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Incidence of Intrahepatic Cholestasis of Pregnancy and Its Impact on Maternal and Neonatal Outcomes: A Systematic Review and Meta-Analysis

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 March 2025 and was last updated on 31 March 2025.

INTRODUCTION

Review question / Objective This study adopted a meta-analysis approach to investigate the incidence of intrahepatic cholestasis of pregnancy (ICP) and its impact on adverse outcomes for both pregnant and lying-in women and neonates.

Condition being studied Intrahepatic cholestasis of pregnancy (ICP) is a liver condition that occurs during pregnancy. It is mainly characterized by intrahepatic cholestasis and heightened bile acid levels. Pruritus is often a significant symptom, especially in the third trimester [1]. ICP is the most common pregnancy-related liver disease that threatens maternal-fetal health, it is associated with maternal risks including preterm labor and postpartum hemorrhage, potential hepatic impairment in postpartum women, and neonatal complications such as asphyxia and meconium aspiration syndrome [2]. As reported, the global incidence of ICP varies widely by region, in certain high-risk populations and regions, the incidence is much higher [3]. In Scandinavia and some Asian countries, including China and India, the incidence of ICP exceeds the global average [3]. Women with a family history of the disease, advanced maternal age, or other existing liver diseases or pregnancy complications are at higher risk of developing ICP [4]. These variations may be closely linked to genetic susceptibility, environmental factors, and the level of prenatal care.

METHODS

Participant or population Relevant data were extracted from the included studies, including study type, groups, sample size, and average maternal age. Obstetric outcomes such as emergency cesarean section rate, preeclampsia, postpartum hemorrhage, gestational age, preterm delivery (spontaneous preterm birth), small for gestational age (SGA) infants, NICU admission rate, and stillbirth rate were also collected, with preterm delivery defined as gestational age less than 37 weeks. Additionally, risk assessment-related parameters from the studies were

extracted. This comprehensive data extraction allowed us to assess the relationships between variables and their potential impact on maternal and neonatal health outcomes.

Intervention We obtained studies published from the inception of the PubMed, Cochrane Library, and Web of Science databases up until 2024. These studies focused on the incidence of ICP and its effects on adverse outcomes in pregnant and lying-in women and neonates. A total of 21 original articles were selected, which reported on ICP and adverse outcomes in maternal and neonatal populations. These studies involved 1,497,951 controls (NO-ICP) and 12,262 ICP patients. A meta-analysis was performed to compare the incidence of ICP and its effects on adverse outcomes in pregnant and lying-in women and neonates. Sensitivity analysis and publication bias evaluation were also conducted.

Comparator We obtained studies published from the inception of the PubMed, Cochrane Library, and Web of Science databases up until 2024. These studies focused on the incidence of ICP and its effects on adverse outcomes in pregnant and lying-in women and neonates. A total of 21 original articles were selected, which reported on ICP and adverse outcomes in maternal and neonatal populations. These studies involved 1,497,951 controls (NO-ICP) and 12,262 ICP patients. A meta-analysis was performed to compare the incidence of ICP and its effects on adverse outcomes in pregnant and lying-in women and neonates. Sensitivity analysis and publication bias evaluation were also conducted.

Study designs to be included Study Design (S): Clinical trials, observational studies, or systematic evaluations.

Eligibility criteria Inclusion criteria were as follows: Participants (P): Pregnant women diagnosed with ICP. Intervention (I): ICP. Control (C): Pregnant women without ICP. Outcomes (O): Adverse maternal and neonatal outcomes. Study Design (S): Clinical trials, observational studies, or systematic evaluations. The inclusion criteria comprised studies examining the impact of ICP on obstetric and neonatal outcomes, with comparisons between the ICP and non-ICP groups.
Exclusion criteria: 1. Studies not directly related to ICP or its associated factors; 2. Articles focused on other liver diseases or conditions, rather than specifically targeting ICP; 3. Studies with unclear methodology; 4. Studies with small sample sizes (e.g., case reports, case series) lacking statistical power or generalizability; 5. Animal studies, in-vitro experiments, or studies involving non-human subjects; 6. Articles published in languages other than English, without a reliable English translation; 7. Studies with inaccessible full texts.

Information sources A thorough search was performed in the PubMed, Cochrane Library, and Web of Science databases. Relevant papers published from the inception of these databases to 2024 were included. The focus was on studying the incidence of ICP and its impact on adverse outcomes in pregnant and lying-in women and neonates. Search terms encompassed: ("Intrahepatic cholestasis of pregnancy") AND ("Emergency cesarean sections" OR "Postpartum hemorrhage" OR "Cesarean delivery" OR "Preeclampsia" OR "Hemorrhage" OR "Unplanned cesarean sections" OR "Preterm birth" OR "Premature delivery" OR "Small for gestational age" OR "Stillbirth" OR "Neonatal intensive care unit" OR "NICU admission" OR "Neonatal outcomes" OR "Perinatal complications"). Search strategies were tailored to meet the requirements of each database. All references from the included studies were manually checked to identify any potentially overlooked research. Two researchers independently conducted the screening and cross-validated the results. If disagreements arose, a third researcher was responsible for making the final decision. The screening process included reviewing titles, abstracts, and full texts.

Main outcome(s) The pooled analysis estimated an ICP incidence of 3% (95% CI: 1%–7%), while the meta-analysis demonstrated the following risk ratios: postpartum hemorrhage showed a reduced risk (RR, 0.82; 95% CI, 0.69–0.99), whereas significant increases were observed for preeclampsia (RR, 2.39; 95% CI, 2.21–2.59), cesarean birth (RR, 1.28; 95% CI, 1.15–1.42), preterm birth (RR, 2.71; 95% CI, 1.77–4.15), and maternal infection (RR, 3.22; 95% CI, 2.48–4.19). Other outcomes included labor induction (RR, 1.60; 95% CI, 0.51–4.99), gestational diabetes mellitus (RR, 1.29; 95% CI, 0.83–2.01), neonatal intensive care unit admission (RR, 1.79; 95% CI, 1.35–2.37), stillbirth (RR, 1.25; 95% CI, 0.64–2.42), and small for gestational age (RR, 1.06; 95% CI, 0.71–1.57), with varying degrees of association.

Quality assessment / Risk of bias analysis The ROBINS-I tool was used to assess the potential risk of bias in cohort studies. Two assessors independently evaluated the methodological quality of the included studies. Any discrepancies were resolved through consultation with a third assessor, who acted as an arbitrator. This rigorous

process ensured a comprehensive and unbiased evaluation of the studies' methodological strengths and limitations.

Strategy of data synthesis A thorough search was performed in the PubMed, Cochrane Library, and Web of Science databases. Relevant papers published from the inception of these databases to 2024 were included. The focus was on studying the incidence of ICP and its impact on adverse outcomes in pregnant and lying-in women and neonates. Search terms encompassed: ("Intrahepatic cholestasis of pregnancy") AND ("Emergency cesarean sections" OR "Postpartum hemorrhage" OR "Cesarean delivery" OR "Preeclampsia" OR "Hemorrhage" OR "Unplanned cesarean sections" OR "Preterm birth" OR "Premature delivery" OR "Small for gestational age" OR "Stillbirth" OR "Neonatal intensive care unit" OR "NICU admission" OR "Neonatal outcomes" OR "Perinatal complications"). Search strategies were tailored to meet the requirements of each database. All references from the included studies were manually checked to identify any potentially overlooked research. Two researchers independently conducted the screening and cross-validated the results. If disagreements arose, a third researcher was responsible for making the final decision. The screening process included reviewing titles, abstracts, and full texts.

Subgroup analysis Relevant data were extracted from the included studies, including study design, sample size, patient characteristics, and adverse outcomes. Two researchers independently extracted the data and cross-validated the data. The 95% confidence interval (CI) was calculated for each parameter. The I2 statistic was employed to assess heterogeneity between studies. An I2 value greater than 50% suggested significant heterogeneity. All meta-analyses were performed using the RevMan 5.3 software. For publication bias assessment, the trim and fill method was adopted, with detection conducted through both the Miller Method and the Harbord Method. Common methods for calculating the pooled effect size include the Mantel-Haenszel method for binary outcomes and the inverse-variance method for continuous outcomes. Based on the heterogeneity results, a random effects model should be chosen if P 50%; otherwise, a fixed-effects model should be used. This study set the significance level at α=0.05. A result was considered statistically significant when the p-value was <0.05 or when the 95% confidence interval (e.g., OR/HR) did not include the null value (1.0).

Sensitivity analysis A sensitivity analysis was performed to assess the impact of each study on the overall effect size. This involved repeating the meta-analysis by removing one study at a time. Any changes in the overall effect size were carefully observed. If removing any study did not lead to a notable change in the effect size, the meta-analysis results were considered stable.

Country(ies) involved China/Hubei Medical University Affiliated Shiyan People's Hospital.

Keywords intrahepatic cholestasis of pregnancy; maternal outcomes; neonatal outcomes; risk factors;meta-analysis.

Contributions of each author

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