INPLASY

Efficacy and Safety of Insulin Therapy for Hyperglycemia in Very Low Birth Weight Infants- A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

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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 10 May 2026 and was last updated on 10 May 2026.

INTRODUCTION

Review question / Objective Hyperglycemia is a common and serious metabolic complication in very low birth weight (VLBW) infants, often necessitating exogenous insulin therapy; however, its comparative effectiveness and safety remain uncertain. This systematic review and meta-analysis aimed to evaluate the efficacy and safety of insulin therapy versus placebo, no treatment, standard care, or alternative hypoglycemic agents in managing hyperglycemia in VLBW infants.

Rationale Hyperglycemia is common in very low birth weight infants, while clinical trials on exogenous insulin therapy show inconsistent findings in efficacy and safety. No updated meta-analysis has pooled evidence on glycemic control, neonatal complications and adverse events of insulin treatment. This review will synthesize available data to clarify the clinical value of insulin therapy for hyperglycemia in VLBW infants.

Condition being studied Hyperglycemia in very low birth weight (VLBW) infants with birth weight less than 1500 g.

METHODS

Search strategy We systematically searched Web of Science, PubMed, EMBASE, and Cochrane Library from database inception to May 6, 2026. The search strategies combined terms related to the population ("very low birth weight infant" OR "VLBW" OR "extremely low birth weight infant" OR "ELBW" OR "preterm infant" OR "hyperglycemia" OR "hyperglycaemia") and the intervention ("insulin" OR "insulin therapy" OR "insulin infusion" OR "continuous insulin infusion" OR "insulin treatment") in combination with terms for outcomes ("efficacy" OR "effectiveness" OR "safety" OR "mortality" OR "morbidity" OR "hypoglycemia" OR "hypoglycaemia" OR "sepsis" OR "infection" OR "length of stay" OR "neurodevelopmental outcome"). No language or publication type restrictions were applied.

Participant or population Participants: Very low birth weight (VLBW) infants (birth weight 150 mg/dL or >8.3 mmol/L, or need for insulin therapy). No restrictions on gender, ethnicity, or mode of delivery.

Intervention Any regimen of exogenous insulin therapy (e.g., continuous intravenous infusion, subcutaneous injection) administered for the treatment of hyperglycemia. Insulin types (e.g., regular insulin, NPH) and dose titration protocols (e.g., weight-based or glucose-monitoring-based adjustments) were considered.

Comparator Placebo, no treatment, standard care (e.g., glycemic control through dextrose reduction/total parenteral nutrition [TPN] adjustment), or alternative hypoglycemic agents (e.g., oral hypoglycemic drugs if applicable). Studies with no comparator (single-arm trials) were excluded.

Study designs to be included Randomized controlled trials (RCTs), quasi-RCTs, controlled clinical trials (CCTs), and prospective or retrospective cohort studies with a comparator group. Studies were included if they had a minimum follow-up period of 7 days or until hospital discharge. Cross-sectional studies, case series, case reports, narrative reviews, editorials, and studies without primary data were excluded. Only studies published in English or with an available English translation were considered.

Eligibility criteria Inclusion criteria include: (1) Participants: Very low birth weight (VLBW) infants (birth weight 150 mg/dL or >8.3 mmol/L, or need for insulin therapy). No restrictions on gender, ethnicity, or mode of delivery. (2) Interventions: Any regimen of exogenous insulin therapy (e.g., continuous intravenous infusion, subcutaneous injection) administered for the treatment of hyperglycemia. Insulin types (e.g., regular insulin, NPH) and dose titration protocols (e.g., weight-based or glucose-monitoring-based adjustments) were considered. (3) Comparator: Placebo, no treatment, standard care (e.g., glycemic control through dextrose reduction/total parenteral nutrition [TPN] adjustment), or alternative hypoglycemic agents (e.g., oral hypoglycemic drugs if applicable). Studies with no comparator (single-arm trials) were excluded. (4) Outcomes: At least one of the following outcomes was reported: Efficacy outcomes: time to normoglycemia, number of hypoglycemic episodes, mean/peak blood glucose levels, incidence of hyperglycemia resolution, mortality (neonatal or in-hospital), incidence of necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), length of hospital stay, or need for additional interventions. Safety outcomes: incidence of hypoglycemia (blood glucose <40-50 mg/dL or as defined by study), sepsis, electrolyte disturbances, or adverse events related to insulin administration. (5) Study Design: Randomized controlled trials (RCTs), quasi-RCTs, controlled clinical trials (CCTs), and prospective or retrospective cohort studies with a comparator group. Studies were included if they had a minimum follow-up period of 7 days or until hospital discharge. Cross-sectional studies, case series, case reports, narrative reviews, editorials, and studies without primary data were excluded. Only studies published in English or with an available English translation were considered.
2.Exclusion criteria include:(1) Studies where the full-text article is not accessible despite reasonable attempts to obtain it (e.g., through institutional subscriptions, inter-library loan, or contacting authors). (2) Studies where the reported data on relevant outcomes are incomplete, inconsistent, or presented in a format (e.g., only graphical data without numerical values) that precludes extraction and quantitative synthesis, and where clarification from the authors is not possible. (3) Studies where the intervention (insulin therapy) is administered for a primary indication other than hyperglycemia in VLBW infants (e.g., for hyperkalemia or as part of a parenteral nutrition protocol not primarily targeting glycemic control). (4) Studies that are secondary publications, interim analyses, or duplicate reports of the same patient cohort from which primary outcome data have already been extracted for the meta-analysis. (5) Studies published exclusively in a language other than English without an available English translation.

Information sources We systematically searched Web of Science, PubMed, EMBASE, and Cochrane Library from database inception to May 6, 2026. The search strategies combined terms related to the population ("very low birth weight infant" OR "VLBW" OR "extremely low birth weight infant" OR "ELBW" OR "preterm infant" OR "hyperglycemia" OR "hyperglycaemia") and the intervention ("insulin" OR "insulin therapy" OR "insulin infusion" OR "continuous insulin infusion" OR "insulin treatment") in combination with terms for outcomes ("efficacy" OR "effectiveness" OR "safety" OR "mortality" OR "morbidity" OR "hypoglycemia" OR "hypoglycaemia" OR "sepsis" OR "infection" OR "length of stay" OR "neurodevelopmental outcome"). No language or publication type restrictions were applied.

Main outcome(s) At least one of the following outcomes was reported: Efficacy outcomes: time to normoglycemia, number of hypoglycemic episodes, mean/peak blood glucose levels, incidence of hyperglycemia resolution, mortality (neonatal or in-hospital), incidence of necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), length of hospital stay, or need for additional interventions. Safety outcomes: incidence of hypoglycemia (blood glucose <40-50 mg/dL or as defined by study), sepsis, electrolyte disturbances, or adverse events related to insulin administration.

Quality assessment / Risk of bias analysis Two independent reviewers will assess the quality of the included randomized controlled trials (RCTs) using the Cochrane Risk of Bias 2 (ROB2) tool. This tool evaluates bias across five key domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential sources of bias. Each domain will be judged as "low risk," "high risk," or "some concerns." Any discrepancies between reviewers will be resolved through discussion or by consulting a third reviewer. The overall risk of bias for each study will be determined based on the domain-level judgments.

Strategy of data synthesis Statistical analyses were performed using the R statistical software environment, specifically leveraging the "meta" and "metafor" packages for meta-analytic computations. These packages provide robust functions for pooling effect sizes, assessing heterogeneity, and conducting sensitivity analyses. Heterogeneity across studies was evaluated using the I^2 statistic, which quantifies the proportion of total variation in effect estimates attributable to between-study variability. According to established guidelines, I^2 values of 25%, 50%, and 75% were interpreted as indicating low, moderate, and high heterogeneity, respectively. The chi-squared test for heterogeneity (Cochran's Q) was also reported, with $p < 0.10$ considered indicative of heterogeneity.
Based on the heterogeneity assessment, the appropriate meta-analytic model was selected. If the I^2 statistic was less than 50%, a fixed-effect model (Mantel-Haenszel method for binary outcomes or inverse variance method for continuous outcomes) was employed, assuming that the observed differences among studies were primarily due to sampling error. Conversely, if I^2 was 50% or greater, a random-effects model (DerSimonian and Laird method) was applied to account for both within-study and between-study variability, thereby providing more conservative and generalizable estimates.
Publication bias was examined through visual inspection of funnel plots, which plot the effect size against its standard error (or precision). In the absence of bias, the plot should resemble a symmetric inverted funnel. Additionally, Egger's regression test was used to quantify asymmetry; a p-value < 0.05 indicated statistical significance for potential publication bias or small-study effects.

Subgroup analysis No predefined subgroup analyses were planned for this meta-analysis.

Sensitivity analysis Sensitivity analyses, such as leave-one-out meta-analysis, were conducted to evaluate the influence of individual studies on the overall pooled estimate and to assess the robustness of the findings.

Language restriction No language or publication type restrictions were applied.

Country(ies) involved China.

Keywords Very low birth weight infants; Hyperglycemia; Insulin therapy; Efficacy; Safety; Meta-analysis.

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