Article

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Meta-Analysis of the Efficacy of Low Molecular Weight Heparin and Aspirin in the Treatment of Thrombosis During Pregnancy and Effects on Coagulation Function

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Background: At present, there is no comprehensive evaluation of the efficacy and safety of low molecular weight heparin (LMWH) for the treatment of thrombophilia during pregnancy in clinical practice. This study aimed to systematically evaluate the efficacy of LMWH in the treatment of patients and its effects on coagulation function, thereby providing a reference for the clinical treatment and prognosis evaluation of thrombophilia during pregnancy.

Methods: Database PubMed, Web of Science and Embase as well as China National Knowledge Infrastructure and Wanfang Database were applied for the search of data. A comparative study on the efficacy of LMWH in the treatment of gestational thrombophilia was enrolled. Stata 16.0 software (Stata, College Station, TX, USA) was utilized to conduct the meta-analysis.

Results: A total of 487 relevant articles were retrieved and 14 studies were finally included. Patients in the LMWH combined with the low-dose aspirin group had a significantly higher live birth rate than those in the aspirin or LMWH treat group (OR (odds ratio) = 4.54, 95% CI (confidence interval): 2.76, 7.45). The adverse effects rate was lower in the LMWH combined with the low-dose aspirin group than in the aspirin or LMWH treatment group (OR = 0.40, 95% CI: 0.29, 0.56). After treatment, patients in the LMWH combined with the low-dose aspirin group had significantly lower D-dimer (SMD (standardized mean differences) = –1.50, 95% CI: –2.19, 0.80) and platelet count (PLT; SMD = –0.13, 95% CI: –0.35, 0.09) than those in the aspirin or LMWH treatment group. However, activated partial thromboplastin time (APTT; SMD = 0.16, 95% CI: –0.10, 0.42), thrombin time (TT; SMD = 0.60, 95% CI: –0.14, 1.34), plasma prothrombin time (PT; SMD = 0.42, 95% CI: –0.71, 1.56), and fibrin values (FIB; SMD = –0.92, 95% CI: –2.12, 0.28) were significantly higher in the LMWH combined with low-dose aspirin group than those in the aspirin or LMWH treatment group.

Conclusions: LMWH heparin combined with low-dose aspirin can effectively correct coagulation function in pregnant women, improve prothrombotic state and increase the live birth rate, which has high clinical value.

Keywords: pregnancy; thrombophilia; coagulation; low molecular weight heparin (LMWH); aspirin; meta-analysis

Introduction

It has been reported that related thrombosis during pregnancy is the leading cause of maternal death in many countries [1]. The main form of thrombophilia during pregnancy is venous thromboembolism (VTE). The risk of VTE increases 4–5 times during pregnancy. Some studies have stated that the risk of VTE in pregnant women is 5 times higher than that in non-pregnant women of the same age. VTE occurs 0.7 to 1.7 times per 1000 deliveries, with a relatively high incidence [2,3]. VTE appears easier in postpartum than in prenatal stages. The highest risk of VTE occurs in the first 3 months after delivery when the risk increases 20–80 times. Meanwhile, VTE that appears postpartum can induce postpartum pulmonary embolism (PE). PE is induced approximately 0.45 times per 1000 deliveries [4]. Besides, some related meta-analysis reports have revealed that, compared with pregnancy without *in vitro* fertilization, secondary pregnancy *in vitro* fertilization is associated with a relatively increased risk of VTE. The risk of VTE in early pregnancy is higher compared with the second or third trimester [5,6]. According to related studies, many classical signs and symptoms of VTE may be related to normal pregnancy. Up to now, the strategy for diagnosis of VTE has not been validated during pregnancy, which makes the diagnosis of VTE during pregnancy and postpartum challenging.

At present, the clinical treatment for thrombophilia during pregnancy is mainly to reduce the coagulation effect of patients through heparin, and the use of heparin cannot cross the placenta to affect the growth and development of the fetus [7]. However, pregnant women with mechanical heart valves or heparin-induced thrombocytopenia cannot undergo the treatment of heparin, so some other therapeutic methods are needed [8]. Besides, long-term use of heparin is easy to cause osteoporosis and thrombocytopenia in patients. Therefore, low molecular weight heparin (LMWH) has become the first drug of choice for the treatment of thrombophilia during pregnancy [9]. Some studies have pointed out that, compared with unfractionated heparin, LMWH has more efficient bioavailability and easier administration. Moreover, the use of LMWH drugs greatly reduces the risk of drug-related osteoporosis and thrombocytopenia [10]. In a clinical trial of anticoagulation in pregnancy, 822 patients with acute VTE were treated with LMWH (Enoxaparin: 1 mg/kg; Dalteparin: 200 U/kg). The result indicated that the patients treated with LMWH had a significantly lower incidence of bleeding events or recurrent VTE [11]. It can be seen that LMWH drugs have a high therapeutic effect on thrombophilia during pregnancy, which can ensure a normal pregnancy and the development of fetal prognosis in patients. However, the efficacy and safety of LMWH drugs have not been comprehensively evaluated in clinical practice. Therefore, this study collected the literature in recent years to conduct a systematic review and meta-analysis. Then, an evaluation was performed for the efficacy and effects of LMWH for the treatment of thromboembolism during pregnancy and the coagulation function of patients. This study aimed to provide references for the clinical treatment and prognosis of thromboembolism during pregnancy.

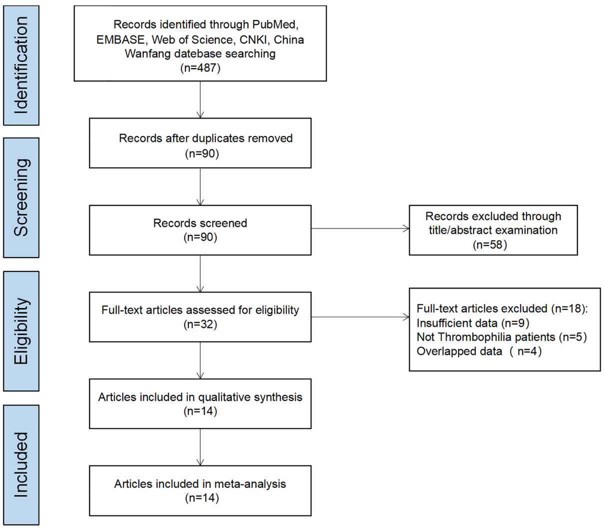

Fig. 1. Literature screening process for inclusion in the meta-analysis. PubMed, Web of Science, Embase, China National Knowledge Infrastructure (CNKI) and Wanfang Database were used to search the literature.

Materials and Methods

Literature Search Methods

PubMed (https://www.ncbi.nlm.nih.gov/sites/entrez?db=PubMed), Web of Science (https://www.webofscience.com/wos/alldb/basic-search), Embase (http://www.embase.com), China National Knowledge Infrastructure (http://www.cnki.net/) and Wanfang Database (http://g.wanfangdata.com.cn/) were adopted for the search of the literature. English and Chinese were set as the retrieval languages. Published studies on the efficacy of LMWH in the treatment of thrombophilia during pregnancy were searched between January 2010 and May 2021.

Combination retrieval was performed using search terms. The preliminary keywords were set as follows: "Pregnancy", "thrombosis" or "venous thromboembolism", "venous thrombosis, vein thrombosis, venous thromboembolic events" and "low molecular weight heparin" or "LMWH", "randomized controlled trial" or "randomized" or "placebo".

Inclusion Criteria

(1) Type of study: Randomized controlled trial (RCT), controlled clinical trial and cohort study.

(2) Research object: For the diagnosis of recurrent miscarriage, it can be diagnosed as a recurrent miscarriage if it meets the criteria of "Obstetrics and Gynecology" where two or more consecutive natural abortions occur. Pre-thrombotic state (PTS) diagnostic criteria for pre-pregnancy screening indicators: Platelet aggregation test, four coagulation tests, and D-dimer, in which one or more indicators are abnormal, that is, patients diagnosed as thrombophilia in pregnancy [12].

(3) Type of intervention: The patients in the control group were treated with aspirin or LMWH, and the patients in the observation group were treated using LMWH combined with low-dose aspirin (75 mg/time).

(4) Evaluation indicators: Live birth rate; Adverse effects rate, pre-therapeutic and post-treatment D-dimer, platelet count, activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT) and fibrin (FIB), etc.

Exclusion Criteria

The exclusion criteria of literature were shown as follows: The literature that did not offer required data for meta-analysis and; The original text of the literature could not be searched or obtained; Data-missing and repeated-reported literature; Conference papers, case reports, systematic reviews, case reports and animal experiment-related literature.

Extraction of Literature Data

Two investigators independently completed the literature screening and data extraction. According to the inclu-

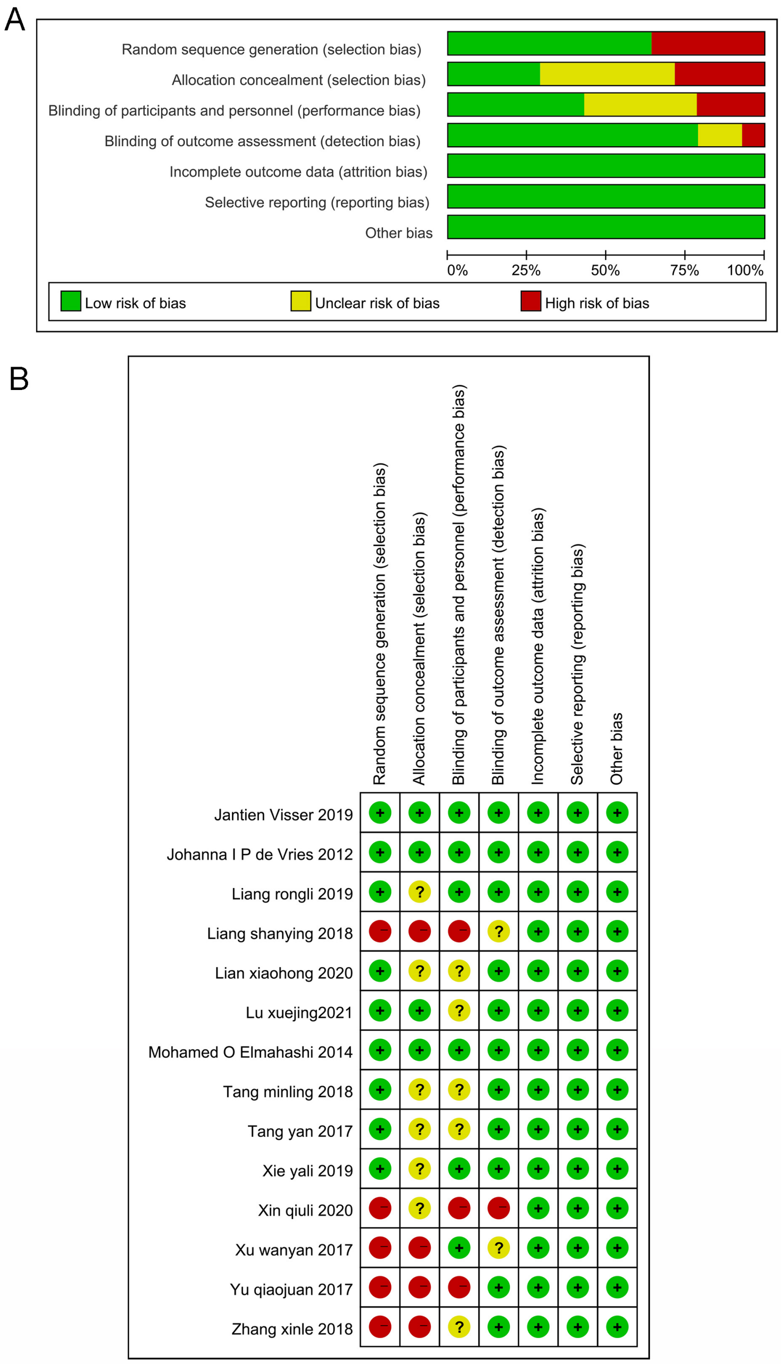

Fig. 2. Risk of bias assessment of included studies. (A) Risk of bias graph. Seven domains were scored for risk of bias. (B) Risk of bias summary. Each item was rated as low (+), uncertain (?) or high (–) risk of bias. The risk of bias was assessed using the Cochrane Collaboration to evaluate the quality of the literature.

sion criteria, the literature that failed to meet the requirements was screened out. Then, literature titles and abstracts were read carefully. If necessary, a thorough reading of the full texts of literature was conducted to identify articles that may be included in this study. After that, related materials were cross-checked, and finally, the literature enrolled in the study was identified. During the process of data extraction, the disagreements were resolved through discussion between the two parties or judged by a third party. The extraction of data in the literature was displayed as follows: First author's name, year of publication, number of patients in each group, treatment methods and main outcomes. In addition, the risk of bias was assessed independently by the two authors using the Cochrane Collaboration (https://training.cochrane.org/handbook).

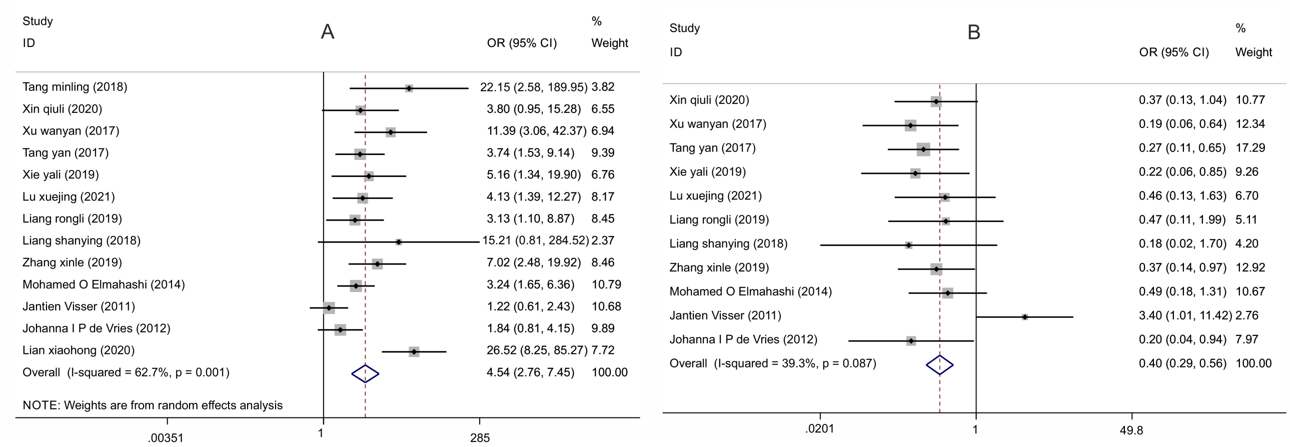

Fig. 3. Comparison of live birth rates and incidence of adverse effects rates after anticoagulant therapy between two groups of patients with thrombophilia during pregnancy. Forest plot of (A) live birth rates and (B) incidence of adverse effects rates were plotted using Stata 16.0 software. The indicators of the results were expressed by odds ratio (OR) and 95% CI.

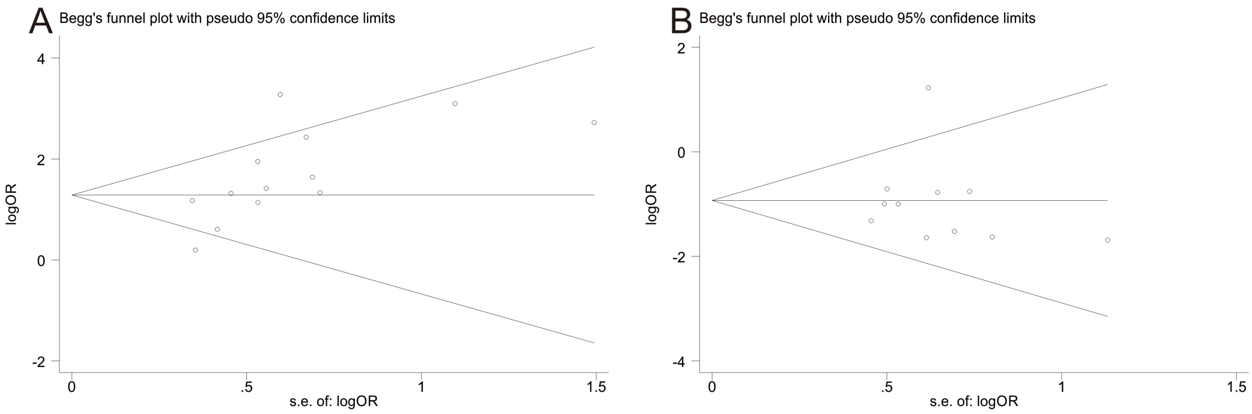

Fig. 4. Publication bias analysis of live birth rates and incidence of adverse effects rates after anticoagulant therapy between two groups of patients with thrombophilia during pregnancy. (A) Funnel plot of live birth rates. (B) Funnel plot of incidence of adverse effects rates. Funnel plots were drawn using Stata 16.0 software, and Begg's test for quantitative detection of publication bias. Each point indicates one of the included studies.

Statistical Analysis

All statistical analyses were conducted with Stata 16.0 software (Stata, College Station, TX, USA). The indicators of the results were expressed by standardized mean difference (SMD) or odds ratio (OR). I^2 statistics were applied to evaluate the heterogeneity of studies. If homogeneity ($p >$ 0.1, $I^2 <$50%) was shown statistically among all studies, the fixed-effect model was used for meta-analysis, otherwise, the random-effect model was used for analysis. Sensitivity analyses were adopted to measure the stability of the overall results. Funnel plots were utilized to assess the publication bias of the studies, and Begg's test was used to verify the presence of publication bias if necessary.

Results

Basic Characteristics of Included Literature

A total of 487 relevant articles were initially retrieved and 397 repeated articles were removed. Then, 32 irrelevant articles were excluded according to the title or abstract. After further reading of the full-text articles, 18 irrelevant or data-lacking articles were excluded, and finally, 14 articles were enrolled [13–26]. The specific literature screening process, results and basic characteristics are detailed in Fig. 1 and Table 1 (Ref. [13–26]). The risk of bias graph and risk of bias summary are presented in Fig. 2A,B.

Live Birth Rate and Adverse Effects Rate of Patients in Both Groups

In inclusion literature, 13 articles [13–21,23–26] compared the live birth rate of two groups after treatment.

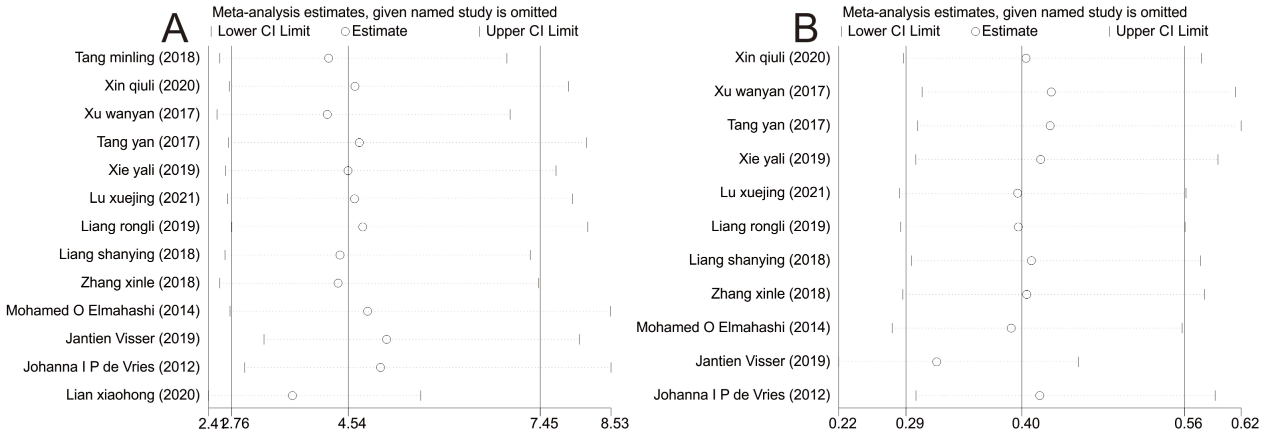

Fig. 5. Sensitivity analyses of live birth rates and incidence of adverse effects rates after anticoagulant therapy between two groups of patients with thrombophilia during pregnancy. (A) Sensitivity analysis of live birth rates. (B) Sensitivity analysis of incidence of adverse effects rates. The graph was drawn by the Stata 16.0 software to evaluate the stability of the meta-analysis.

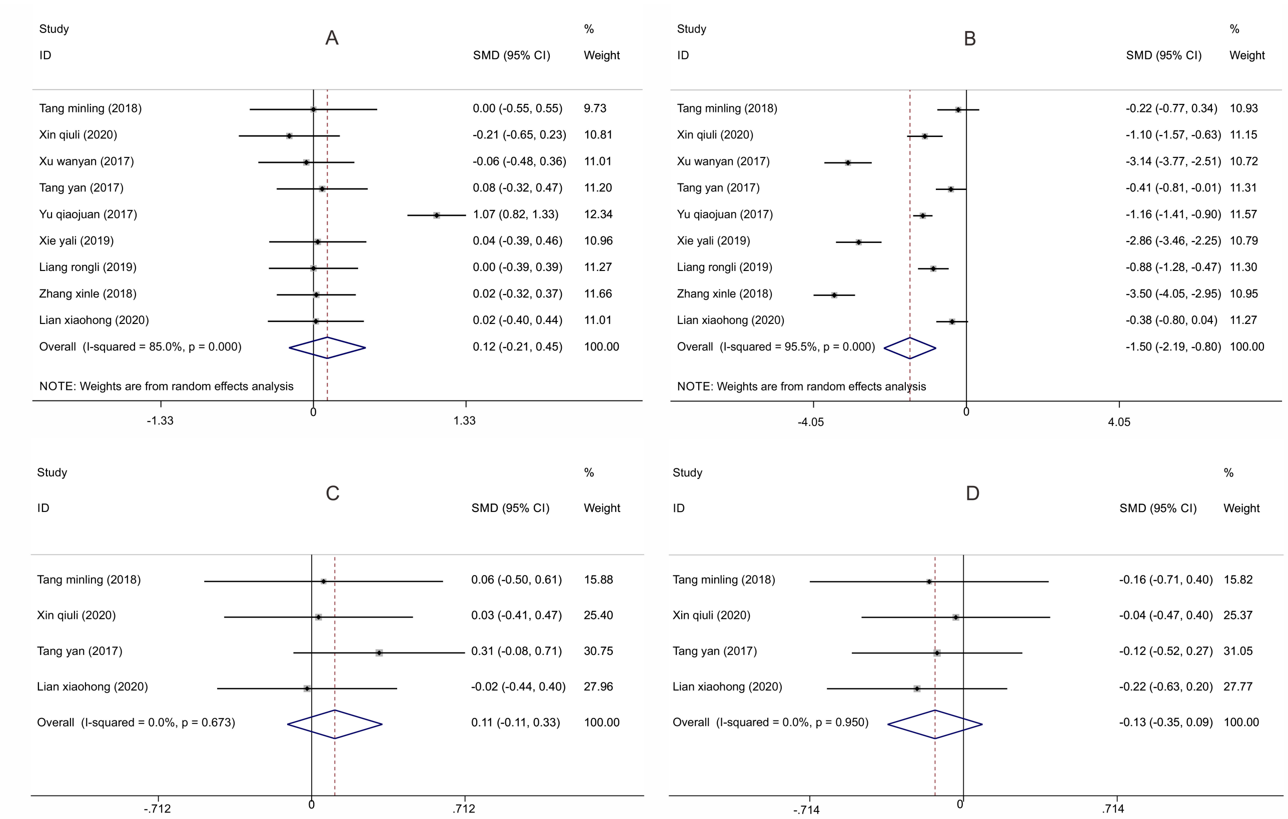

Fig. 6. Comparisons of D-dimer and platelet count between two groups of patients with thrombophilia before and after treatment. (A,B) Forest plots of D-dimer before and after treatment. (C,D) Forest plots of platelet count before and after treatment. Stata 16.0 software was used to draw the forest plots. The indicators of the results were expressed by standardized mean difference (SMD) and 95% CI.

There was significant heterogeneity ($I^2 = 62.7\%$, $p = 0.001$) among the included studies, and a random-effects model was applied to combine effect sizes. Based on the results of the meta-analysis, the live birth rate was higher in the LMWH combined with low-dose aspirin group than in the aspirin or LMWH treatment group (OR = 4.54, 95% CI: 2.76, 7.45) (Fig. 3A). The adverse effects rates of the two groups after treatment were compared in 11 articles

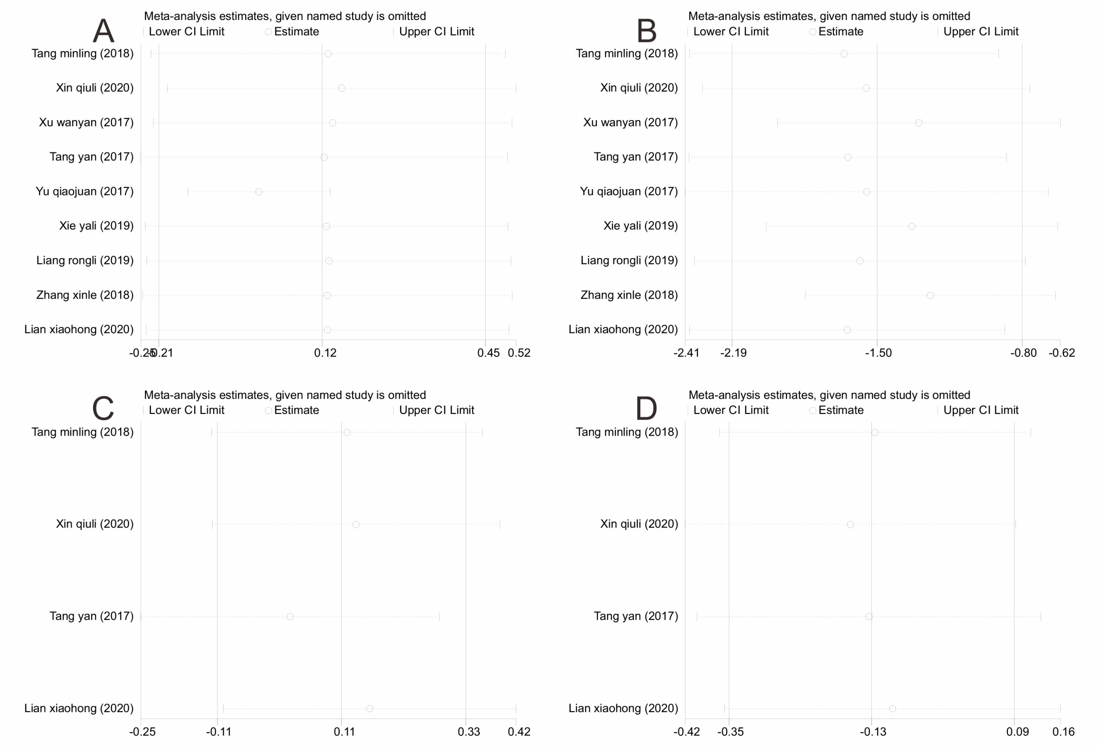

Fig. 7. Sensitivity analysis of D-dimer and platelet count in two groups of patients with thrombophilia. (A,B) Sensitivity analysis of D-dimer level before and after treatment. (C,D) Sensitivity analysis of platelet count before and after treatment. The graph was drawn by the Stata 16.0 software to evaluate the stability of the meta-analysis.

[14–21,23–25]. There was significant heterogeneity (I^2 = 39.3%, p = 0.087) in inclusion studies. Meta-analysis was conducted by random-effects models. According to the results of the meta-analysis, the adverse effects rate was lower in the LMWH combined with low-dose aspirin group than in the aspirin or LMWH treatment group (OR = 0.40, 95% CI: 0.29, 0.56) (Fig. 3B). Besides, the results of the funnel plot suggested that both sides were symmetrical, and the included literature had few possibilities of publication bias (Fig. 4A,B). To perform sensitivity analysis on the meta-analysis results, the study reports were eliminated one by one. The results of the elimination revealed that the forest plot orientation was not changed significantly before and after the elimination. The results above indicated that this study was relatively stable and reliable (Fig. 5A,B).

Changes in Blood-Related Parameters before and after Treatment in Both Groups

Among inclusion literature, the differences in D-dimer before and after treatment between the two groups were compared in 9 articles [13,17,19,21–26]. Meta-analysis was performed using a random-effects model before (I^2 = 85.0%, p = 0.000) and after treatment (I^2 = 0.0%, p = 0.950). According to the results of the meta-analysis, the differences in D-dimer between the two groups before treatment were not significant (SMD = 0.12, 95% CI: –0.21, 0.45) (Fig. 6A). After treatment, D-dimer in the LMWH combined with low-dose aspirin group was significantly lower than that in the aspirin or LMWH treatment group (SMD = –1.50, 95% CI: –2.19, –0.80) (Fig. 6B). In inclusion literature, the differences of PLT before and after treatment between both groups were compared in 4 studies [13,23,25,26]. Meta-analysis was conducted using a fixed-effect model before (I^2 = 0.0%, p = 0.673) and after treatment (I^2 = 0.0%, p = 0.950). According to the results of the meta-analysis, there was no significant difference in PLT between the two groups before treatment (SMD = 0.11, 95% CI: –0.11, 0.33) (Fig. 6C). After treatment, the PLT in the LMWH combined with low-dose aspirin group was lower than that in the aspirin or LMWH treatment group (SMD = –0.13, 95% CI: –0.35, 0.09) (Fig. 6D). To conduct sensitivity analysis for the results of meta-analysis, the reports of the study were eliminated one by one. The results of elimination showed that the forest plot orientation was not changed significantly before and after the elimination (Fig. 7A–D).

The differences in APTT were compared in two groups before and after treatment in 6 articles [13,18,22,23,25,26]. Before treatment (I^2 = 31.4%, p = 0.200), the meta-analysis was conducted using a fixed-effect model. After treatment (I^2 = 57.5%, p = 0.038), a random-effects model was applied to conduct the meta-analysis. According to the results of the meta-analysis, the differences in APTT be-

Table 1. The basic characteristics of inclusion in the literature.

Study	Year	Sample time (year. month)	Cases Treat /Con	Age (years)		Pregnancy (weeks)		Study design	Outcome measures
				Treat group	Con group	Treat group	Con group		
Tang minling [26]	2018	2017.01–2018.01	25/25	35.0 ± 4.5	35.2 ± 5.1	24.5 ± 4.3	24.1 ± 4.0	RCT	①③④⑤⑥
Xing qiuli [25]	2020	2017.02–2019.04	41/39	35.2 ± 4.7	35.2 ± 5.0	24.9 ± 5.7	24.9 ± 5.8	RCT	①②③④⑤⑥
Xu wanyan [24]	2017	2013.12–2015.12	44/44	31.2 ± 5.3	31.5 ± 5.8	NP	NP	RCT	①②③⑦⑧
Tang yan [23]	2017	2014.08–2016.08	49/49	30.5 ± 4.0	29.4 ± 3.9	NP	NP	RCT	①②③④⑤⑥⑦⑧
Yu qiaojuan [22]	2018	2014.02–2015.02	200/100	38.0 ± 2.6	39.0 ± 3.9	30	30	RCT	②⑤⑥⑦⑧
Xie yali [21]	2019	2016.01–2017.12	43/43	31.7 ± 4.3	31.0 ± 4.9	NP	NP	RCT	①②③⑦⑧
Lu xuejing [20]	2021	2016.08–2019.06	54/54	31.5 ± 2.0	31.6 ± 2.1	31.6 ± 2.7	32 ± 2.7	RCT	①②
Liang rongli [19]	2019	2016.01–2017.01	51/51	33.1 ± 3.3	32.1 ± 3.2	32.0 ± 4.4	31.2 ± 4.4	RCT	①②③
Liang shanying [18]	2018	2016.08–2017.01	27/29	24.7 ± 2.9	26.0 ± 3.7	NP	NP	RCT	①②⑤⑥⑦⑧
Zhang xinle [17]	2019	2015.01–2017.02	65/65	31.1 ± 5.2	30.1 ± 4.8	NP	NP	RCT	①②③⑥⑦
Mohamed O Elmahashi [16]	2014	2009.01–2010.12	75/75	27.3 ± 4.8	26.5 ± 2.7	33.2 ± 5.6	32.4 ± 6.4	RCT	①②
Jantien Visser [15]	2011	2017.09–2018.12	63/76	31.6 ± 4.6	32.0 ± 4.5	38.6 ± 2.9	39.1 ± 1.9	RCT	①②
Johanna I P de Vries [14]	2012	2000.01–2009.12	70/69	29.1 ± 4.7	29.2 ± 4.4	27.8 ± 2.9	27.4 ± 2.8	RCT	①②
Lian xiaohong [13]	2020	2018.01–2018.12	44/44	33.7 ± 3.5	34.1 ± 3.8	22.5 ± 3.5	22.7 ± 3.7	RCT	②④⑤⑥

Note: Treat, Treatment; Con, Control; RCT, randomized controlled trial; NR, Not reported; ①, live birth rate; ②, Adverse effects rate; ③, D-Dimer; ④, Platelet (PLT); ⑤, Activated partial thromboplastin time (APTT); ⑥, Prothrombin time (PT); ⑦, Thrombin time (TT); ⑧, Fibrin (FIB).

tween the two groups before treatment were not significant (SMD = –0.25, 95% CI: –0.41, –0.09) (Fig. 8A). However, after treatment, the levels of APTT were notably higher in the LMWH combined with low-dose aspirin group than that in the aspirin or LMWH treatment group (SMD = 0.16, 95% CI: –0.10, 0.42) (Fig. 8B).

The differences in TT before and after treatment in the two groups were reported in 6 studies [17,18,21–24]. The meta-analysis was performed using a random-effects model before (I^2 = 64.4%, p = 0.015) and after treatment (I^2 = 95.3%, p = 0.000). The results indicated that there were no significant differences in APTT between the two groups before treatment (SMD = 0.15, 95% CI: –0.11, 0.41) (Fig. 8C). After treatment, the TT was notably higher in the LMWH combined with low-dose aspirin group than that in the aspirin or LMWH treatment group (SMD = 0.60, 95% CI: –0.14, 1.34) (Fig. 8D). To perform sensitivity analysis for the meta-analysis results, the reports of the study were eliminated one by one. According to the elimination results, there were no significant changes in the forest plot orientation before and after the elimination (Fig. 9A–D).

Besides, the differences in PT before and after treatment in the two groups were compared in 7 articles [13,17,18,22,23,25,26]. A random-effects model was adopted to conduct the meta-analysis before (I^2 = 96.3%, p = 0.000) and after treatment (I^2 = 98.0%, p = 0.000). The results

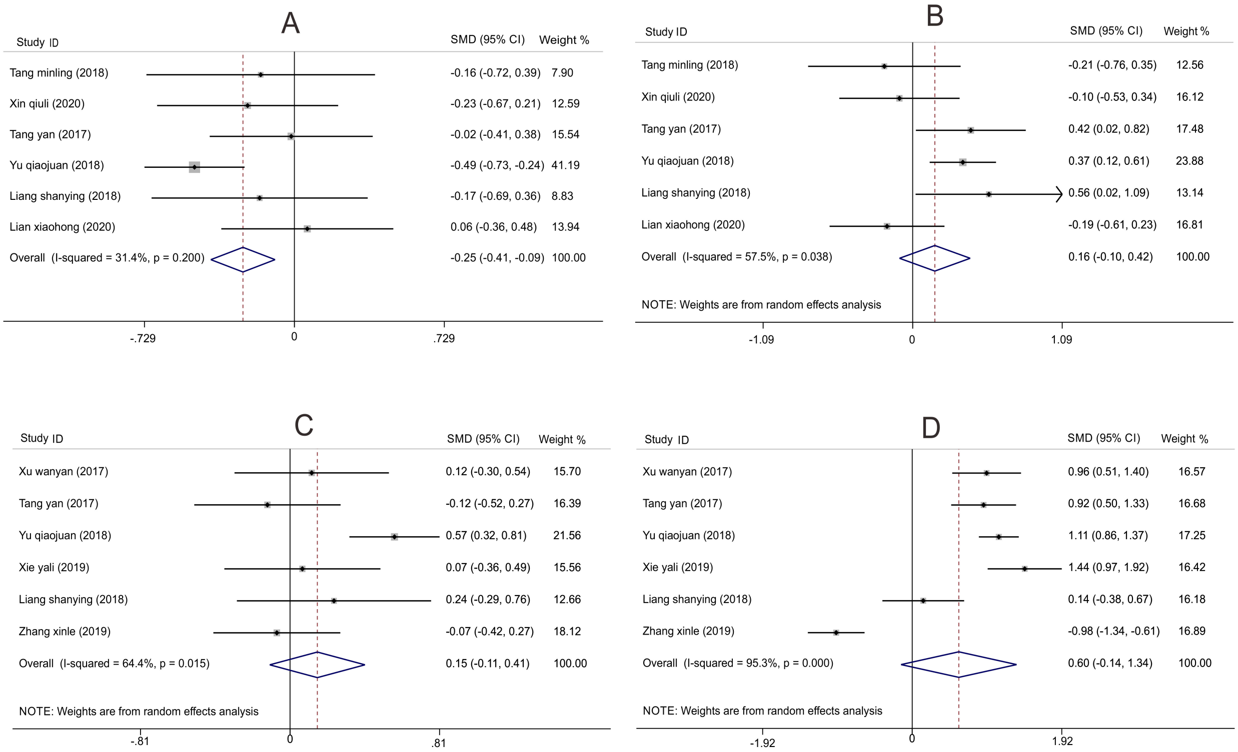

Fig. 8. Comparisons of activated partial thromboplastin time and thrombin time between the two groups before and after treatment. (A,B) Forest plots of activated partial thromboplastin time before and after treatment. (C,D) Forest plots of thrombin time before and after treatment. Stata 16.0 software was used to draw the forest plots. The indicators of the results were expressed by standardized mean difference (SMD) and 95% CI.

of the meta-analysis revealed that there were no significant differences in PT between the two groups before treatment (SMD = 0.02, 95% CI: –0.78, 0.81) (Fig. 10A). However, after treatment, the PT was significantly higher in the LMWH combined with low-dose aspirin group than that in the aspirin or LMWH treatment group (SMD = 0.42, 95% CI: –0.71, 1.56) (Fig. 10B).

Among inclusion literature, the differences in fibrin (FIB) before and after treatment in the two groups were compared in 5 articles [18,21–24]. Before treatment (I^2 = 42.8%, p = 0.136), the meta-analysis was conducted with a fixed-effect model. After treatment (I^2 = 97.6%, p = 0.000), the meta-analysis was performed using a random-effects model. According to the results of the meta-analysis, before treatment, there were no remarkable differences in FIB between the two groups (SMD = –018, 95% CI: –0.34, –0.02) (Fig. 10C). After treatment, FIB was notably higher in the LMWH combined with low-dose aspirin group than that in the aspirin or LMWH treatment group (SMD = –0.92, 95% CI: –2.12, 0.28) (Fig. 10D). To conduct sensitivity analysis for the meta-analysis results, the study reports were eliminated one by one. Based on elimination results, there were no significant changes in the forest plot orientation before and after the elimination (Fig. 11A–D).

Discussion

At present, clinical venous thrombophilia during pregnancy is a common condition [27]. It has been pointed out that the main risk factor for the occurrence of VTE during pregnancy is a history of thrombosis. In total, 15% to 25% of cases of thrombophilia during pregnancy are recurrent events [28], whether VTE or arterial thromboembolism is mainly due to abnormal coagulation function of patients. Therefore, effective treatments are required to avoid postpartum hemorrhage in pregnant women during childbirth. Currently, the use of unfractionated heparin and LMWH are the main methods for the treatment of abnormal coagulation function. LMWH forms an inhibitory complex with antithrombin to inactivate activated factor X (Xa) and regulate the body's coagulation response [29]. This paper offered RCT data on the treatment of thrombophilia during pregnancy with LMWH combined with low-dose aspirin. After a comprehensive literature search and evaluation, 14 studies were included in the synthesis of the final results. According to the results of the meta-analysis, the live birth rate was remarkably higher while the adverse effects rate was lower in the LMWH combined with low-dose aspirin group than that in the aspirin or LMWH treatment group.

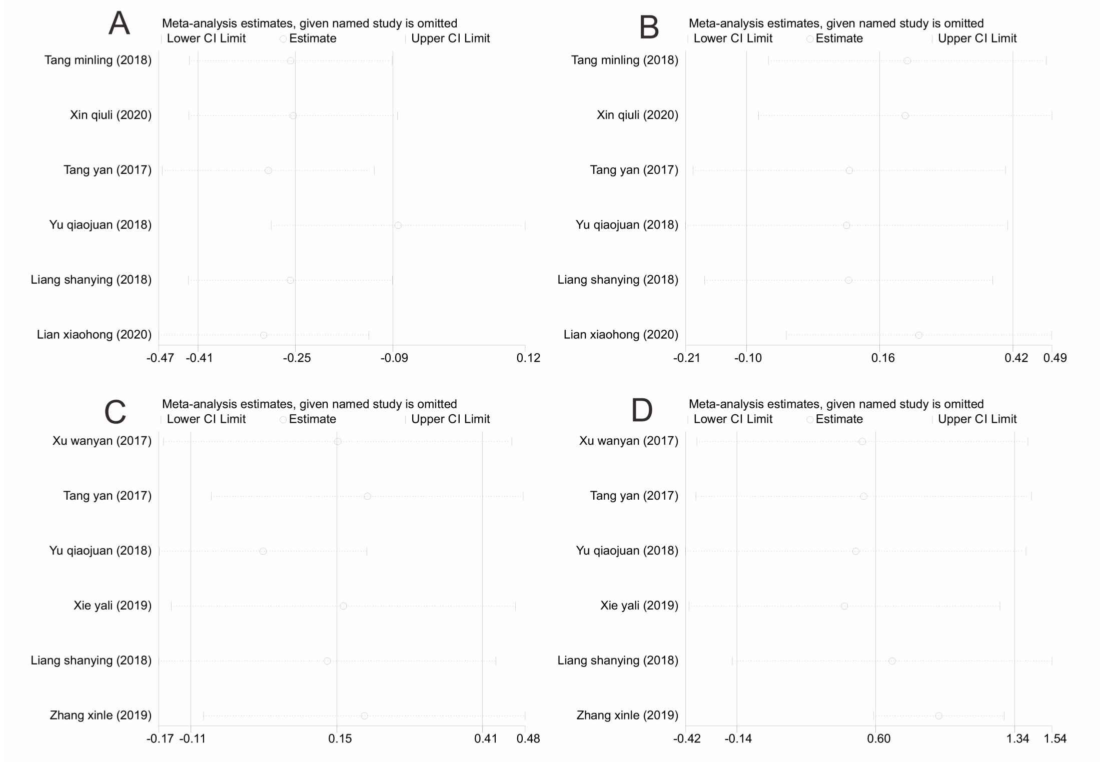

Fig. 9. Sensitivity analysis of activated partial thromboplastin time (APTT) and thrombin time (TT) in the two groups. (A,B) Sensitivity analysis of APTT before and after treatment. (C,D) Sensitivity analysis of TT before and after treatment. The graph was drawn by the Stata 16.0 software to evaluate the stability of the meta-analysis.

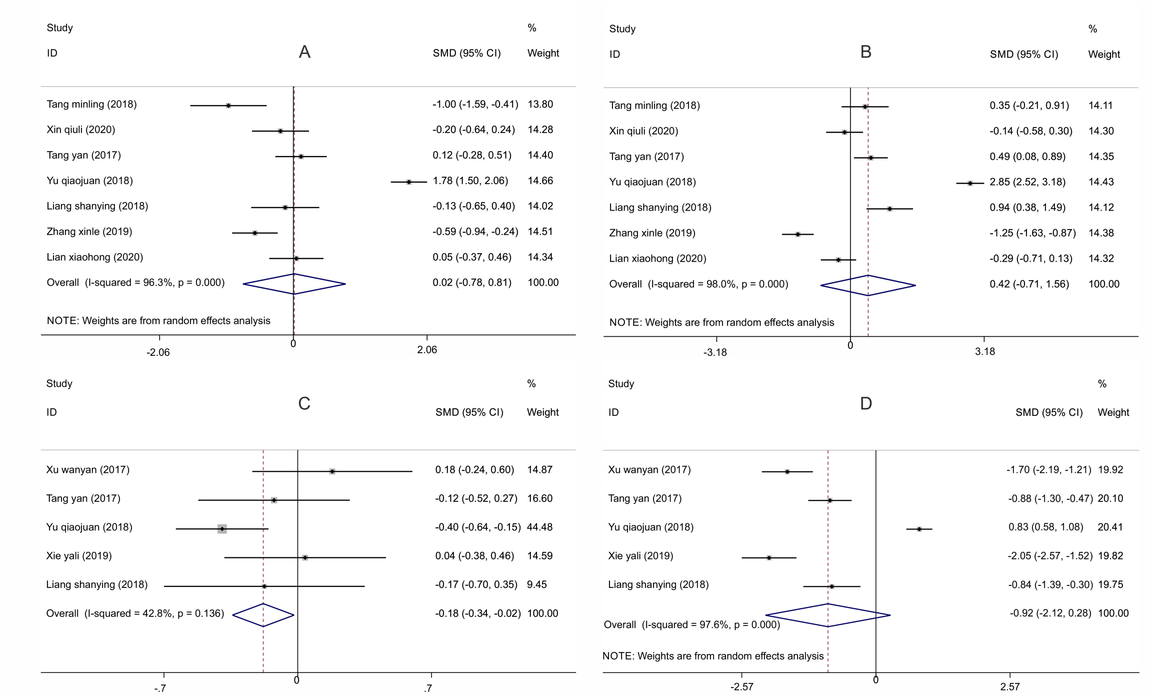

Fig. 10. Comparisons of prothrombin time and fibrin between two groups before and after treatment. (A,B) Forest plots of prothrombin time before and after treatment. (C,D) Forest plots of fibrin before and after treatment. Stata 16.0 software was used to draw the forest plots. The indicators of the results were expressed by standardized mean difference (SMD) and 95% CI.

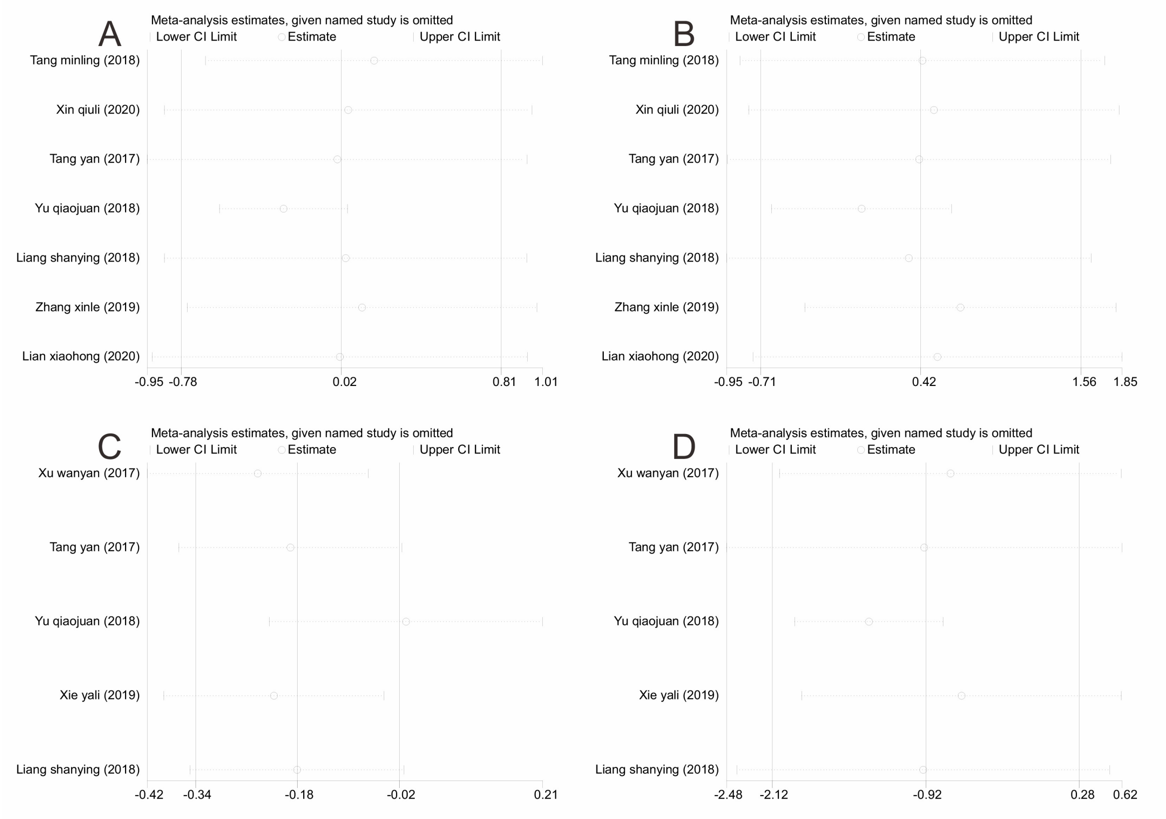

Fig. 11. Sensitivity analysis of prothrombin time and fibrin in the two groups. (A,B) Sensitivity analysis of prothrombin time before and after treatment. (C,D) Sensitivity analysis of fibrin before and after treatment. The graph was drawn by the Stata 16.0 software to evaluate the stability of the meta-analysis.

Previous studies have shown that aspirin is effective in the treatment of hypercoagulation during pregnancy, but the adverse effects of aspirin itself such as gastrointestinal reactions, liver and kidney damage and risk of bleeding are problems that should not be ignored in clinical practice [17]. Studies have shown that pregnant women with thrombophilia receiving anticoagulation therapy have a higher risk of postpartum hemorrhage [30]. As a soluble fibrin degradation product, D-dimer is formed from the orderly breakdown of thrombus by the fibrinolysis system [31]. Numerous studies have shown that D-dimer can be applied as an important marker for the activation of coagulation and fibrinolysis system. Therefore, the effect of D-dimer on the diagnosis of VTE has been extensively studied [32]. LMWH is frequently used in the treatment of deep venous thrombosis and PE in non-pregnant women. In related studies, LMWH can effectively reduce the content of D-dimer in the blood [33]. In this study, D-dimer was significantly lower in the LMWH combined with the low-dose aspirin group than that in the aspirin or LMWH treatment group. Besides, Heparin-induced thrombocytopenia is an adverse drug reaction that manifests as a promoted-thrombosis disease associated with antibody-mediated platelet activation. Heparin-induced thrombocytopenia is a paradoxical immune response, causing the occurrence of thrombin *in vivo*, hypercoagulable state and venous or arterial thrombosis [34]. Different types of heparin, including unfractionated heparin and LMWH can induce thrombocytopenia [35]. In this study, platelets of patients with thrombophilia during pregnancy in the LMWH combined with low-dose aspirin treatment were reduced. The efficacy of LMWH combined with the low-dose aspirin treatment has no difference from traditional treatment regimens. The results above indicated that LMWH has the risk of inducing thrombocytopenia, so the treatment regimens should be reasonably designed and the drug dosage should be optimized. In addition, it is reported that LMWH has a less inhibitory effect on thrombin than unfractionated heparin, so LMWH has some advantages in reducing the occurrence of massive hemorrhage during delivery [36]. Moreover, compared with unfractionated heparin, LMWH has good predictability, dose-dependent plasma levels, a long half-life, less hemorrhage in specific antithrombotic events, as well as lower risks in the occurrence of osteoporosis when long-term use, heparin-induced thrombocytopenia and thrombophilia [37]. In this study, APTT, TT, PT, and FIB were significantly higher in the LMWH combined with the low-dose aspirin group than those in the aspirin or LMWH treatment group. These results suggest that low-molecular-weight heparin combined with aspirin treatment reduces adverse drug reactions better than alone.

However, this meta-analysis has the following limitations: (1) Only 14 studies were included, the sample size per test was small and the statistical power was insufficient; (2) Partial funnel plots for publication bias assessment were not performed because the analysis of some outcome measures included few studies; (3) Long-term follow-up results are also required in this study.

Conclusions

In summary, from the perspective of meta-analysis, this study points out that, in the treatment of patients with thrombosis during pregnancy, LMWH combined with aspirin can promote anticoagulation, effectively improve pregnancy outcomes, and reduce adverse effects.

Consent for Publication

Not applicable.

Abbreviations

LMWH, low molecular weight heparin; VTE, venous thromboembolism; PE, pulmonary embolism; RCT, randomized controlled trial; APTT, partial thromboplastin time; PT, prothrombin time; TT, thrombin time; FIB, fibrin; SMD, standardized mean difference; OP, odds ratio.

Availability of Data and Materials

The dataset generated and/or analysed during the study are available from the corresponding author on reasonable request.

Author Contributions

MY and XQ—designed the research study; XQ—performed the research; MY—provided acquisition of data; XQ—analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Say L, Chou D, Gemmill A, *et al*. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health.* 2014;2(6):e323–e333. doi: 10.1016/S2214-109X(14)70227-X
[2] Silvis SM, Lindgren E, Hiltunen S, *et al*. Postpartum Period Is a Risk Factor for Cerebral Venous Thrombosis. *Stroke.* 2019;50(2):501–503. doi: 10.1161/STROKEAHA.118.023017
[3] Maughan BC, Marin M, Han J, *et al*. Venous Thromboembolism During Pregnancy and the Postpartum Period: Risk Factors, Diagnostic Testing, and Treatment. *Obstet Gynecol Surv.* 2022;77(7):433–444. doi: 10.1097/OGX.0000000000001043
[4] Konkle BA. Diagnosis and management of thrombosis in pregnancy. *Birth Defects Res C Embryo Today.* 2015;105(3):185–189. doi: 10.1002/bdrc.21104
[5] Henriksson P, Westerlund E, Wallén H, Brandt L, Hovatta O, Ekbom A. Incidence of pulmonary and venous thromboembolism in pregnancies after *in vitro* fertilisation: cross sectional study. *BMJ.* 2013;346:e8632. doi: 10.1136/bmj.e8632
[6] Park JE, Park Y, Yuk JS. Incidence of and risk factors for thromboembolism during pregnancy and postpartum: A 10-year nationwide population-based study. *Taiwan J Obstet Gynecol.* 2021;60(1):103–110. doi: 10.1016/j.tjog.2020.11.016
[7] Jacobson B, Rambiritch V, Paek D, *et al*. Safety and Efficacy of Enoxaparin in Pregnancy: A Systematic Review and Meta-Analysis. *Adv Ther.* 2020;37(1):27–40. doi: 10.1007/s12325-019-01124-z
[8] Güner A, Bayam E, Kalkan S, Gündüz S, Özkan M. Is the use of low molecular weight heparin a rational choice during pregnancy in patients with a mechanical heart valve: a report of three cases. *Turk Kardiyol Dern Ars.* 2019;47(1):63–68. doi: 10.5543/tkda.2018.83364
[9] Lu E, Shatzel JJ, Salati J, DeLoughery TG. The Safety of Low-Molecular-Weight Heparin During and After Pregnancy. *Obstet Gynecol Surv.* 2017;72(12):721–729. doi: 10.1097/OGX.0000000000000505
[10] Middeldorp S, Ganzevoort W. How I treat venous thromboembolism in pregnancy. *Blood.* 2020;136(19):2133–2142. doi: 10.1182/blood.2019000963
[11] Hamulyák EN, Scheres LJ, Marijnen MC, Goddijn M, Middeldorp S. Aspirin or heparin or both for improving pregnancy outcomes in women with persistent antiphospholipid antibodies and recurrent pregnancy loss. *Cochrane Database Syst Rev.* 2020;5(5):CD012852. doi: 10.1002/14651858.CD012852.pub2
[12] Xie X, Gou WL. Obstetrics and Gynecology. Beijing: People's Health Publishing House. 2014.
[13] Lian XH. Effect and evaluation of low dose aspirin combined with low molecular weight heparin on patients with thrombosis during pregnancy. *Capital Medicine.* 2020;27(1):90–91.
[14] de Vries JI, van Pampus MG, Hague WM, Bezemer PD, Joosten JH; FRUIT Investigators. Low-molecular-weight heparin added to aspirin in the prevention of recurrent early-onset pre-eclampsia in women with inheritable thrombophilia: the FRUIT-RCT. *J Thromb Haemost.* 2012;10(1):64–72. doi: 10.1111/j.1538-7836.2011.04553.x
[15] Visser J, Ulander VM, Helmerhorst FM, *et al*. Thromboprophylaxis for recurrent miscarriage in women with or without throm-

bophilia. HABENOX: a randomised multicentre trial. *Thromb Haemost*. 2011;105(2):295–301. doi: 10.1160/TH10-05-0334

[16] Elmahashi MO, Elbareg AM, Essadi FM, Ashur BM, Adam I. Low dose aspirin and low-molecular-weight heparin in the treatment of pregnant Libyan women with recurrent miscarriage. *BMC Res Notes.* 2014;7:23. doi: 10.1186/1756-0500-7-23

[17] Zhang XL, Zhao BX, Wang XF, Zhang J. Effect of Low Molecular Weight Heparin on Uterine Artery Blood Flow and Coagulation-fibrinolytic Indexes in Recurrent Spontaneous Abortion Women. *China Licensed Pharmacist.* 2019;16(5):104–107.

[18] Liang SY, He HQ, Zhao ZY. The curative effect of low molecular heparin treating pregnant women with recurrent miscarriage and prethrombotic state. *Journal of Taishan Medical College.* 2018;1(39):46–48.

[19] Liang RL, Luo L. Influence of low molecular weight heparin combined with low dosage aspirin on the pre-thrombotic state and immune function of women with unexplained recurrent spontaneous abortion. *Chinese Journal of Family Planning.* 2019;27(2):184–188.

[20] Lu XJ, Liang JM, Shen LL, Bai YQ, Qin LX, Gao JX, Wang YF. Effects of low molecular weight heparin combined with low dose aspirin on prethrombotic state, liver function and immune function in patients with recurrent abortion. *Journal of Developmental Medicine (Electronic Version).* 2021;9(3):214–219.

[21] Xie YL, Wei LH, Wang P. Clinical effect of low molecular weight heparin combined with aspirin in the treatment of prethrombotic state of recurrent abortion. *Modern Diagnosis & Treatment.* 2019;30(22):3926–3927.

[22] Yu QJ, Wang JF, Wang YP, Wu KN, Li LY. Effect of low molecular weight heparin calcium on prevention of lower limb venous thrombosis in pregnant women with perinatal acquired thrombosis. *Journal Of China Prescription Drug.* 2018;16(10):76–77.

[23] Tang Y, He J, Ma T. Effect of low molecular weight heparin combined with aspirin on the blood coagulation state of recurrent spontaneous abortion patients. *Journal of Hunan Normal University (Medical Science).* 2017;14(2):165–167.

[24] Xu WY, Lin CF, Xu XF. Clinical value of Low Molecular Weight Heparin combined with Aspirin in the treatment of prethrombotic state of recurrent abortion. *China Modern Medicine.* 2017;24(4):141–143+146.

[25] Xing QL. Effect of low molecular weight heparin calcium combined with low dose aspirin on hemorheological parameters and pregnancy outcome in patients with gestational thrombophilia. *Journal of Huaihai Medicine.* 2020;38(3):306–308. doi: 10.14126/j.cnki.1008-7044.2020.03.031

[26] Tang ML. Clinical effect of low dose aspirin combined with low molecular weight heparin in the treatment of gestational thrombophilia. *Chinese Journal of Family Planning.* 2018;26(10):107–109.

[27] Friedman AM, D'Alton ME. Expert review: prevention of obstetrical venous thromboembolism. *Am J Obstet Gynecol.* 2021;225(3):228–236. doi: 10.1016/j.ajog.2021.05.004

[28] Hovsepian DA, Sriram N, Kamel H, Fink ME, Navi BB. Acute cerebrovascular disease occurring after hospital discharge for labor and delivery. *Stroke.* 2014;45(7):1947–1950. doi: 10.1161/STROKEAHA.114.005129

[29] Streiff MB, Agnelli G, Connors JM, *et al*. Guidance for the treatment of deep vein thrombosis and pulmonary embolism. *J Thromb Thrombolysis.* 2016;41(1):32–67. doi: 10.1007/s11239-015-1317-0

[30] Lian Y, Wang XT. Evaluation of the screening and anticoagulation therapy for inherited thrombophilias in pregnancy. *Chinese Journal of Practical Gynecology and Obstetrics.* 2017;33(7):678–684. doi: 10.19538/j.fk2017070105

[31] Weitz JI, Fredenburgh JC, Eikelboom JW. A Test in Context: D-Dimer. *J Am Coll Cardiol.* 2017;70(19):2411–2420. doi: 10.1016/j.jacc.2017.09.024

[32] Linkins LA, Takach Lapner S. Review of D-dimer testing: Good, Bad, and Ugly. *Int J Lab Hematol.* 2017;39 Suppl 1:98–103. doi: 10.1111/ijlh.12665

[33] Walton M, Wade R, Claxton L, *et al*. Selective internal radiation therapies for unresectable early-, intermediate- or advanced-stage hepatocellular carcinoma: systematic review, network meta-analysis and economic evaluation. *Health Technol Assess.* 2020;24(48):1–264. doi: 10.3310/hta24480

[34] Junqueira DR, Zorzela LM, Perini E. Unfractionated heparin versus low molecular weight heparins for avoiding heparin-induced thrombocytopenia in postoperative patients. *Cochrane Database Syst Rev.* 2017;4(4):CD007557. doi: 10.1002/14651858.CD007557.pub3

[35] Zhou P, Yin JX, Tao HL, Zhang HW. Pathogenesis and management of heparin-induced thrombocytopenia and thrombosis. *Clin Chim Acta.* 2020;504:73–80. doi: 10.1016/j.cca.2020.02.002

[36] Pardun N, Lemmer J, Belker K, Pringsheim M, Ewert P, Wolf CM. Low-molecular-weight heparin administered by subcutaneous catheter is a safe and effective anti-coagulation regimen in selected inpatient infants and children with complex congenital heart disease. *Cardiol Young.* 2021;31(9):1439–1444. doi: 10.1017/S1047951121000317

[37] Hao C, Sun M, Wang H, Zhang L, Wang W. Low molecular weight heparins and their clinical applications. *Prog Mol Biol Transl Sci.* 2019;163:21–39. doi: 10.1016/bs.pmbts.2019.02.003