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Hyperuricemia/Gout and Adverse Pregnancy Outcomes: A Dose-Response Meta-Analysis of Risk Factors

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ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Data analysis.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 September 2025 and was last updated on 11 September 2025.

INTRODUCTION

Review question / Objective This dose-response meta-analysis investigated the association between maternal hyperuricemia/gout (and specific SUA levels) and the risk of various adverse pregnancy outcomes. It synthesizes evidence from observational studies comparing exposed pregnant women to those with normal uric acid levels. P (Population): Pregnant women. I (Exposure): Hyperuricemia and/or gout. A dose-response analysis of serum uric acid (SUA) levels was also conducted. C (Comparison): Pregnant women without hyperuricemia/gout (with normal SUA levels). O (Outcomes): The primary outcome was adverse pregnancy outcomes (APOs). Specific outcomes analyzed included: general adverse pregnancy outcomes, small for gestational age (SGA) infant, low birth weight (LBW), preterm birth (PTB), and fetal growth restriction (FGR). S (Study design): Observational studies, including cohort studies, case-control studies, and cross-sectional studies.

Condition being studied Hyperuricemia is a metabolic condition defined by elevated serum uric acid levels, with the diagnostic threshold set at ≥360 μmol/L (6.0 mg/dL) for women. It serves as the primary risk factor for gout, an inflammatory arthritis characterized by severe joint pain caused by urate crystal deposition. The global prevalence of hyperuricemia and gout is rising, driven by factors including Westernized diets (high in purine-rich foods and sugars), increasing obesity rates, and higher life expectancy. Adverse pregnancy outcomes primarily encompass two aspects: obstetric complications and adverse neonatal outcomes. Obstetric complications include hypertensive disorders of pregnancy, gestational diabetes mellitus, premature rupture of membranes, and preterm birth. Adverse neonatal outcomes include fetal distress, fetal growth

restriction, low birth weight, and small for gestational age infants. Previous studies have found that abnormal uric acid metabolism is not only associated with renal and cardiovascular diseases but may also affect female reproductive health. Serum uric acid levels can serve as a predictive indicator for pregnancy complications and adverse fetal outcomes. The relationship between rheumatic diseases and adverse pregnancy outcomes is a complex and important field of research. When managing rheumatic diseases in pregnancy, rheumatologists must consider multiple factors, including disease activity, medication use, and pregnancy management strategies. This article aims to provide rheumatologists with a new perspective to better understand and manage the relationship between rheumatic diseases and adverse pregnancy outcomes.

METHODS

Participant or population This review addresses pregnant women, with or without comorbidities (e.g., gestational hypertension, preeclampsia, gestational diabetes mellitus, or intrahepatic cholestasis of pregnancy), regardless of gestational age, geographic region, or ethnic background.

Intervention The primary exposure was hyperuricemia, defined as serum uric acid (SUA) levels reaching or exceeding 360 μmol/L (6.0 mg/dL) in women, and/or a clinical diagnosis of gout. A crucial component of the analysis involved a dose-response evaluation of continuous SUA levels to identify specific risk thresholds and characterize the nature of the association.

Comparator The comparison group consisted of pregnant women with normal serum uric acid levels, specifically those maintaining SUA concentrations below the hyperuricemia diagnostic threshold of 360 μmol/L.

Study designs to be included Observational studies, including cohort studies, case-control studies, and cross-sectional studies.

Eligibility criteria To evaluate the association between adverse pregnancy outcomes and hyperuricemia or gout, eligible studies must involve individuals diagnosed with adverse pregnancy outcomes and report uric acid levels as well as hyperuricemia-related risks. Additionally, studies are required to use multivariable-adjusted statistical measures to report the association, such as relative risk (RR), odds ratio (OR), and 95% confidence intervals (CI). Exclusion criteria: 1) Non-research publications, including reviews, commentaries, conference abstracts, etc.; 2) Unavailable full text or missing required study data; 3) Non-Chinese/English literature.

Information sources A systematic literature retrieval was executed in PubMed, Cochrane Library, Embase, Web of Science, CNKI, Wanfang Data, China Biology Medicine disc (CBMdisc). The time endpoint of the online search was September 10, 2025.

Main outcome(s) The primary outcome was a composite of adverse pregnancy outcomes (APOs). This encompassed both maternal complications and adverse neonatal outcomes. Specific outcomes quantitatively analyzed included: general/unspecified APOs, small for gestational age (SGA) infant, low birth weight (LBW), preterm birth (PTB), and fetal growth restriction (FGR). The strength of association for each outcome was measured using Odds Ratios (ORs) with corresponding 95% confidence intervals (CIs).This systematic review and meta-analysis evaluated the association between maternal hyperuricemia/gout and the risk of various adverse pregnancy outcomes (APOs). The primary effect measure was the pooled odds ratio (OR) with its 95% confidence interval (95% CI), derived from multivariate-adjusted data extracted from the included observational studies. The timing of outcome assessment spanned the entire pregnancy period up to delivery and the immediate neonatal period.

Quality assessment / Risk of bias analysis The risk of bias in the included studies was independently assessed by two investigators using the Newcastle-Ottawa Scale (NOS), with cross-checking of evaluation results. The NOS evaluates studies based on three domains: selection of study groups (4 points), comparability of groups (2 points), and ascertainment of outcomes (3 points). A total NOS score of ≥7 was considered indicative of high study quality and low risk of bias.

Strategy of data synthesis The pooled odds ratios (ORs) and their 95% confidence intervals (95% CIs) for factors influencing adverse pregnancy events were calculated using Stata 12.0 software. Heterogeneity was assessed using the I^2 statistic. If $I^2 \leq 50\%$ and $P > 0.05$, indicating low or no heterogeneity, a fixed-effects model was applied. If $I^2 > 50\%$ and $P \leq 0.05$, indicating substantial heterogeneity, a random-effects model was used. Further subgroup analyses and meta-regression were performed to explore potential

sources of heterogeneity. Publication bias was evaluated using funnel plots and Egger's test, and sensitivity analysis was conducted using the leave-one-out method. Publication bias was also assessed using the trim-and-fill method based on funnel plot symmetry. Dose-response meta-analysis was performed using Stata 15.0 software. The dose for each exposure category was defined as the midpoint between the lower and upper bounds of the interval, which was set as the central dose. For open-ended intervals, the lowest dose group was assigned the midpoint of the interval.

Subgroup analysis We plan to do subgroup analysis according to different maternal comorbidities (including gestational hypertension, diabetes, cholestasis, and no comorbidities) and geographic region.

Sensitivity analysis We will consider running sensitivity analysis to identify the robustness and stability of merged results by excluding studies with high risk of bias.

Country(ies) involved China.

Keywords Hyperuricemia; Gout; Adverse Pregnancy Outcomes; Dose-Response Meta-Analysis.

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