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INPLASY

Meta-Analysis of the Clinical Efficacy and Adverse Reactions of Different Combined Heparin Methods in the Treatment of Recurrent Pregnancy Loss

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ADMINISTRATIVE INFORMATION

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Review stage at the time of initial registration - Completed but not published.

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 November 2026 and was last updated on 11 November 2026.

INTRODUCTION

Review question / Objective This systematic review evaluates low-molecular-weight heparin (LMWH)-based strategies for recurrent pregnancy loss. Across 18 randomized trials, pooled estimates for live birth, miscarriage, and reported adverse reactions showed substantial variation across treatment comparisons. Etiology- and regimen-specific evidence supports careful selection of LMWH-related therapy based on clinical risk and indication.We conducted a systematic review and meta-analysis of randomized controlled trials to evaluate live birth, miscarriage, and adverse reactions with LMWH-based treatment strategies in women with RPL. Clinical comparisons were explored by underlying RPL category and treatment regimen, with sensitivity analyses to assess the robustness of pooled estimates.
Recurrent pregnancy loss (RPL) has multiple etiologies, and the clinical benefit of low-molecular-weight heparin (LMWH) beyond established indications remains uncertain.
An evidence synthesis that distinguishes true live birth from earlier pregnancy response and separates treatment comparisons is therefore clinically relevant.

Condition being studied Recurrent pregnancy loss (RPL) is a major reproductive health concern that is defined using different thresholds for the number of previous losses. Clinical evaluation may begin after two losses, while contemporary guidelines use more restrictive definitions in some settings. Its causes include chromosomal, anatomical, endocrine, immune, and thrombotic factors; however, in a substantial proportion of affected women, no specific cause is identified. Recurrent pregnancy loss (RPL) has multiple etiologies, and the clinical benefit of low-molecular-weight heparin (LMWH) beyond established indications remains uncertain. Abnormal maternal–placental interactions and

thrombosis-related pathways have been proposed as contributors to selected forms of RPL. Low-molecular-weight heparin (LMWH) has anticoagulant activity and possible additional effects on implantation and trophoblast development. The 18 trials included women with unexplained or idiopathic RPL, APS or antiphospholipid antibody positivity, inherited thrombophilia, mixed etiologies, or populations without a specified etiologic subtype.

METHODS

Participant or population Women with Recurrent pregnancy loss (RPL) as defined by each trial, generally involving at least two previous pregnancy losses; the original diagnostic criteria were extracted.

Intervention Low-molecular-weight heparin alone or with ASA, progesterone, HCQ, corticosteroids, or herbal treatment compared with ASA, progesterone, placebo, surveillance, standard care, intravenous immunoglobulin (IVIG), or another prespecified regimen.

Comparator Trials of LMWH-based treatment were reported across several countries and used a range of comparators including ASA, placebo, progesterone, IVIG, clinical surveillance, and standard care. Other randomized comparisons evaluated LMWH alone or in combination with ASA against specific control regimens. Treatment-contrast analyses are presented for live birth and miscarriage. The study-level test for subgroup differences yielded p = 0.0008, although the APS/aPL trials compared LMWH plus ASA with IVIG rather than the comparators used in the other populations.

Study designs to be included Randomized controlled trials reporting LMWH-containing intervention arms. Randomized trials of LMWH-based interventions were identified through systematic searches of six databases and assessed using Cochrane Risk of Bias 1. Eighteen trials met the eligibility criteria. Eighteen randomized trials were included in the review. Reviews, observational reports, case reports, conference abstracts without analyzable original trial data, and nonrandomized comparative studies.

Eligibility criteria Inclusion criteria
Trials were eligible when they met the following criteria:
Study design: Randomized controlled trials reporting LMWH-containing intervention arms.
Participants: Women with RPL as defined by each trial, generally involving at least two previous pregnancy losses; the original diagnostic criteria were extracted.
Intervention and comparator: Low-molecular-weight heparin alone or with ASA, progesterone, HCQ, corticosteroids, or herbal treatment compared with ASA, progesterone, placebo, surveillance, standard care, intravenous immunoglobulin (IVIG), or another prespecified regimen.
Outcomes: Live birth, miscarriage, maternal adverse reactions, or defined early-pregnancy treatment outcomes.
Exclusion criteria
Reviews, observational reports, case reports, conference abstracts without analyzable original trial data, and nonrandomized comparative studies.
Studies without a randomized LMWH-containing treatment arm or without extractable trial-level outcomes.
Studies outside the clinical population of women with RPL.
Studies evaluating unfractionated heparin without a qualifying LMWH treatment arm.
Overlapping reports of the same participant population were considered as a single study for each outcome.

Information sources PubMed, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, the China National Knowledge Infrastructure, and Wanfang.

Main outcome(s) Live birth, miscarriage, maternal adverse reactions, or defined early-pregnancy treatment outcomes. Live birth and miscarriage were extracted as separately defined outcomes using their trial-specific denominators. Pregnancy preservation success and response assessed at an early gestational time point were described separately from live birth. Overall reported adverse reactions were pooled only when participant-level event counts were available. Individual event types were presented separately. Dichotomous outcomes were expressed as risk ratios (RRs) with 95% confidence intervals (CIs). For each eligible two-arm comparison, log(RR) was pooled using inverse-variance random-effects models with restricted maximum-likelihood (REML) estimation of between-study variance (τ^2). Outcome-specific numerators and denominators were checked against the original trialreports.

Quality assessment / Risk of bias analysis Two reviewers independently evaluated each included trial with Cochrane Risk of Bias 1 (RoB 1). The

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seven domains comprised sequence generation, allocation concealment, participant and personnel blinding, outcome assessment blinding, incomplete outcome data, selective reporting, and other bias. Each domain was assigned low, unclear, or high risk based on trial-reported information, and discrepancies were resolved by consensus. Each trial was assessed based on its published methods and reported outcomes.

Strategy of data synthesis Dichotomous outcomes were expressed as risk ratios (RRs) with 95% confidence intervals (CIs). For each eligible two-arm comparison, log(RR) was pooled using inverse-variance random-effects models with restricted maximum-likelihood (REML) estimation of between-study variance (τ^2). Cochran's Q test, between-study heterogeneity (I^2), and 95% prediction intervals were used to describe heterogeneity where estimable. Subgroup analyses considered trial-reported RPL etiology and the specific treatment contrast; subgroup differences were examined by interaction tests without interpreting comparisons across etiologies as randomized head-to-head comparisons. Low-molecular-weight heparin preparation, dose, and dosing schedule were tabulated separately because preparations and dosing conventions varied across trials. Sensitivity analyses included fixed-effect and DerSimonian–Laird models, leave-one-out analysis, selected trial exclusions, a domain-focused analysis excluding trials at high risk in sequence generation, allocation concealment, incomplete outcome data, or other bias, and an additional trial-arm comparison. Exploratory random-effects meta-regression examined mean maternal age when reported by at least 10 studies. Funnel plots, Egger regression, and L0 trim-and-fill analyses were used to explore small-study effects for outcomes with at least 10 studies. Analyses were conducted using R (version 4.6.1); scientific figures were produced with R (version 4.6.1) and Matplotlib (version 3.10.8). Outcome-specific numerators and denominators were checked against the original trial reports. For studies with multiple randomized arms, one defined two-arm comparison was included per outcome to avoid reusing a shared comparator.

Subgroup analysis Subgroup analyses considered trial-reported RPL etiology and the specific treatment contrast; subgroup differences were examined by interaction tests without interpreting comparisons across etiologies as randomized head-to-head comparisons. Low-molecular-weight heparin preparation, dose, and dosing schedule were tabulated separately because preparations and dosing conventions varied across trials. Underlying RPL classification, including antiphospholipid syndrome (APS) and antiphospholipid antibody (aPL) positivity, was examined for live birth and miscarriage. Treatment-contrast analyses are presented for live birth and miscarriage. Because LMWH preparations and dosing conventions varied across trials, apparent differences between dosing schedules were not interpreted as direct evidence of a dose–response relationship.

Sensitivity analysis Sensitivity analyses included fixed-effect and DerSimonian–Laird models, leave-one-out analysis, selected trial exclusions, a domain-focused analysis excluding trials at high risk in sequence generation, allocation concealment, incomplete outcome data, or other bias, and an additional trial-arm comparison. Exploratory random-effects meta-regression examined mean maternal age when reported by at least 10 studies. Funnel plots, Egger regression, and L0 trim-and-fill analyses were used to explore small-study effects for outcomes with at least 10 studies. Funnel plots were examined for live birth (13 trials) and miscarriage (10 trials). Egger regression suggested small-study effects for live birth ($p = 0.005$) and miscarriage ($p = 0.042$). Exploratory L0 trim-and-fill analysis estimated one additional study for live birth, giving an adjusted RR of 1.07 (95% CI, 0.97–1.18), and two for miscarriage, giving an adjusted RR of 0.83 (0.60–1.14). These methods assess funnel-plot asymmetry and do not establish its cause. Study-level meta-regression showed no clear association of mean maternal age with the treatment effect on live birth (11 studies; $\beta = -0.0074$ per year; 95% CI, −0.0598–0.0450; $p = 0.756$) or miscarriage (10 studies; $\beta = 0.0538$; 95% CI, −0.1844–0.2921; $p = 0.617$).

Country(ies) involved China.

Keywords recurrent pregnancy loss; low-molecular-weight heparin; combination therapy; live birth; miscarriage; meta-analysis.

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