

INPLASY

Efficacy of Low-Molecular-Weight Heparin for the Treatment of Fetal Growth Restriction: A Meta-Analysis of Randomized Controlled Trials

INPLASY2025100063

doi: 10.37766/inplasy2025.10.0063

Received: 17 October 2025

Published: 18 October 2025

Yuan, L; Liu, HY.

Corresponding author:

lin yuan

yuan_lin93@163.com

Author Affiliation:

Sichuan University West China
Second University Hospital.

ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2025100063

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 October 2025 and was last updated on 18 October 2025.

INTRODUCTION

Review question / Objective There is growing evidence that placental-mediated FGR may have a thrombotic component, suggesting that anticoagulant therapy, such as heparin, could improve placental perfusion and fetal growth. While several randomized controlled trials (RCTs) and observational studies have investigated the effect of low-molecular-weight heparin (LMWH) on prolonging gestation and improving neonatal outcomes, the results have been inconsistent and often limited by small sample sizes.

p: Pregnant women diagnosed with fetal growth restriction (FGR).

I: low-molecular-weight heparin (LMWH)

C: Nutritional support therapy or placebo control

O: To evaluate the efficacy of heparin therapy in pregnancies complicated by FGR

S: RCTs.

Condition being studied There is growing evidence that placental-mediated FGR may have a

thrombotic component, suggesting that anticoagulant therapy, such as heparin, could improve placental perfusion and fetal growth. While several randomized controlled trials (RCTs) and observational studies have investigated the effect of low-molecular-weight heparin (LMWH) on prolonging gestation and improving neonatal outcomes, the results have been inconsistent and often limited by small sample sizes.

METHODS

Search strategy

Cochrane: 71

#1 MeSH descriptor: [Heparin, Low-Molecular-Weight] explode all trees

#2 (Heparin, Low Molecular Weight):ti,ab,kw OR (LMWH):ti,ab,kw OR (Low Molecular Weight Heparin):ti,ab,kw OR (Low-Molecular-Weight Heparin):ti,ab,kw (Word variations have been searched)

#3 #1 or #2

#4 MeSH descriptor: [Fetal Growth Retardation] explode all trees

#5 (Growth Retardation, Intrauterine):ti,ab,kw OR (Intrauterine Growth Restriction):ti,ab,kw OR (Fetal Growth Restriction):ti,ab,kw OR (Intrauterine Growth Retardation):ti,ab,kw (Word variations have been searched)

#6 #4 or #5

#7 (randomized controlled trial):pt OR (randomized):ti,ab,kw OR (placebo):ti,ab,kw (Word variations have been searched)

#8 #3 and #6 and #7

Embase: 118

#8 #3 AND #6 AND #7 118

#7 ('randomized controlled trial':it OR randomized:ti,ab,kw OR placebo:ti,ab,kw) AND [embase]/lim 1161637

#6 #4 OR #5 61045

#5 (('congenital hypotrophy':ti,ab,kw OR 'fetal growth disorder':ti,ab,kw OR 'fetal growth restriction':ti,ab,kw OR 'fetal growth retardation':ti,ab,kw OR 'fetus growth disorder':ti,ab,kw OR 'fetus growth retardation':ti,ab,kw OR 'foetal growth retardation':ti,ab,kw OR 'growth retardation in utero':ti,ab,kw OR 'hypotrophy, congenital':ti,ab,kw OR 'in utero growth restriction':ti,ab,kw OR 'in utero growth retardation':ti,ab,kw OR 'intra-uterine fetal growth restriction':ti,ab,kw OR 'intra-uterine growth restriction':ti,ab,kw OR 'intra-uterine growth retardation':ti,ab,kw OR 'intrauterine fetal growth restriction':ti,ab,kw OR 'intrauterine growth restriction':ti,ab,kw OR iugr:ti,ab,kw) AND 'intrauterine growth retardation':ti,ab,kw OR 'prenatal growth retardation':ti,ab,kw OR 'retardation of fetal growth':ti,ab,kw OR 'retardation of intrauterine growth':ti,ab,kw OR 'retarded intrauterine growth':ti,ab,kw OR 'intrauterine growth retardation':ti,ab,kw) AND [embase]/lim 7596

#4 ('intrauterine growth retardation'/exp OR 'intrauterine growth retardation') AND [embase]/lim 60954

#3 #1 OR #2 90244

#2 ('bm 2123':ti,ab,kw OR 'bm2123':ti,ab,kw OR 'choay':ti,ab,kw OR 'depolymerized heparin':ti,ab,kw OR 'ebpm 1':ti,ab,kw OR 'ebpm 2':ti,ab,kw OR 'ebpm 3':ti,ab,kw OR 'ebpm1':ti,ab,kw OR 'ebpm2':ti,ab,kw OR 'ebpm3':ti,ab,kw OR 'ff 1034':ti,ab,kw OR 'ff1034':ti,ab,kw OR 'fr 860':ti,ab,kw OR 'fr860':ti,ab,kw OR 'gag 869':ti,ab,kw OR 'heparin lmw 2133':ti,ab,kw OR 'heparin, low molecular weight':ti,ab,kw OR 'heparin, low-molecular-weight':ti,ab,kw OR 'heparin, low molecular weight fraction':ti,ab,kw OR 'low molecular heparin':ti,ab,kw OR 'nm heparin':ti,ab,kw OR 'pk 007':ti,ab,kw OR 'sandoz 5100':ti,ab,kw OR 'sandoz 6700':ti,ab,kw OR 'traxyparine':ti,ab,kw

OR 'low molecular weight heparin':ti,ab,kw) AND [embase]/lim 20668

#1 ('low molecular weight heparin'/exp OR 'low molecular weight heparin') AND [embase]/lim 90111

Pubmed: 55

8 (((('Heparin, Low-Molecular-Weight'[Mesh]) OR (((('Heparin, Low Molecular Weight[Title/Abstract]) OR (Low Molecular Weight Heparin[Title/Abstract]) OR (Low-Molecular-Weight Heparin[Title/Abstract]) OR (LMWH[Title/Abstract]))) AND (('Fetal Growth Retardation'[Mesh]) OR (((('Fetal Growth Restriction[Title/Abstract]) OR (Intrauterine Growth Restriction[Title/Abstract]) OR (Growth Retardation, Intrauterine[Title/Abstract]) OR (Intrauterine Growth Retardation[Title/Abstract]))) AND (((randomized controlled trial[Publication Type]) OR (randomized[Title/Abstract]) OR (placebo[Title/Abstract])) ("heparin, low molecular weight"[MeSH Terms] OR ("heparin low molecular weight"[Title/Abstract] OR "low molecular weight heparin"[Title/Abstract] OR "LMWH"[Title/Abstract])) AND ("Fetal Growth Retardation"[MeSH Terms] OR ("fetal growth restriction"[Title/Abstract] OR "intrauterine growth restriction"[Title/Abstract] OR "growth retardation intrauterine"[Title/Abstract] OR "intrauterine growth retardation"[Title/Abstract])) AND ("randomized controlled trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract]) 55

7 ((randomized controlled trial[Publication Type]) OR (randomized[Title/Abstract]) OR (placebo[Title/Abstract]) "randomized controlled trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] 1,152,045

6 ("Fetal Growth Retardation"[Mesh]) OR (((('Fetal Growth Restriction[Title/Abstract]) OR (Intrauterine Growth Restriction[Title/Abstract]) OR (Growth Retardation, Intrauterine[Title/Abstract]) OR (Intrauterine Growth Retardation[Title/Abstract]) "Fetal Growth Retardation"[MeSH Terms] OR "fetal growth restriction"[Title/Abstract] OR "intrauterine growth restriction"[Title/Abstract] OR "growth retardation intrauterine"[Title/Abstract] OR "intrauterine growth retardation"[Title/Abstract] 30,591

5 (((('Fetal Growth Restriction[Title/Abstract]) OR (Intrauterine Growth Restriction[Title/Abstract]) OR (Growth Retardation, Intrauterine[Title/Abstract]) OR (Intrauterine Growth Retardation[Title/Abstract]) "fetal growth restriction"[Title/Abstract] OR "intrauterine growth restriction"[Title/Abstract] OR "growth retardation intrauterine"[Title/Abstract] OR "intrauterine growth retardation"[Title/Abstract] 21,274

4 "Fetal Growth Retardation"[Mesh] Most Recent "Fetal Growth Retardation"[MeSH Terms] 20,072

3 ("Heparin, Low-Molecular-Weight"[Mesh]) OR (((Heparin, Low Molecular Weight[Title/Abstract]) OR (Low Molecular Weight Heparin[Title/Abstract])) OR (Low-Molecular-Weight Heparin[Title/Abstract])) OR (LMWH[Title/Abstract]) "heparin, low molecular weight"[MeSH Terms] OR "heparin low molecular weight"[Title/Abstract] OR "low molecular weight heparin"[Title/Abstract] OR "low molecular weight heparin"[Title/Abstract] OR "LMWH"[Title/Abstract] 21,459

2 (((Heparin, Low Molecular Weight[Title/Abstract]) OR (Low Molecular Weight Heparin[Title/Abstract])) OR (Low-Molecular-Weight Heparin[Title/Abstract])) OR (LMWH[Title/Abstract]) "heparin low molecular weight"[Title/Abstract] OR "low molecular weight heparin"[Title/Abstract] OR "low molecular weight heparin"[Title/Abstract] OR "LMWH"[Title/Abstract] 14,721

1 "Heparin, Low-Molecular-Weight"[Mesh] Most Recent "heparin, low molecular weight"[MeSH Terms] 14,913

Participant or population Pregnant women diagnosed with fetal growth restriction (FGR) ,defined by estimated fetal weight <10th percentile and/or abnormal Doppler findings, in singleton pregnancies.

Intervention This review will include studies in which pregnant women with fetal growth restriction (FGR) receive low-molecular-weight heparin (LMWH). Studies will be included whether heparin is used alone or in combination with other agents, such as low-dose aspirin, and whether heparin can be identified or analyzed separately. No restrictions will be placed on the gestational age at initiation of treatment.

Comparator Nutritional support therapy or placebo control.

Study designs to be included RCTs.

Eligibility criteria 1.Population

Included

Pregnant women diagnosed with fetal growth restriction (FGR) , defined by estimated fetal weight <10th percentile and/or abnormal Doppler findings, in singleton pregnancies.

Excluded

Multiple pregnancies.

FGR due to congenital anomalies or chromosomal abnormalities.

2.Intervention(s) or exposure(s)

Included

Heparin; Low Molecular Weight Heparin; Enoxaparin; Bemiparin; Unfractionated Heparin Therapy

This review will include studies in which pregnant women with fetal growth restriction (FGR) receive low molecular weight heparin (LMWH), including but not limited to enoxaparin, dalteparin, nadroparin, tinzaparin, reviparin, and fraxiparine. All prophylactic and therapeutic dosing regimens, routes of administration (e.g., subcutaneous, intravenous), and treatment durations will be eligible. Studies will be included whether heparin is used alone or in combination with other agents such as low-dose aspirin, and whether heparin can be identified or analyzed separately. No restrictions will be placed on the gestational age at initiation of treatment.

Excluded

Studies will be excluded if:

Heparin is used for indications unrelated to fetal growth restriction (e.g., prevention of venous thromboembolism in otherwise normal pregnancies, management of antiphospholipid syndrome without documented FGR).

The intervention involves anticoagulants other than low molecular weight heparin (LMWH) as the main treatment (e.g., warfarin, fondaparinux, direct oral anticoagulants).

The effect of heparin cannot be distinguished from that of other concomitant treatments because results are not reported separately.

Heparin is administered exclusively in the postpartum period or after delivery.

The study involves animal models or in vitro experiments.

3.Comparator(s) or control(s)

Included

PICO tags selected: Usual Care; Placebo

4.Study design

Included

Randomized controlled trials (RCTs)

Excluded

Prospective cohort studies,Retrospective cohort studies,Case reports, case series, and review articles will be excluded.

Information sources The main databases to be searched are PubMed, Embase, and Cochrane.

Main outcome(s) Gestational age at delivery, birth weight.

Additional outcome(s) Prolongation of pregnancy (from diagnosis to delivery), neonatal intensive care unit (NICU) admission, perinatal mortality, Apgar score <7 at 5 minutes, composite beneficial outcome (≥1 endpoint improved).

Quality assessment / Risk of bias analysis

Cochrane Tool.

Strategy of data synthesis Data will be pooled using a random-effects meta-analysis model (DerSimonian-Laird method) to account for between-study heterogeneity. Continuous outcomes will be summarized using mean differences (MD) or standardized mean differences (SMD) with 95% confidence intervals, and dichotomous outcomes using risk ratios (RR) with 95% confidence intervals. Heterogeneity will be assessed with the I^2 statistic and the Chi-square test.

Subgroup analysis Data will be pooled using a random-effects meta-analysis model (DerSimonian-Laird method) to account for between-study heterogeneity. Continuous outcomes will be summarized using mean differences (MD) or standardized mean differences (SMD) with 95% confidence intervals, and dichotomous outcomes using risk ratios (RR) with 95% confidence intervals. Heterogeneity will be assessed with the I^2 statistic and Chi-square test.

Sensitivity analysis After deleting any one of them, the combined results of the remaining documents show little difference compared to when none were deleted, indicating that the sensitivity analysis has been passed.

Country(ies) involved China.

Keywords Low-Molecular-Weight Heparin, Fetal Growth Restriction.

Contributions of each author

Author 1 - Lin Yuan.

Author 2 - Hongyan Liu.