

ORIGINAL RESEARCH

Meta-analysis of Clinical Efficacy of Aspirin and Low Molecular Weight Heparin in the Treatment of Recurrent Spontaneous Abortion

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ABSTRACT

Objective • To investigate the clinical effect of aspirin (ASA) combined with low molecular weight heparin (LMWH) in the treatment of recurrent spontaneous abortion (RSA).

Methods • PubMed, Cochrane, Wanfang, CNKI, and other databases were searched to collect randomized controlled trials (RCT) of aspirin combined with LMWH in the treatment of RSA from the establishment of the database to July 31, 2023. The literature was screened, and the information was extracted according to the pre-established criteria. The Reviews Manager 5.4 software was used for data analysis.

Results • A total of 10 RCTs containing 1865 patients with RSA were included in this study. Meta-analysis showed that the regimen of aspirin combined with LMWH

treatment significantly increased the neonatal birth rate ($P < .01$); and the occurrence of preeclampsia was significantly reduced when compared with regimens such as aspirin alone ($P = .02$); there were no significant differences between the two groups in the incidence of preterm birth ($P = .21$), neonatal birth weight ($P = .38$), the incidence of a small amount of patient hemorrhage ($P = .41$) and fetal growth restriction ($P = .93$).

Conclusion • The combination of aspirin and LMWH offers a clinically significant improvement in live birth rates and reduction in preeclampsia for RSA patients, suggesting a beneficial strategy for clinical practice and future research directions. (*Altern Ther Health Med.* [E-pub ahead of print.]

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INTRODUCTION

Recurrent spontaneous abortion (RSA) is defined as two or more consecutive spontaneous abortions. The etiology of RSA is complex and can be caused by a variety of factors, including uterine malformations, endocrine disorders, immunological causes, infection, chromosomal abnormalities, maternal autoimmune abnormalities, etc. However, the etiology of RSA is still unknown in 50-60% of cases. Each etiological factor uniquely influences the prognosis and management of RSA. Understanding these underlying causes is crucial for tailoring effective treatment strategies, setting the stage for the potential benefits of LMWH and ASA combination therapy.¹ Experts suggest that spontaneous abortion more than two times should be paid

attention to,² because the risk of a second abortion is similar to that of more than three times. It is necessary to evaluate the cause in time. If no timely intervention measures are taken, it will have a serious impact on the family and personal physical and mental health. At present, it is believed that the etiology of RSA includes anatomical factors, prethrombotic state, endocrine factors, genetic factors, infectious factors, and immune factors, among which RSA caused by immune factors includes autoimmune RSA and alloimmune RSA.³

In discussing the context of Recurrent Spontaneous Abortion (RSA), it is particularly important to clearly define "Pre-thrombotic State" (PTS). PTS is a complex pathological state involving the blood coagulation system, referring to the dysfunction or disorder of the blood clotting, anticoagulant, and fibrinolytic systems triggered by various factors. This state increases the risk of thrombus formation, especially during certain clinical conditions, such as pregnancy. In PTS, blood fluidity is reduced, enhancing the likelihood of intravascular thrombus formation. These thrombi can further obstruct vital blood vessels, leading to insufficient blood supply to tissues and organs. In the context of RSA, PTS is of particular concern as it may cause placental blood flow obstruction, affecting fetal growth and development, and potentially leading to

miscarriage. PTS during pregnancy can arise from various factors, including genetic predispositions, lifestyle factors (such as smoking and obesity), and certain pathological conditions (like antiphospholipid antibody syndrome). Therefore, timely identification and treatment of PTS are crucial for preventing and managing RSA.⁴ At present, the commonly used anticoagulant drugs are low molecular weight heparin (LMWH), aspirin (ASA), and warfarin, etc. The commonly used LMWH include dalteparin, enoxaparin, and nadroparin calcium. ASA has dual antithrombotic and anti-inflammatory effects, which can inhibit the synthesis of thromboxane A2 to prevent platelet aggregation and play an antithrombotic role.⁵ Low molecular weight heparin has multiple effects on anticoagulation, fibrinolysis, phospholipid protection, immune regulation, proliferation, and differentiation of trophoblast cells.⁶ The combination of the two drugs for the treatment of RSA caused by prethrombotic state has been included in the expert consensus. LMWH and ASA are employed for their complementary anticoagulant effects. LMWH targets the coagulation cascade, reducing thrombus formation, while ASA inhibits platelet aggregation. Their combination potentially offers a synergistic effect, enhancing placental blood flow and reducing the risk of RSA through distinct yet complementary mechanisms. In this study, we investigate the use of Low Molecular Weight Heparin (LMWH) and Aspirin in treating Recurrent Spontaneous Abortion (RSA). LMWH types such as Enoxaparin and Dalteparin work by binding with Antithrombin III, speeding up thrombin inhibition, thereby reducing blood clotting and preventing thrombosis. Aspirin reduces thrombosis risk by inhibiting Cyclooxygenase, which decreases Thromboxane A2 production and thus inhibits platelet aggregation. Combining these drugs in RSA can enhance placental blood flow and reduce thrombus formation, improving pregnancy outcomes. Current research presents mixed findings on the efficacy of ASA and LMWH in treating RSA, with some studies highlighting benefits while others show limited effects. Our study aims to clarify these inconsistencies and contribute a comprehensive analysis to the existing literature, addressing the crucial research gap in effective management of RSA.

This study specifically aims to assess the clinical effectiveness of combining ASA and LMWH in treating RSA, with a focus on live birth rates, incidence of preeclampsia, and other secondary outcomes like preterm birth rates and fetal growth. We also aim to explore the effects of this combination therapy in specific RSA patient subgroups, further delineating its therapeutic scope and potential. RSA poses not only a psychological burden on patients but also presents a substantial healthcare challenge, contributing to increased medical costs and resource utilization. This underscores the necessity of effective management strategies, thereby highlighting the importance of our study in addressing this significant clinical issue. Although current treatments have limitations, finding effective therapies for RSA patients is imperative. Using Meta-analysis, this paper compares the efficacy of combined LMWH and Aspirin treatment to Aspirin alone in treating recurrent

miscarriages. It examines differences in live birth rates, preterm birth rates, pre-eclampsia, and minor bleeding incidents between the two treatments. It also evaluates variations in newborn birth weight, fetal growth restriction, and conditions.

MATERIALS AND METHODS

Search strategy

Chinese databases such as China National Knowledge Infrastructure (CNKI), Wanfang Data, VIP Database, China Biology Medicine Disc (CBMdisc) and English databases such as PubMed, Embase, Cochrane Library were searched. The search terms were: aspirin; low molecular weight heparin; recurrent spontaneous abortion or recurrent miscarriage or recurrent abortion; pre-thrombotic state. Search time: database establishment to July 31, 2023. According to different database conditions, subject words and free words were searched comprehensively to ensure the systematization and completeness of the search.

Literature inclusion and exclusion criteria

Inclusion criteria. (1) All patients included in the literature had a history of two or more miscarriages and were in a pre-thrombotic state, characterized by abnormalities in one or several of the following indicators: D-Dimer (a product of fibrinolysis, commonly used to assess the status of thrombus formation and dissolution), coagulation profile (levels of coagulation factors reflecting the activity of the blood clotting system), thromboelastography (a laboratory test that assesses the entire clotting process and provides information about the balance of blood coagulation and dissolution), antithrombin III (a natural anticoagulant factor, with level changes reflecting the state of the anticoagulation system), fibrinogen (a key protein in blood clotting, with level changes indicating coagulation activity), plasminogen activator inhibitor and tissue-type plasminogen activator (factors regulating the formation and dissolution of fibrin, reflecting the status of the fibrinolytic system), and uterine artery resistance (assessing the status of uterine blood flow, indirectly reflecting the balance of blood coagulation and anticoagulation) (2) The observation group was treated with aspirin combined with LMWH (usually 4100U, 5000U, QD subcutaneous injection) and general treatment, while the control group was treated with placebo, aspirin and general treatment. General treatment' in both groups is defined as standard prenatal care excluding the use of aspirin or LMWH. This clarification aids in comparing the additive effect of aspirin combined with LMWH. (3) The included literatures had complete data, including at least one or several of the outcome indicators. (4) Published randomized controlled trial (RCT).

Exclusion criteria. (1) Sham-randomized or semi-randomized controlled trials; (2) outcome indicators were not included in the study or lack of key data; (3) excluding abortion caused by another endocrine system, reproductive organ malformation, chromosomal factors, viral infection, mental factors, etc; (4) animal experiments, case reports, reviews, meta-analyses, non-randomized studies, articles published repeatedly

Table 1. Basic characteristics of the included literatures (n=10)

	Age (SD)		Number of abortions	Number of cases		Intervention measures		Time to Discontinuation
	Observation group	Control group		Observation group	Control group	Observation group	Control group	
Karadağ, 2020 ⁸	29.71(3.80)	28.37(3.38)	≥4	59	61	Enoxaparin+ASA	ASA	35 weeks of gestation or before delivery; When a spontaneous abortion occurs
Laskin, 2009 ⁹	34.6(3.9)	33.8(4.1)	≥2	45	43	LMWH+ASA	ASA	35 weeks of gestation or before delivery; When a spontaneous abortion occurs
Frankin, 2002 ¹⁰	33.2(3.9)	33.0(4.4)	≥2	28	26	LMWH+ASA	ASA	Aspirin and low molecular weight heparin were stopped at 38 weeks and 37 weeks of pregnancy, respectively. When a spontaneous abortion occurs
Goel, 2006 ¹¹	23.8(1.28)	24.9(3.1)	≥2	33	39	LMWH+ASA	ASA	36 weeks of gestation or before delivery; When a spontaneous abortion occurs
Kutteh, 1996 ¹²	33.2(4.2)	33.5(5.8)	≥2	25	25	LMWH+ASA	ASA	37 weeks of gestation or before delivery; When a spontaneous abortion occurs
Bao, 2017 ¹³	35	34	≥3	497	518	LMWH+ASA	ASA	36 weeks of gestation or before delivery; When a spontaneous abortion occurs
Farquharson, 2002 ¹⁴	33(4.8)	33(4.8)	≥3	51	47	LMWH+ASA	ASA	36 weeks of gestation or before delivery; When a spontaneous abortion occurs
Rai, 1997 ¹⁵	32(23-40)	34(22-44)	≥4	45	45	LMWH+ASA	ASA	36 weeks of gestation or before delivery; When a spontaneous abortion occurs
Zhang, 2022 ¹⁶	30.96(4.05)	29.93(4.51)	≥2	52	76	LMWH+ASA	ASA	36 weeks of gestation or before delivery; When a spontaneous abortion occurs
Mohamed, 2014 ¹⁷	27.3(4.8)	26.5(2.7)	≥3	75	75	LMWH+ASA	ASA	37 weeks of gestation or before delivery; When a spontaneous abortion occurs

in different databases and articles with duplicate data; (5) allergic to the drugs used in the study; (6) repeated publications. The diagnostic criteria for complications listed are based on universally accepted standards and cited from reputable sources to ensure the credibility of the study and its findings.

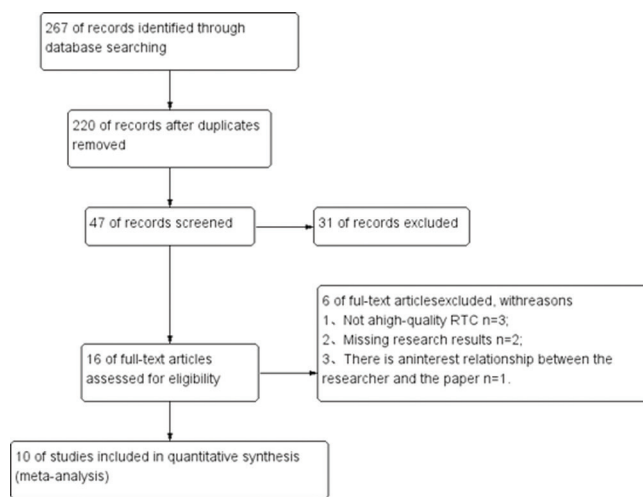
Literature screening and data extraction

Researchers who had received training in evidence-based methods independently screened the literature, extracted the data, and cross-checked the literature according to the inclusion and exclusion criteria. If there were differences of opinion, consensus was reached through discussion or with another researcher to assist in the ruling. The following contents were included: (1) Study identification: first author’s name and publication year; (2) Subject information: gender, age, number of previous abortions and termination time of medication; (3) Group data: follow-up time, sample size, intervention (treatment plan), available outcome indicators.

Literature quality evaluation

In this study, we employed the latest version of the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0, to assess the quality of our research’s randomized controlled trials (RCTs). This handbook provides a comprehensive set of guidelines and standards for evaluating the risk of bias in RCTs. The specific assessment criteria include the generation of random sequences, concealment of allocation schemes, blinding of participants and interventionists, blinding of outcome assessors, completeness of outcome data, selective reporting of results, and other potential sources of bias. Each criterion is judged as having a “low risk of bias,” “high risk of bias,” or “unclear risk of bias.” The process of screening and extracting information from the literature was independently completed and cross-verified by researchers trained in evidence-based medicine methods. In cases of disagreement, consensus was reached through discussion or with the assistance of a third researcher. Through this process, we ensured that the quality assessment of the included studies was both systematic and objective, based on internationally recognized evaluation standards. Furthermore, we paid special attention to the risks of implementation bias, measurement bias, and follow-up bias in each study to ensure the reliability and validity of our analysis results. Any disagreements in the assessment of studies will be resolved through discussion or, if necessary, by consulting a third,

Figure 1. Literature screening flow chart



independent reviewer, adding an extra layer of objectivity to our study. To address publication bias, funnel plot analysis will be employed. If this suggests the presence of bias, further steps such as Egger’s test or other alternative statistical methods will be used to assess its impact on our findings.

Statistical analysis

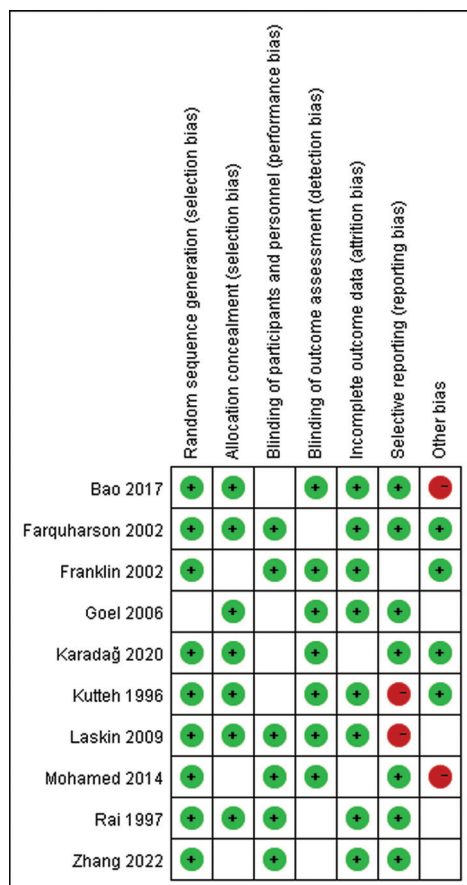
RevMan5.4 software was used for Meta-analysis. The heterogeneity of the included studies was evaluated by I^2 statistic and Chi^2 . If $P < .10$ or $I^2 > 50\%$ by Chi^2 test, the heterogeneity was significant, then the random effect model was used for combined analysis, otherwise, the fixed effect model was used. The odds ratio (RR) and 95% confidence interval (CI) were used as the effect indicators of the study. To ensure the stability of the results, a sensitivity analysis was performed by excluding individual study reanalysis, and in addition, the degree of publication bias was assessed by looking at funnel plots.

RESULTS

Literature search results

The initial search yielded 267 articles. We obtained 47 articles by EndNote X9 software after eliminating duplicates, and then after reading the titles, abstracts, and full texts, we excluded 37 articles that did not meet the inclusion criteria and finally included 10 articles, and the screening process and the study profiles of the included articles are shown in Figure 1 and Table 1.⁸⁻¹⁷ The risk of bias of the included

Figure 2. Risk of bias summary chart



articles was assessed by the assessment form recommended by the Co-chrane Evaluator’s Manual, and all the included studies were of high quality. All the included studies were of high quality, with low risk of bias for implementation bias, measurement bias, and follow-up bias (Figure 2).

Meta-analysis

Neonatal birth rate. Ten studies reported a total of 1865 patients included in the analysis of neonatal birth outcomes, with a neonatal birth rate of 765/910 (84.07%) in the observation group and 623/955 (65.24%) in the control group. Due to the results of the heterogeneity test between studies ($P = .06$, $I^2=44%$), a fixed effects model was used. On statistical analysis, the observation group had a significantly higher neonatal birth rate than the control group [OR=2.94, 95%CI (2.34, 3.69), $P < .01$] (Figure 3). The significant increase in neonatal birth rate in the observation group may suggest a potential improvement in clinical outcomes for RSA patients treated with the combination of LMWH and ASA.

Preeclampsia. A total of 318 patients were included in the analysis of preeclampsia. The incidence of preeclampsia in the observation group was 5/178 (17.92%), and that in the control group was 14/140 (18.84%). A fixed effects model was used due to heterogeneity test results between studies ($P = .80$, $I^2=0%$). The results showed that the incidence of preeclampsia in the observation group was lower than that in

Figure 3. Meta-analysis of birth rate of newborns in both groups

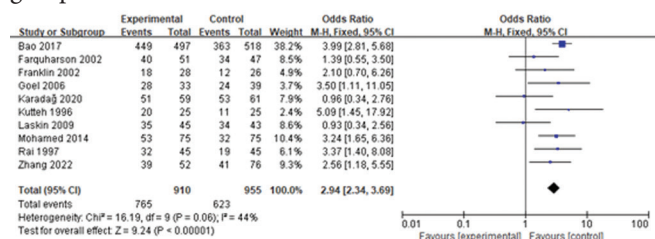


Figure 4. Meta-analysis of the incidence of preeclampsia in the two groups

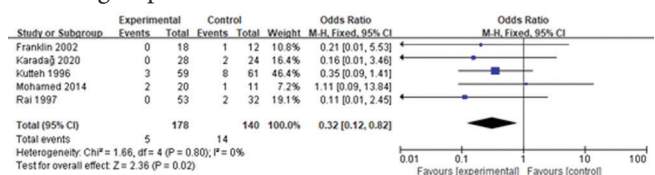


Figure 5. Meta-analysis of the incidence of prematurity in the two groups

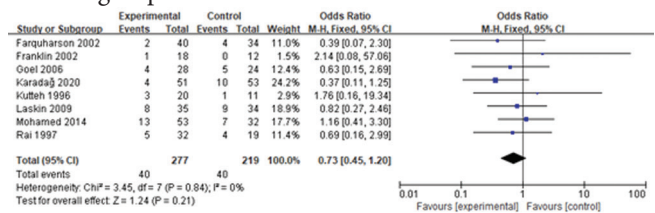
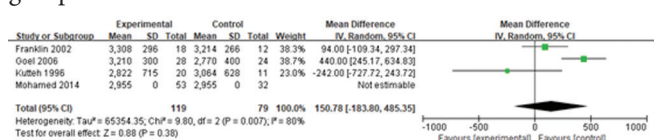


Figure 6. Meta-analysis of neonatal birth weight in the two groups



the control group, and the impact on the incidence of preeclampsia was statistically significant [OR=0.32, 95%CI (0.12, 0.82), $P = .02$] (Figure 4).

Incidence of premature infants. All 596 patients were included in the analysis of preterm birth rate. The preterm birth rate was 40/277 (17.92%) in the observation group and 40/219 (18.84%) in the control group. A fixed effects model was used due to the heterogeneity test results between studies ($P = .84$, $I^2=0%$). There was no significant difference in adverse pregnancy outcomes of preterm birth between the two medication regimens in the treatment of RSA [OR=0.73, 95%CI (0.45, 1.20), $P = .21$] (Figure 5).

Birth weight. In the included literature, the birth weight of newborns was described in four studies, and a total of 298 newborns were included in birth weight statistics. The heterogeneity test ($P = .007$, $I^2=80%$) showed that the heterogeneity of all literatures was large, so the random effects model was used to combine the effect size. There were 119 cases in the observation group and 79 cases in the control group. After combination [MD=150.78, 95%CI (-183.80, 485.35), $P = .38$], the two groups had no statistical difference in birth weight. See Figure 6 for details.

Minor bleeding. The observation group had small bleeding (22/137, 13.64%), and the control group had 16/107 (8.51%). A fixed effects model was used due to heterogeneity test results between studies ($P = .63$, $I^2=0\%$). The difference was not statistically significant [OR=1.37, 95%CI (0.65, 2.91), $P = .41$] (Figure 7).

Fetal growth restriction. The incidence of fetal growth restriction was 12/184 (9.90%) in the observation group and 10/153 (16.0%) in the control group. Due to the results of the test of heterogeneity between studies ($P = .87$, $I^2=0\%$), a fixed effects model was used. Statistically, the difference in the incidence of fetal growth restriction between the two treatment groups was not statistically significant [OR=1.04, 95%CI (0.44, 2.49), $P = .93$] (Figure 8). There was no statistically significant difference in the role of the two treatment regimens in improving fetal growth restriction.

DISCUSSION

The incidence of recurrent spontaneous abortion (RSA) is increasing year by year in clinical practice. pro thrombotic state (PTS) is an important factor leading to RSA and its pathogenesis is very complex. It has become a research hotspot in recent years. Anticoagulant therapy is the main treatment for PTS at present, and the current anticoagulant drugs mainly include low molecular weight heparin (LMWH) and aspirin (ASA). Aspirin is an inhibitor of cyclooxygenase (COX), which can inhibit the activity of COX and thus the synthesis of thromboxane A2, thereby inhibiting platelet aggregation, inhibiting prostaglandin synthase activity, relieving vasospasm, reducing uterine artery resistance, and improving placental blood supply.¹⁸ Existing studies have shown that aspirin has no obvious adverse effects, does not increase the rate of fetal malformation, does not increase the incidence of fetal and neonatal bleeding, does not affect fetal platelets and pulmonary circulation, and is a class C drug recommended by the FDA for pregnancy.¹⁹ In addition to aligning with previous research, our findings may suggest a potential shift in clinical practice for RSA treatment. The combination of LMWH and aspirin, as evidenced by our study, could be considered more frequently in clinical protocols, especially in cases where traditional treatments have limited success. LMWH is an AT-III dependent thrombin inhibitor, which can bind to AT-III, promote the synthesis and release of TFPI and t-PA from endothelial cells, and down-regulate PAI-I. LMWH can promote the conversion of fibrinogen to thrombin, thus exerting anticoagulant and antithrombotic effects. In addition, studies have shown that LWMH can also play a variety of effects, such as inhibiting Toll-like receptor 4-mediated API inflammatory response, inhibiting the binding of APL to anti-β2-GPI, activating epidermal growth factor receptor, inhibiting trophoblast apoptosis, protecting vascular endothelium, and increasing endometrial blood supply.²⁰ LMWH has little effect on platelets, rarely causes bleeding tendency, cannot cross the placenta, and has no secretion in breast milk, which is an ideal anticoagulant drug for pregnant

Figure 7. Meta-analysis of the incidence of minor bleeding in the two groups

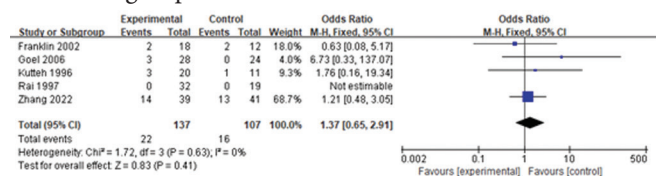
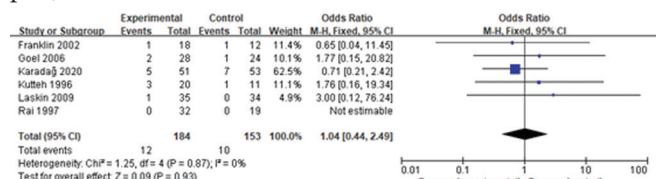


Figure 8. Comparison of IUGR meta-analysis results (forest plot)



women. To further elaborate on the interaction between LMWH and aspirin, our study delves into their synergistic effects. The combination of these drugs addresses multiple pathways involved in RSA pathogenesis, offering a comprehensive therapeutic approach that covers both anticoagulant and anti-inflammatory aspects, potentially improving pregnancy outcomes more effectively than either drug alone.

This systematic review and Meta-analysis explored the clinical effect of aspirin combined with LMWH in the treatment of RSA. The results of this study showed that compared with the control group, the birth rate of the observation group was significantly increased [OR=2.94, 95%CI (2.34, 3.69), $P < .01$]. The therapeutic effect of the combination of LMWH and aspirin was significantly better than that of aspirin alone, and the risk of abortion was significantly reduced. This is related to the better anticoagulant effect of combination drugs than single drugs. The mechanisms of LMWH in anticoagulation and improving the success rate of pregnancy are as follows: (1) It can inhibit the activity of coagulation factors, particularly having a strong effect on inhibiting thrombin, which suppresses platelet aggregation, improves hypercoagulable states, and prevents thrombus formation. This is crucial in preventing Recurrent Spontaneous Abortion (RSA) since thrombosis can lead to placental dysfunction and insufficient embryonic blood supply. (2) It promotes the repair and growth of vascular endothelial cells and reduces the apoptosis of trophoblast cells. (3) LMWH helps improve placental blood supply, thereby promoting healthy fetal development. Aspirin also aids this process by inhibiting platelet aggregation, but the effect is more significant when used in combination with LMWH. (4) Besides its anticoagulant effect, LMWH may also improve pregnancy outcomes by modulating the immune response. This is particularly important for RSA caused by immune factors. (5) LMWH has also been found to promote the proliferation and differentiation of trophoblastic cells, which is crucial for maintaining pregnancy. Therefore, our study results support the

advantages of combining Aspirin with Low Molecular Weight Heparin in treating RSA. This combined treatment, through multiple mechanisms, not only increases fertility rates in patients but also reduces the risk of miscarriage. However, further research is needed to understand these mechanisms and their interactions in depth. The results of this study showed a significant reduction in the occurrence of preeclampsia in the observation group compared to the control group [OR=0.32, 95%CI (0.12, 0.82), $P = .02$]; at the same time, we observed that there was no significant difference in the incidence of preterm births between the two groups [OR=0.73, 95%CI (0.45, 1.20), $P = .21$]. There was also no significant difference in neonatal birth weight between the two groups [MD=150.78, 95%CI (-183.80, 485.35), $P = .38$], and there was also no significant difference in a small amount of haemorrhage in patients between the two groups [OR=1.37, 95%CI (0.65, 2.91), $P = .41$]. Finally, there was also no significant difference in fetal growth restriction between the two groups [OR=1.04, 95%CI (0.44, 2.49), $P = .93$]. Previous studies have explored the effectiveness of aspirin and LMWH in treating RSA. A study of assisted reproductive technology treatment in a large sample of RSA patients showed that the addition of anticoagulants to 12 weeks of gestation in artificial cycle hormone replacement therapy improved the pregnancy outcome of patients. The use of LMWH was more favourable to embryo implantation. The addition of aspirin after clinical pregnancy was established was more effective in reducing the rate of early miscarriage in patients with RSA, which was similar to the results of the present study. In this paper, we used systematic evaluation and Meta-analysis to explore the clinical efficacy of aspirin combined with LMWH in the treatment of RSA, which systematically and comprehensively included all retrievable RCTs. The outcome indexes included the birth rate of neonates, the incidence of pre-eclampsia in patients, the weight of neonates, the incidence of preterm births, the growth restriction of neonates, and the incidence of a small amount of haemorrhage in patients, which is of some significance as a guide for RSA.

There are also shortcomings in this study: Firstly, The data in this study primarily come from samples in Asia and Europe. It is important to note that differences in genetic background, environmental factors, and lifestyles across regions could affect the generalizability of our results on a global scale. Therefore, while our findings are significant within these regions, caution should be exercised when applying these results to other areas due to geographical and demographic differences. Additionally, most studies did not specifically describe the random allocation methods for the experimental and control groups, indicating a need for larger sample sizes and more extensive clinical research to avoid publication bias. Secondly, the etiology of pre-thrombotic RSA is complex, and the pathogenesis cannot be completely clarified, so its diagnostic criteria have not yet been completely unified, and it is difficult to completely unify the medication course, dosage, and routine treatment of experimental groups

in each literature. Therefore, more randomized controlled trials with strictly standardized and unified setting criteria are needed for further verification to provide more reliable and accurate evidence-based medicine. While acknowledging the study's limitations, including publication bias and the lack of uniform diagnostic criteria, we recognize these could impact result interpretation. Future research should aim for methodological improvements, such as more stringent randomization processes and standardization in diagnostic criteria, to enhance the reliability of findings in the field of RSA treatment.

This study detected a certain degree of publication bias through funnel plot analysis. Publication bias often arises when studies with positive or significant results are more likely to be published, potentially leading to overestimating treatment efficacy. The publication bias observed in our analysis could have impacted the final results. Specifically, studies showing significant effects of combined Aspirin and Low Molecular Weight Heparin treatment may have been more likely to be published, while those with less significant or negative results might not have been included. Therefore, although our results suggest that combined treatment is more effective than using Aspirin alone, we must consider that these findings might be overestimated due to publication bias. To address this bias, we have taken a cautious approach in interpreting the results and suggest that more research is needed to validate these conclusions further before applying these findings to clinical practice. Future studies should endeavor to include unpublished or negative outcome studies to obtain a more comprehensive and balanced evidence base. Additionally, exploring the effects of ASA and LMWH at different dosages and treatment timelines is an important direction for future research. Understanding how these drugs interact in various clinical scenarios and how they affect the treatment outcomes of different types of RSA patients will be significant in optimizing treatment regimens and improving patient prognoses. The clinical implications of our findings extend to treatment decisions and patient counseling. Clinicians may consider the combined treatment of LMWH and aspirin more proactively, particularly for patients with recurrent miscarriages where traditional approaches have been unsuccessful. Our study could also inform the development of updated clinical guidelines, emphasizing tailored treatments based on individual patient profiles. For future research, we propose conducting multicenter trials with a diverse patient population to confirm the generalizability of our results. Investigating the optimal dosage and treatment duration for the combined treatment of LMWH and aspirin in RSA could be pivotal. Studies focusing on specific patient subgroups, such as those with different etiologies of RSA, would also contribute significantly to our understanding and management of this condition.

In summary, the available evidence suggests that aspirin combined with LMWH regimen can improve the live birth rate and reduce the incidence of preeclampsia in patients with RSA to a certain extent compared with aspirin alone

regimen. Aspirin combined with LMWH may have some adjunctive significance as an empirical regimen in the clinical management of recurrent miscarriage. However, due to the study's limitations, the results need to be proved by large samples, high-quality clinical studies, and the results of this systematic evaluation and Meta-analysis need to be demonstrated again in the future with the inclusion of more Chinese and English RCTs.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to report relevant to this article.

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This study did not receive any funding in any form.

AUTHOR CONTRIBUTIONS

XL and CM designed the study and performed the experiments, XL and WZ collected the data, CM and WZ analyzed the data, XL and CM prepared the manuscript. All authors read and approved the final manuscript.

ETHICAL COMPLIANCE

Not applicable.

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