

Effect of low molecular weight heparin combined with aspirin on pregnancy outcomes of unexplained recurrent abortion: a systematic review and meta-analysis

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ADMINISTRATIVE INFORMATION**Support** - None.**Review Stage at time of this submission** - Preliminary searches.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2023100005**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 02 October 2023 and was last updated on 02 October 2023.**INTRODUCTION**

Review question / Objective To explore the clinical effect, pregnancy outcome and adverse reactions of low molecular weight heparin combined with aspirin in the treatment of unexplained recurrent abortion compared with conventional treatment and aspirin alone. Population: Patients with unexplained recurrent abortion; Intervention: Low molecular weight heparin combined with aspirin; Comparison: Placebo, aspirin alone, progesterone, or conventional treatment; Outcome: Pregnancy outcomes (such as live birth rate, success rate lasting more than 12 weeks of pregnancy, preterm birth rate, pregnancy complications rate), adverse reactions; Study: randomized controlled trial.

Condition being studied The definition of recurrent spontaneous abortion is still controversial. According to the "China Expert Consensus on the Diagnosis and Treatment of spontaneous Abortion 2020 edition", recurrent

spontaneous abortion refers to two or more consecutive embryo loss with the same sexual partner before 28 weeks of pregnancy, including biochemical pregnancy, which is one of the difficult areas in reproductive medicine. The causes of recurrent abortion were different in different periods. The common causes of early recurrent abortion were chromosomal abnormality, immune function abnormality, luteal atrophy insufficiency, thyroid function abnormality, and late anatomic abnormality, autoimmune abnormality, and prethrombotic state. However, more than half of the causes are still unknown, and there is a lack of unified diagnostic criteria and effective treatment. With the opening of the "three-child policy", people are paying more and more attention to fertility problems. The existence of recurrent spontaneous abortion can lead to psychological pressure, anxiety, depression and the decline of life quality. Aspirin has antithrombotic and anti-inflammatory effects. It can inhibit the synthesis of thromboxane A₂, thus preventing platelet aggregation and playing an antithrombotic role. Low molecular weight heparin has the advantages of

anticoagulation, promoting fibrinolysis, protecting phospholipid, immune regulation and low risk of bleeding, and is not easy to pass through the placenta, not secreted in milk, and is safe and effective during pregnancy. The use of both in the treatment of recurrent abortion caused by prethrombotic state has been included in the expert consensus, but the use of unexplained recurrent abortion is still controversial. Therefore, we systematically explored the clinical efficacy, pregnancy outcomes and adverse reactions of low molecular weight heparin combined with aspirin in the treatment of unexplained recurrent abortion in combination with existing studies.

METHODS

Participant or population Patients with unexplained recurrent abortion.

Intervention Low molecular weight heparin combined with aspirin.

Comparator Placebo, aspirin alone, progesterone, or conventional treatment.

Study designs to be included Only randomized controlled trials(RCTs) will be included in this study.

Eligibility criteria 1. All patients included were in line with RSA diagnostic criteria, and genetic factors, endocrine factors, infectious factors, anatomical factors, pre-thrombotic status and autoimmune factors were excluded. 2. The observation group was treated with aspirin combined with LMWH before or during pregnancy, while the control group was treated with the regimens were placebo, aspirin alone, progesterone, or conventional treatment (vitamins, folic acid, etc.). 3. randomized controlled trial (RCT). 4. Outcome indicators: pregnancy outcomes (such as live birth rate, success rate lasting more than 12 weeks of pregnancy, preterm birth rate, pregnancy complication rate) and adverse reactions. 5. Non-Chinese and English literature. 6. Repeated publications. 7. Incomplete materials and data make it impossible to extract effective information for statistical analysis. 8. Review and conference documents.

Information sources Related studies in the following databases will be searched from inception to October 02, 2023: PubMed, Embase, Cochrane Library, Web of Science, China National Knowledge Infrastructure (CNKI), the Chinese BioMedical database (CBM), VIP and Wanfang.

Main outcome(s) Live birth rate, success rate lasting more than 12 weeks of pregnancy, preterm birth rate.

Quality assessment / Risk of bias analysis The quality of all RCTs will be assessed using the Cochrane collaboration tool, the two authors will conduct quality assessments independently, and any disputes will be discussed with the other author.

Strategy of data synthesis Review Manager 5.3 software was used to conduct meta-analysis and draw forest maps for each group. The odds ratio (OR) was used as the effect size for statistical analysis, and the interval estimation was expressed by 95% confidence interval (95%CI). The I² and Q tests were used to evaluate the heterogeneity among the studies. If $P \geq 0.01$ or $I^2 \leq 50\%$, the studies were homogenous, and the fixed-effect model was used for analysis; if $P < 0.01$ or $I^2 > 50\%$, the studies were heterogeneous, and the random effects model was used for analysis. Chi-square test was used to compare the obtained components, and the test level $\alpha = 0.05$, $P < 0.05$ was considered statistically significant. Sensitivity analysis was conducted to evaluate the stability of results by observation of the change in heterogeneity of results and the difference of the combined effect size (OR value) of each group after article by article removal. The funnel plot was used to evaluate the detection of publication bias. If the distribution of each scatter point in the funnel plot was basically symmetric, it could be considered that there was no significant publication bias; otherwise, it could be considered that there was publication bias.

Subgroup analysis None.

Sensitivity analysis In order to check the stability and reliability of the results of this study, we conducted sensitivity analysis based on the quality of the method, sample size, and missing data. After that, we will analyze the data again and compare the results. If there is no directional change in sensitivity analysis, the results are stable.

Country(ies) involved China.

Keywords unexplained recurrent abortion; Low molecular weight heparin.

Contributions of each author

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