 | ICP: 1.44±0.54; Control: 1.41±0.18 | ICP: 4.38±1.83; Control: 3.52±0.46 |
| Zhang18 (2014)    | 40 42      | ICP: 4.01±1.11; Control: 2.68±0.97 | ICP: 6.86±1.31; Control: 5.29±1.05 | ICP: 1.35±0.89; Control: 2.34±1.12 | ICP: 3.78±1.10; Control: 2.60±0.87 |
| Martineau19 (2015)| 26 27      | ICP group has significantly higher TG level than healthy controls | ICP group has significantly higher TC level than healthy controls | ICP group has significantly lower HDL level than healthy controls | ICP group has significantly higher LDL level than healthy controls |
| Hao20 (2016)      | 30 30      | ICP: 3.21±1.34; Control: 2.48±0.87 | ICP: 6.88±1.68; Control: 6.19±0.86 | ICP: 1.53±0.38; Control: 1.72±0.32 | ICP: 3.25±1.17; Control: 3.02±0.59 |
| Basaranoglu21 (2017) | 35 40    | ICP: 3.38±1.51; Control: 3.52±1.01 | ICP: 5.97±1.77; Control: 4.78±0.83 | ICP: 0.59±0.38; Control: 1.02±0.25 | ICP: 3.57±1.70; Control: 2.16±0.75 |
| Xu22 (2019)       | 54 54      | ICP: 4.32±0.56; Control: 3.59±0.30 | ICP: 6.56±0.36; Control: 5.76±0.25 | ICP: 1.50±0.14; Control: 1.69±0.05 | ICP: 3.90±0.40; Control: 3.42±0.26 |
| Kukla23 (2021)    | 26 20      | ICP: 2.96±0.44; Control: 2.80±1.26 | ICP: 8.08±0.90; Control: 7.81±0.83 | ICP: 1.94±0.26; Control: 2.14±0.26 | ICP: 4.90±0.83; Control: 4.00±0.81 |

Abbreviations: HDL, high-density lipoprotein; ICP, intrahepatic cholestasis of pregnancy; LDL, low-density lipoprotein; NA, not available; NOS, Newcastle–Ottawa Scale; TC, total cholesterol; TG, triglycerides.

<sup>a</sup>Values are % difference (95% CI).

<sup>b</sup>Changes are given in absolute units (95% CI) (mmol/L).
and 48.3% ($P = 0.145$) for TG, TC and LDL cholesterol, respectively, which is acceptable. The $I^2$ of the high-quality group for HDL cholesterol was also reduced to 76.2% ($P = 0.006$).

A sensitivity analysis of the individual studies was performed by repeating the WMD (95% CI) calculation when any single study was deleted (Appendix S2). Statistically similar results indicated that a single study had no influence on the stability of the overall WMD estimate in this meta-analysis, meaning that the estimated association between ICP and maternal lipid concentration was robust.

### 3.3 Publication bias

The graphical funnel plots of this meta-analysis showed no significant imbalance (Appendix S3). The trim-and-fill method was used to test the symmetry of each funnel plot; the results for each overall WMD did not change. In addition to funnel plots, Egger’s and Begg’s tests were performed to identify the potential presence of publication bias. All statistical analyses showed a low risk of publication bias in the association between ICP and maternal dyslipidemia (Tables 2 and 3).
TABLE 3 Assessment of publication bias

|                  | Egger's test | Begg's test |
|------------------|--------------|-------------|
|                  | t           | 95% CI      | P-value | z-value | P-value |
| TG               | -0.46       | -3.93 to 2.64 | 0.657   | 0.52    | 0.602   |
| TC               | 0.77        | -2.71 to 5.33 | 0.468   | 0.31    | 0.754   |
| HDL cholesterol  | -2.09       | -5.46 to 0.34 | 0.075   | 1.36    | 0.175   |
| LDL cholesterol  | 1.62        | -1.84 to 9.05 | 0.157   | 0.37    | 0.711   |

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride.

4 | DISCUSSION

To our knowledge, the current study is the first to evaluate the association between ICP and maternal dyslipidemia. The data showed a significant association between ICP and maternal dyslipidemia, with significantly increased levels of TG, TC and LDL cholesterol and decreased levels of HDL cholesterol in women with ICP vs healthy pregnant women. Statistical heterogeneity was low in the meta-analysis of TG, TC and LDL cholesterol among the subgroup analyses of high-quality studies. After the sensitivity test, the association was robust and insensitive to any single study. In addition, this meta-analysis had a low risk of publication bias according to the statistical analyses.

Dysregulated lipid and glucose metabolism can be contributed to the pathophysiology of ICP. Martineau et al. investigated ICP metabolic outcomes and revealed that ICP pregnancy was associated with impaired glucose tolerance and dyslipidemia. In Zhang’s study, maternal dyslipidemia was more obvious in the severe ICP group, which suggested that maternal dyslipidemia severity may be associated with ICP severity. In a recent meta-analysis, women with ICP were more likely to have GDM (pooled odds ratio, 2.19; 95% CI 1.58–3.03), but the temporal association between ICP and GDM was unclear. In a recent retrospective cohort study, ICP was diagnosed 6 weeks after GDM, and no major difference in glycem ic control was noted between the GDM and the combined GDM and ICP groups.

The association between ICP and maternal dyslipidemia can be explained by the important role that BA plays in lipid metabolism. BA is essential for the solubilization, digestion and absorption of dietary lipids and fat-soluble vitamins. BA is now considered a signal molecule, and there is now abundant evidence to suggest that BA regulates lipid, glucose and energy homeostasis via FXR. FXR activation represses the synthesis of endogenous bile acids and reduces plasma TG, cholesterol and glucose plasma levels. Reduced FXR expression and activity have been reported in human cholestatic conditions. In another study, increased levels of the 3β-sulfated progesterone metabolite epiallopregnanolone sulfate in ICP pregnancies antagonized the FXR. Therefore, the downregulation of FXR activity may be involved in ICP pregnancies and influence maternal metabolism. However, the mechanism of ICP and dysregulated lipid profiles remains unclear and complicated, and may involve other aspects such as changes in the gut microbiota during ICP pregnancies.

It is unclear whether maternal dyslipidemia is the primary causative factor of ICP pathogenesis or is secondary to its pathophysiology. Maternal dyslipidemia may contribute to the disease, presenting before elevated BA levels, which makes maternal dyslipidemia a diagnostic factor for ICP. In Dann’s study, continuous monitoring of maternal lipid profiles showed that the maternal LDL cholesterol level increased before the clinical diagnosis of ICP was made. A retrospective population-based study in China revealed that high maternal TG levels in late pregnancy were independently associated with an increased risk of ICP. In another prospective study, TC concentration during the entire pregnancy and LDL cholesterol level in the last two trimesters were positively associated with ICP.

UDCA remains the first-line treatment for ICP. In the study by Dann et al., UDCA treatment did not alter maternal plasma lipid concentrations. However, a recent study revealed that UDCA treatment could ameliorate ICP-associated fetal dyslipidemia. Further animal models have confirmed that UDCA treatment in cholestatic pregnancy can induce hepatoprotective mechanisms in the fetal liver and improve glucose tolerance in adult offspring. UDCA may improve metabolic outcomes in ICP pregnancies, supporting the effectiveness of UDCA treatment in women with ICP.

The main limitation of the current study was that most of the included studies collected only one blood sample from each participant and lacked continuous monitoring of lipid profiles, and the methodology of the maternal lipid profile tests was inconsistent among the included studies. However, the gestational ages at the time of testing differed among the studies; most of the included studies obtained blood samples in the third trimester. In addition, one study obtained blood samples in the non-fasting state, but this study was not included in the meta-analysis. Another limitation of our study was the considerable heterogeneity among the studies. This inconsistency in blood sample collection could be a major potential source of heterogeneity. Furthermore, this might be attributed to variations in region, ethnicity, dietary habits and maternal body mass index. Even so, the sensitivity test showed the results were robust and the heterogeneity among the high-quality studies was acceptable after subgroup analysis. Thirdly, most of the included studies included a modest number of patients. Future large-scale cohort studies with dynamic observations of maternal lipid profiles during ICP pregnancy are needed.
5  |  CONCLUSION

This meta-analysis revealed a significant association between ICP and maternal dyslipidemia, providing direct evidence to support the theory that ICP is associated with dysregulated lipid metabolism. Further large-scale prospective well-designed studies are needed to confirm the temporal relation between ICP and maternal dyslipidemia.

AUTHOR CONTRIBUTIONS
YZ, TX, TC and XW were responsible for acquiring the data. All authors were responsible for interpreting the data and writing the article.

CONFLICT OF INTEREST
None.

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**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher’s website.

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