

Meta-analysis on aspirin combined with low-molecular-weight heparin for improving the live birth rate in patients with antiphospholipid syndrome and its correlation with D-dimer levels

Ting Shi, MD^a, Zhong-Deng Gu, MD^b, Qi-zhi Diao, MD^{c,*}

Abstract

Background: Antiphospholipid antibody syndrome (APS) is a systemic, autoimmune, prothrombotic disease characterized by persistent antiphospholipid antibodies, thrombosis, recurrent abortion, complications during pregnancy, and occasionally thrombocytopenia. At present, there is no consensus on the treatment of this disease. Long-term anticoagulation is recommended in most cases in patients with thrombotic APS. This study aimed to evaluate whether aspirin combined with low-molecular-weight heparin (LMWH) can improve the live birth rate in antiphospholipid syndrome and its correlation with D-dimer.

Methods: The data were retrieved from the WanFang Data, CBM, VIP, CNKI, the Cochrane Library, PubMed, EMBASE, OVID, and Web of Science databases. We collected data on randomized controlled trials of aspirin combined with LMWH in the treatment of pregnant women with APS. The "Risk of Bias Assessment" tool and the "Jadad Scale" provided by the Cochrane Collaboration were used to evaluate the risk of bias and quality of the collected literature. The risk ratio (RR) and its 95% confidence interval (CI) were determined using Statase-64 software.

Results: In this study, a total of 11 studies were included, comprising a total of 2101 patients. The live birth rate in pregnant women with APS was higher on administration of aspirin combined with LMWH than with aspirin alone (RR = 1.29, 95% CI = 1.22–1.35, $P < .001$). D-dimer concentration in plasma predicted the live birth rate, which was higher below the baseline than above it (RR = 1.16, 95% CI = 1.09–1.23, $P < .001$). The subgroup analysis of the live birth rate was carried out based on the course of treatment, and the results were consistent with the overall results. Begg funnel plot test revealed no publication bias. Sensitivity analysis showed that deleting any study did not affect the results.

Conclusion: Aspirin combined with LMWH for APS may improve live birth rate, and detection of D-dimer levels in APS pregnant women may predict pregnancy complications and guide the use of anticoagulants.

Abbreviations: 95% CI = 95% confidence interval, aPL = antiphospholipid antibodies, APS = antiphospholipid antibody syndrome, LDA = low-dose aspirin, LMWH = low-molecular-weight heparin, RCT = randomized controlled trial, RR = risk ratio.

Keywords: antiphospholipid syndrome, aspirin, D-dimer, live birth rate, low-molecular-weight heparin

Editor: Milan Perovic.

The authors report no conflicts of interest.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

^a The Department of Blood Transfusion, ^b The Department of Rehabilitation, ^c The Department of Clinical Laboratory Medicine, Yongchuan Hospital, Chongqing Medical University, Yongchuan, Chongqing, China.

* Correspondence: Qi-Zhi Diao, The Department of Clinical Laboratory Medicine, Yongchuan Hospital, Chongqing Medical University, Yongchuan, Chongqing 400010, China (e-mail: 125314506@qq.com).

Copyright © 2021 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Shi T, Gu ZD, Diao Qz. Meta-analysis on aspirin combined with low-molecular-weight heparin for improving the live birth rate in patients with antiphospholipid syndrome and its correlation with D-dimer levels. *Medicine* 2021;100:25(e26264).

Received: 28 December 2020 / Received in final form: 30 April 2021 / Accepted: 22 May 2021

<http://dx.doi.org/10.1097/MD.00000000000026264>

1. Introduction

Antiphospholipid antibody syndrome (APS) is a systemic, autoimmune, prothrombotic disease characterized by persistent antiphospholipid antibodies (aPL), thrombosis, recurrent abortion, complications during pregnancy, and occasionally thrombocytopenia.^[1] At present, there is no unified opinion on the treatment of this disease, especially the treatment via immunoglobulins and other drugs like glucocorticoids.^[2] Administration of appropriate thromboprophylaxis helps prevent thromboembolic complications during pregnancy in women with APS and also in giving birth to healthy children.^[3] For patients with thrombotic APS, long-term anticoagulation is recommended in most cases.^[4] As APS is a rare disease, there are less well-designed clinical trials, resulting in a lack of reliable clinical data. Without formal clinical guidelines, APS diagnosis and treatment are largely based on consensus and expert opinion. It is not clear whether low-dose aspirin affects the risk of thrombosis.^[5,6] With the combination of low-dose aspirin and low-molecular heparin, most aPL-related pregnancy loss can be prevented.^[7] The study by Hamulyak et al could not conclude whether aspirin alone could contribute to a lower live birth rate than low-molecular-weight heparin (LMWH) plus aspirin.^[8] D-dimer has high

sensitivity and specificity in predicting pregnancy complications in patients with APS treated with LMWH. Its use also allows the dose of LMWH to be increased to improve the effectiveness of the treatment.^[9] Randomized controlled trials (RCTs) comparing live birth rates in APS during pregnancy with aspirin combined with LMWH and aspirin alone were included in this study to provide more reasonable evidence for clinical practice.

2. Materials and methods

2.1. Literature search

We searched the literature with “low molecular weight heparin,” “antiphospholipid syndrome,” and “aspirin” as the main headings with a free word. The database included WanFang Data, CBM, VIP, CNKI, Cochrane Library, PubMed, EMBASE, OVID, and Web of Science. The retrieval time was before August 2020 and the language was limited to Chinese and English.

2.2. Literature selection

The inclusion criteria were as follows: RCTs; studies in which all subjects were pregnant women with clinical diagnosis of APS; experimental groups treated with aspirin combined with LMWH and control group with aspirin alone; and outcome indicator of live birth rate. Studies were excluded according to the following criteria: conference abstracts, reviews, case reports, and comments; and samples of studies derived from cell lines or animals. All studies were screened independently by 2 authors based on inclusion and exclusion criteria. When the studies were published by the same group, only the latest research with the largest sample size was included.

2.3. Data extraction and quality assessment

The 2 authors (TS and ZDG) independently extracted data from qualified studies and used the Jadad rating scale^[10] for quality evaluation, and the risk assessment criteria for bias recommended

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bao et al 2017	+	+	-	-	+	+	+
Deng et al 2012	+	+	-	-	+	+	+
Granger, K. A et al 1997	+	+	-	-	+	+	+
Jiang et al 2016	+	+	-	-	+	+	+
Laskin, C. A et al 2009	+	+	-	-	+	+	+
Mohamed, Kaa et al 2014	+	+	-	-	+	+	+
Shi et al 2020	+	+	?	?	+	+	+
Wang et al 2020	+	+	-	-	+	+	+
Zhao et al 2016	+	+	-	-	+	+	+
Zhou et al 2020	+	+	-	-	+	+	+
Zhou xiao et al 2012	+	+	-	-	+	+	+

Figure 1. 11 Summary of risk assessment of the included literature.

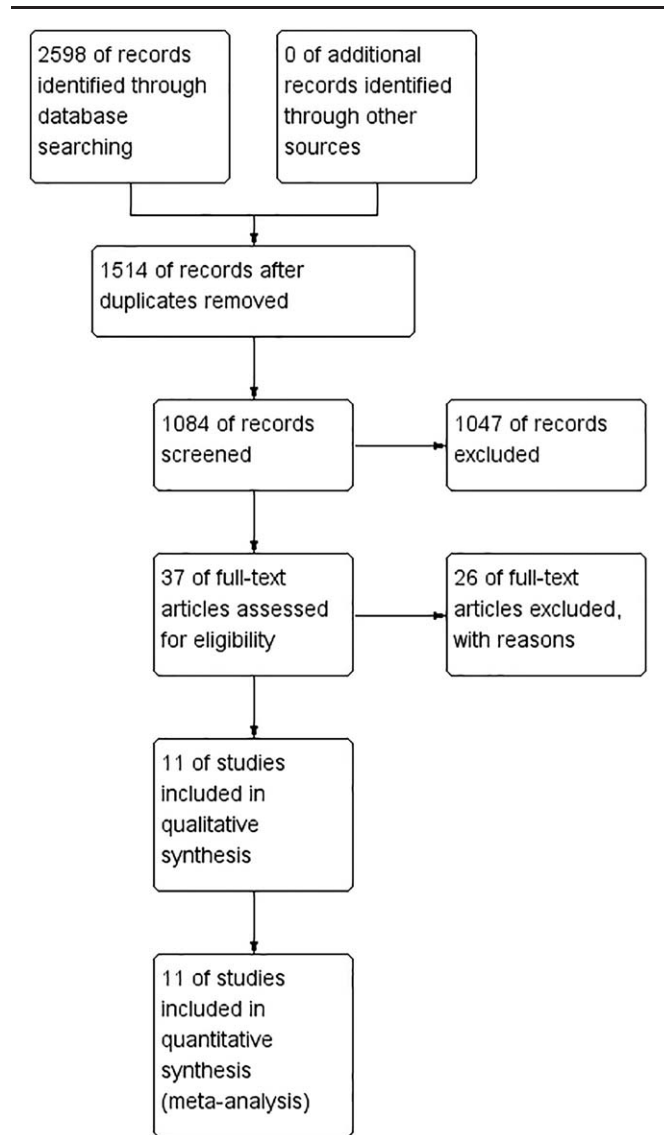


Figure 2. Literature screening flow chart.

by the Cochrane manual were used to assess the risk of bias in the included studies.^[11] The scoring items mainly included randomization sequence generation (0–2 points), blindness method (0–2 points), allocation and conceal (0~2 points), and exit or loss of follow-up (0–1 points), as shown in Figure 1. The following relevant details were extracted from each study: first author name, year of publication, country, number of patients, average age, dose, course of treatment, outcome indicators, and score. Aspirin combined with LMWH and aspirin alone in APS pregnant women had a live birth rate of risk ratio (RR) and 95% confidence interval (95% CI) were obtained directly in reported studies.

2.4. Statistical analysis

The meta-analysis was performed using Statase-64 software (StataCorp LP, College Station, TX). RR and 95% CI were used for representing data. If only the median and upper and lower limits were given, $x \pm s$ (mean and standard deviation model) can be obtained by using the conversion formula.^[12] Higgins et al^[13] research showed that: $I^2 > 50\%$ implies heterogeneity and the effect of combined application of random effects model; therefore, there is a need to further find out the cause of high heterogeneity and sources by subgroup analysis, sensitivity analysis, or eventually eliminating obvious heterogeneity in the studies. $I^2 < 50\%$ implies that the heterogeneity of the included data is low, and a fixed-effect model is applied. This meta-analysis was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.^[14]

2.5. Ethics approval

Patients were not directly involved in the study; therefore, ethical approval was not required.

3. Results

3.1. Eligible studies

The literature retrieval flow chart is shown in Figure 2. A total of 2598 related clinical studies were retrieved in this study. By screening the research titles and abstracts and the full text, 11 RCTs^[15–25] were finally included in this study based on the selection criteria.

3.2. Study characteristics

A total of 2101 pregnant women (1102 in the experimental group and 999 in the control group) diagnosed with APS were included in this study. Basic information on these patients is shown in Tables 1 to 3. Eleven studies were conducted in 4 countries, including China, the United States, United Kingdom, and Egypt. Two doses of low-dose aspirin (LDA), 4100 U, or 5000 U LMWH were used. Seven^[15,16,21–25] studies used the data throughout the course of pregnancy (long-term therapy), and three^[18–20] identified continuous use of LDA and LMWH for 30 days and 10 days after pregnancy (short-term therapy). Eleven studies used live birth rates as the primary outcome. The correlation between D-dimer and the fetal live birth rate was analyzed in 2 studies.^[15,22] All the 11 studies were of high quality: one had a score of 6 on the Jadad scale, and the other 10 had a

Table 1

Basic characteristics of included literature.

Study ID	Year	Country	Participant (N)	Intervention/control (N)	Maternal mean age (SD)	Doses of medication	Initiation of treatment	Outcome	Score
Shi et al ^[15]	2020	China	362	a (241)/b (121)	Unclear	LDA 75 mg daily LMWH 4100 U daily	A	①②	6
Deng et al ^[16]	2012	China	50	a (25)/b (25)	Unclear	LDA 50 mg daily LMWH 5000 U daily	A	①	5
Jiang et al ^[17]	2016	China	48	a (24)/b (24)	a (32.1 ± 3.8) b (31.1 ± 5.1)	LDA 75 mg daily LMWH 5000 U daily	LDA Before pregnancy LMWH Confirmation of pregnancy to 6w after delivery	①	5
Wang et al ^[18]	2020	China	104	a (52)/b (52)	a (29.23 ± 3.68) b (30.05 ± 3.25)	LDA 25 mg daily LMWH 5000 U daily	B	①	5
Zhao et al ^[19]	2016	China	74	a (37)/b (37)	a (28.17 ± 2.63) b (27.42 ± 2.84)	LDA 25 mg daily LMWH 5000 U daily	B	①	5
Zhou et al ^[20]	2020	China	176	a (88)/b (88)	a (27.30 ± 4.00) b (27.32 ± 3.98)	LDA 100 mg daily LMWH 4100 U daily	B	①	5
Zhou et al ^[21]	2012	China	61	a (30)/b (31)	a (35 ± 4.23) b (34 ± 4.68)	LDA 100 mg daily LMWH 4100 U daily	A	①	5
Bao et al ^[22]	2017	China	1015	a (497)/b (518)	Unclear	LDA 75 mg daily LMWH 4100 U daily	A	①②	5
Granger et al ^[23]	1997	Kingdom	53	a (16)/b (37)	Unclear	LDA 75 mg daily LMWH 5000 U daily	A	①	5
Laskin et al ^[24]	2009	USA	88	a (45)/b (43)	Unclear	LDA 81 mg daily LMWH 5000 U daily	A	①	5
Mohamed and Saad et al ^[25]	2014	Egypt	70	a (47)/b (23)	Unclear	LDA 81 mg daily LMWH 5000 U daily	A	①	5

① = aspirin combined with low molecular weight heparin vs. aspirin alone Live birth rate, ② = D-dimer below baseline vs above baseline Live birth rate, A = confirm pregnancy to 37w or termination of pregnancy, B = confirmation of pregnancy and continuous medication for 30 days and 10 days, a = low-molecular-weight heparin combined with aspirin, b = aspirin, LDA = low-dose aspirin, LMWH = low molecular weight heparin.

Table 2
Subgroup analysis of studies included in the outcome of treatment.

Analysis	No. of studies	No. of patients	RR (95% CI)	Heterogeneity	P
Treatment course	10	2053	1.28 (1.21–1.35)	$I^2 = 34.8\%$, $P = .129$	<.001
A	7	1699	1.27 (1.19–1.34)	$I^2 = 54.6\%$, $P = .040$	<.001
B	3	354	1.34 (1.18–1.52)	$I^2 = 0\%$, $P = .986$	<.001

A = confirm pregnancy to 37w or termination of pregnancy (long-term therapy), B = confirmation of pregnancy and continuous medication for 30 days and 10 days (short-term therapy), CI = confidence interval, RR = risk ratio.

Table 3
D-Dimer below baseline versus above baseline live birth rate.

Study/d-dimer level	Year	Negative live birth (n)	Negative total (n)	Positive live birth (n)	Positive total (n)
Shi et al ^[15] (b)	2020	40	56	24	65
Shi et al ^[15] (a)	2020	84	116	77	125
Bao et al ^[22] (b)	2017	165	197	198	321
Bao et al ^[22] (a)	2017	182	209	267	288

Treatment a = aspirin combined with low molecular weight heparin, Treatment b = aspirin.

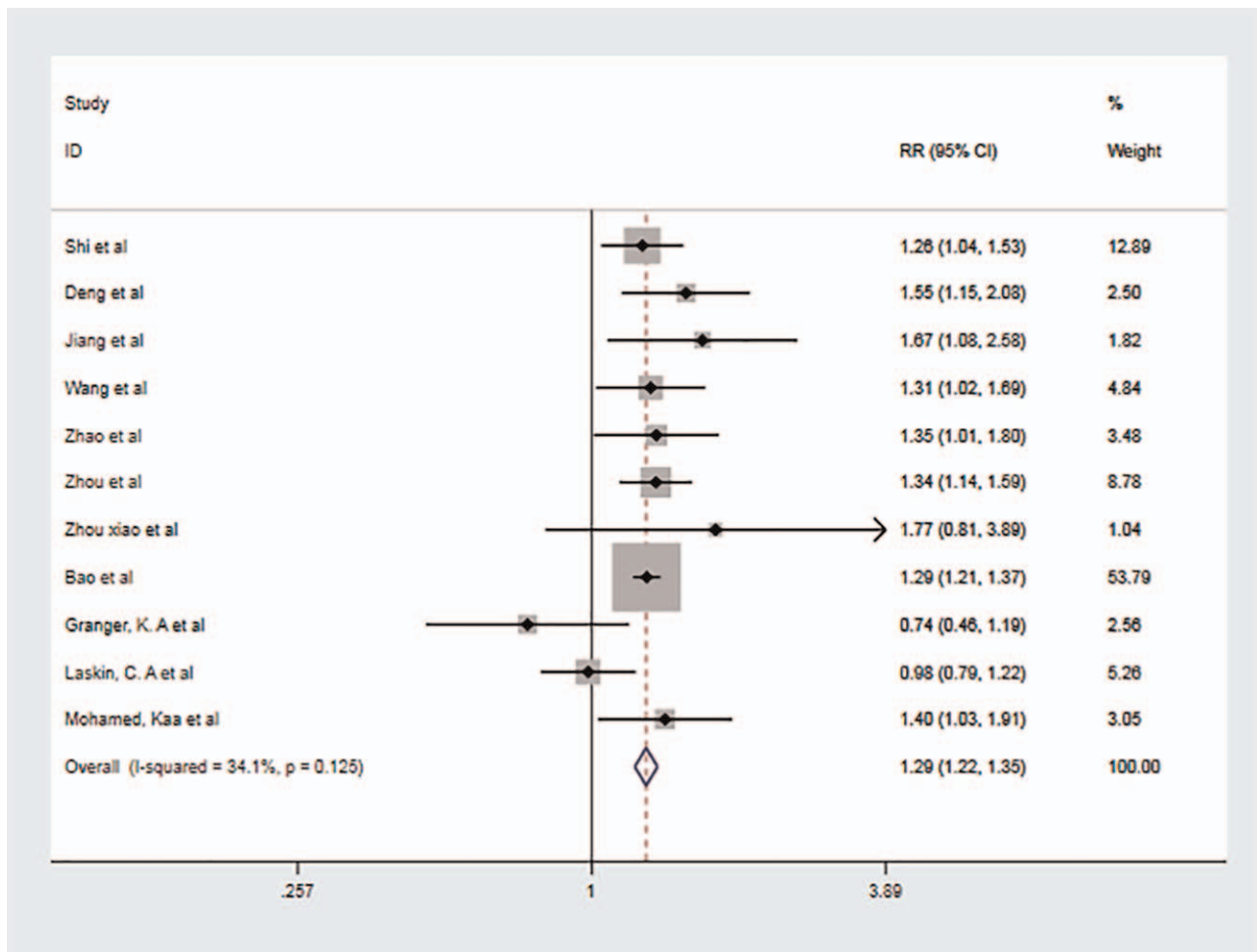


Figure 3. Forest map assessing the difference in live birth rates between aspirin combined with low molecular weight heparin and aspirin antiphospholipid antibody syndrome alone.

score of 5 each. Among them, 10 studies were at high risk in the blinding method, because such drug therapy studies had to obtain informed consent from patients, and it was impossible to blind the method.

3.3. Effect of LDA with LMWH on live birth rate

Eleven studies^[15-25] reported the live birth rate in women with APS treated with aspirin combined with LMWH compared with aspirin alone. The degree of heterogeneity among studies was low ($I^2=34.1\%$), and the fixed effect model was used to combine the effect size (RR=1.29, 95% CI=1.22-1.35, $P<.001$) (Fig. 3). The results showed that the combination of aspirin and LMWH could significantly improve the live birth rate of the fetus in women with APS. According to the subgroup analysis of the course of treatment^[15,16,18-25] (Fig. 4), RR was 1.27 (95% CI=1.19-1.34) and 1.34 (95% CI=1.18-1.52) for the treatments A and B, respectively. Compared with the heterogeneity of the course of treatment A, that of course B decreased significantly ($I^2=54.6\%$, $P=.040$ vs $I^2=0\%$, $P=.986$). The combination of aspirin and LMWH has been shown to improve the live birth rate of the fetus in women with APS, regardless of the course of treatment.

3.4. Effect of D-dimer levels on thrombus formation and fetal viability

According to the definition of pulmonary embolism level, the D-dimer baseline levels of above 0.50 mg/L fibrinogen equivalent units is positive, whereas that <0.50 mg/L fibrinogen equivalent units is negative. Two studies^[15,22] reported the difference in live birth rates between negative and positive D-dimers. The heterogeneity among studies was high ($I^2=95.1\%$), and the random-effect model was used to combine the effect size (RR=1.16, 95% CI=1.09-1.23, $P<.001$) (Fig. 5). The live birth rates of those with D-dimer below baseline were higher than those above baseline, and the difference was statistically significant.

3.5. Publication bias and sensitivity analysis

For each deletion of a study, there was no statistically significant difference in the effect size after deletion compared with the total effect size before deletion, indicating that the results of this study are indeed statistically reliable (Fig. 6). A total of 11 RCTs were included in this study. Begg test ($P=.35$) (Fig. 7) indicated that the possibility of publication bias in the included literature was relatively small.

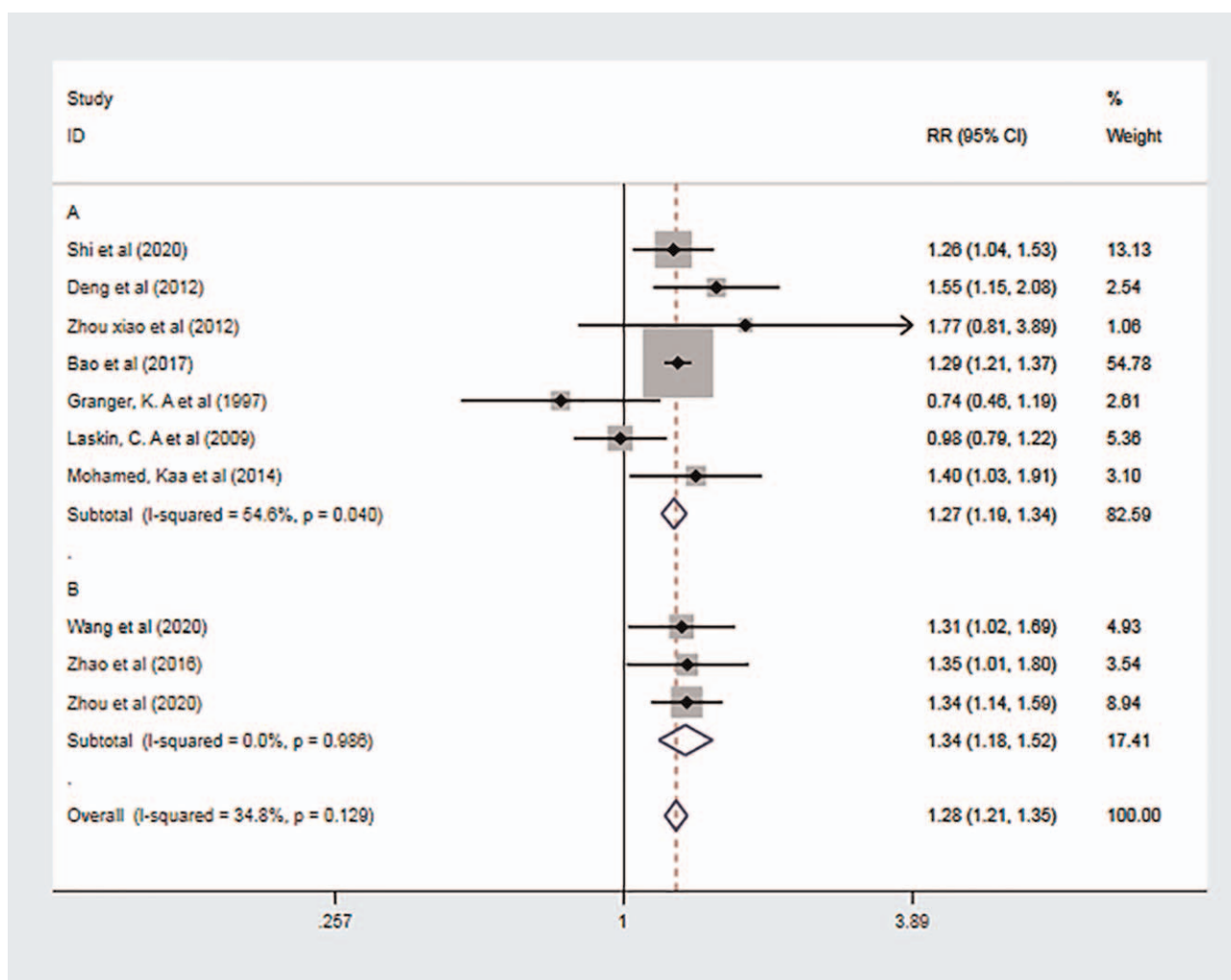


Figure 4. Subgroup analysis of the difference in live birth rate between long and short course aspirin combined with low molecular weight heparin in antiphospholipid antibody syndrome pregnant women.

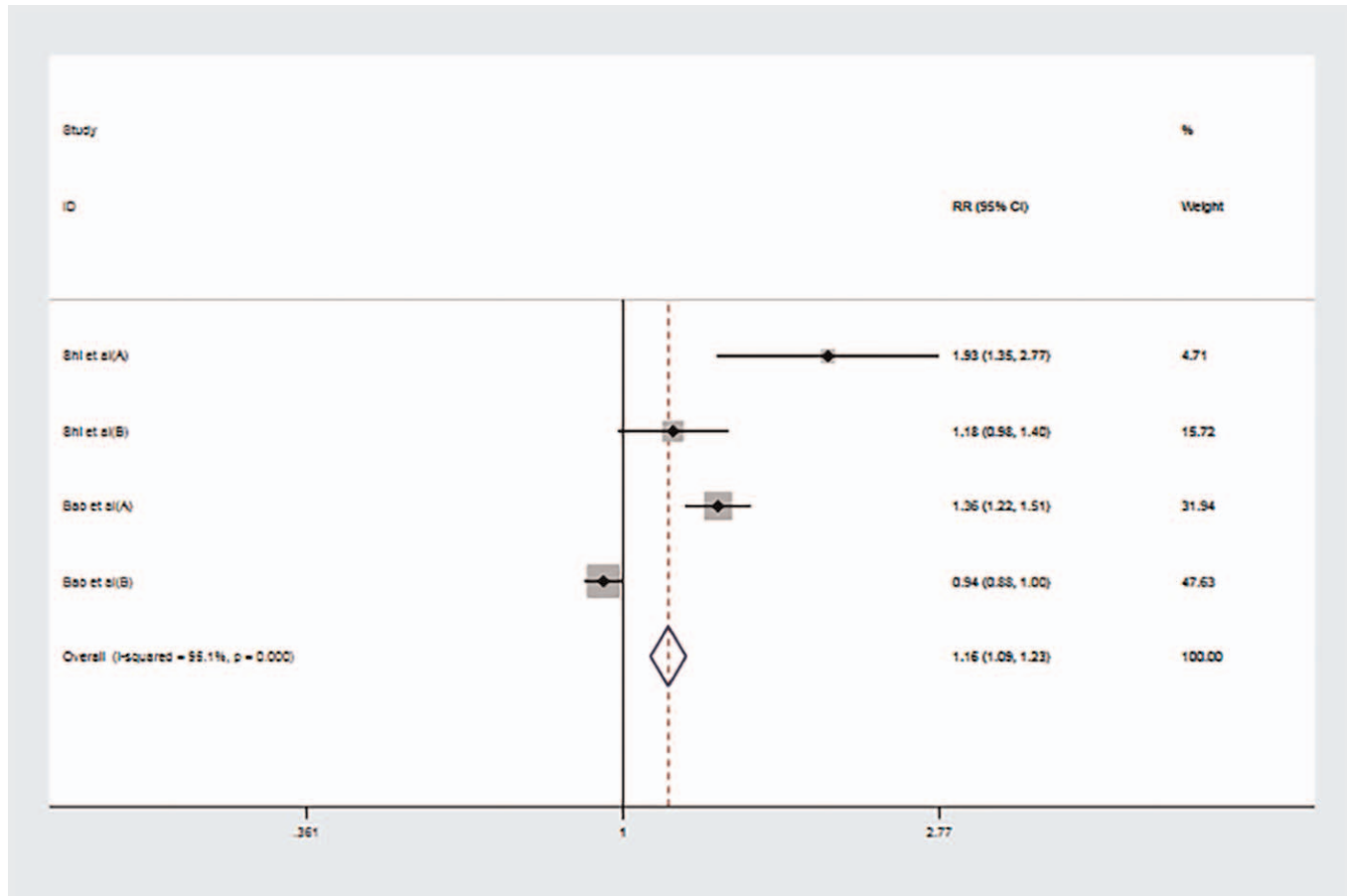


Figure 5. Forest map of the difference in live birth rates below and above baseline for D-dimer.

4. Discussion

APS is characterized by arterial and venous thromboembolism events and persistent laboratory evidence of aPL. Obstetric complications such as recurrent abortion, preterm birth, oligohydramnios, intrauterine growth restriction, fetal distress,

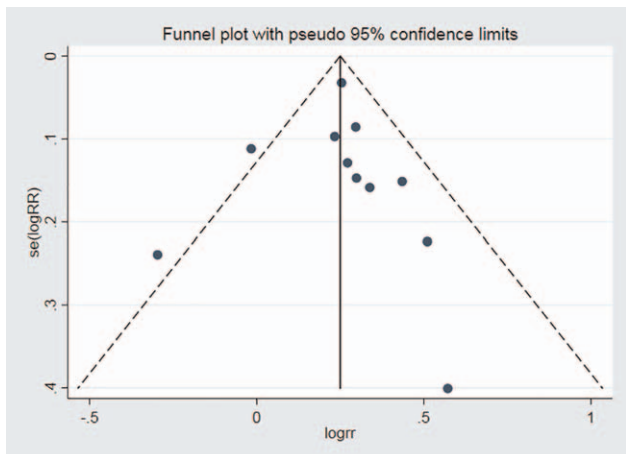


Figure 6. The Begg funnel plot was used to evaluate potential publication bias in meta-analyses.

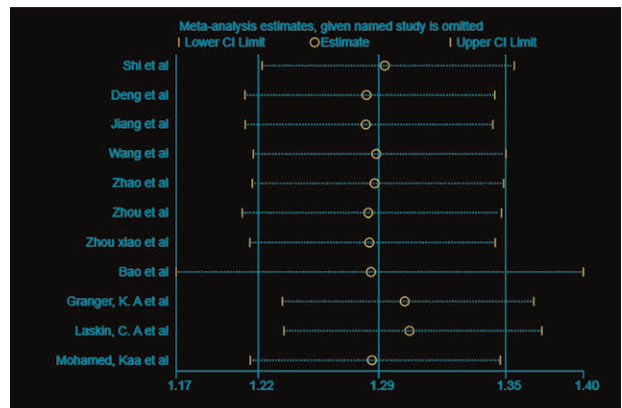


Figure 7. Sensitivity analysis of the meta-analysis.

fetal or neonatal thrombosis, preeclampsia/eclampsia, and hemolysis, elevated liver enzyme levels, and low platelet levels/HELLP syndrome are also hallmarks of APS. Changes in the hemostatic system during normal pregnancy can also lead to hypercoagulability, which increases the risk of thrombosis. Thromboembolic events are responsible for the vast majority of maternal and fetal deaths.^[3]

Aspirin is currently the most widely prescribed medication for the prevention of cardiovascular complications.^[26] LMWH have been shown to be a safe and effective therapy in conditions similar to APS, such as hereditary thrombophilia.^[27,28] Low-dose aspirin is widely used to prevent pregnancy-related vascular diseases, such as preeclampsia and intrauterine growth restriction as well as APS.^[29] The combined use of LMWH and aspirin in patients with recurrent spontaneous abortion who test positive for aPL has become routine practice.^[30,31] In recent years, a number of clinical trials have shown that the combination of low-dose aspirin and LMWH is superior to aspirin alone in preventing pregnancy loss, and that there is no difference in the live birth rate among women on aspirin, aspirin combined with LMWH, and placebo.^[32,33] Xuefenglu et al^[34] found that the LMWH therapy could maintain function and a state of hemostasis among patients with unexplained recurrent spontaneous abortion. In addition, they indicate that platelet aggregation in response to arachidonic acid and D-dimer levels are both good indicators for the use of aspirin and LMWH. D-dimer increases early in pregnancy and continues throughout pregnancy. During pregnancy, the hemostatic system activates hypercoagulable blood, which increases the risk of maternal bleeding. Detection of D-dimer levels can predict the risk of thrombosis to a certain extent.^[35]

We included 2101 patients from 11 studies. The combined results showed that the combination of aspirin and LMWH significantly increased the live birth rate in women with APS. Subgroup analysis based on the course of treatment showed that aspirin combined with LMWH increased the live birth rate in women with APS regardless of course A or B. Therefore, both short and long courses of treatment can improve the live birth rate of the fetus. The significant decrease in the heterogeneity of course B may be related to the small number of included studies. The concentration of D-dimer in plasma may predict the fetal live birth rate, which was higher below the baseline than above it. Detection of D-dimer levels in the prevention of thrombosis may predict pregnancy complications and guide the use of anticoagulants, but more studies are needed to support this conclusion due to the lack of included literature. A sensitivity analysis of the main results showed that the outcome was not affected after the cancellation of any study.

There are several limitations to this meta-analysis. First, studies published in languages other than Chinese and English were not included. Second, the number of studies included in the merger analysis was limited. Third, of the 11 studies, 6 were in Chinese and 5 in English, and the results showed certain regional deviation. Finally, there are many factors affecting obstetric complications, including some confounding factors, which cannot be completely avoided in this study. Future studies can expand the geographic scope and try to control for obstetric uncertainties.

5. Conclusions

Both short and long courses of treatment with aspirin combined with LMWH in the treatment of APS can improve the live birth

rate in pregnant women. Detection of D-dimer levels in APS pregnant women for thromboprophylaxis may predict the risk of pregnancy complications and guide the use of anticoagulants. However, this needs to be supported by more adequate clinical trials to determine D-dimer's role in preventing thrombosis and obstetric complications.

Author contributions

Writing – original draft: Ting Shi, Zhong Deng Gu.

Writing – review & editing: Qi zhi Diao.

References

- [1] Rodrigues VO, Soligo AGES, Pannain GD. Antiphospholipid antibody syndrome and infertility. *Rev Bras Ginecol Obstet* 2019;41:621–7.
- [2] Li XY, Zhao JX, Liu XY. Diagnosis and treatment of antiphospholipid antibody-related recurrent spontaneous abortion and analysis of therapeutic drugs and pregnancy outcome in 75 patients with antiphospholipid syndrome. *Beijing Da Xue Bao Yi Xue Ban* 2018; 50:956–61.
- [3] Gadó K, Domján G. Antiphospholipid syndrome and pregnancy. *Orv Hetil* 2012;153:1207–18.
- [4] Rahman A. Management of antiphospholipid syndrome. *Clin Rheumatol* 2020;39:2111–4.
- [5] Arnaud L, Mathian A, Ruffatti A, et al. Efficacy of aspirin for the primary prevention of thrombosis in patients with antiphospholipid antibodies: an international and collaborative meta-analysis. *Autoimmun Rev* 2014;13:281–91.
- [6] Erkan D, Harrison MJ, Levy R, et al. Aspirin for primary thrombosis prevention in the antiphospholipid syndrome: a randomized, double-blind, placebo-controlled trial in asymptomatic antiphospholipid antibody-positive individuals. *Arthritis Rheum* 2007;56:2382–91.
- [7] de Jesus GR, Agmon-Levin N, Andrade CA, et al. 14th International Congress on Antiphospholipid Antibodies Task Force report on obstetric antiphospholipid syndrome. *Autoimmun Rev* 2014;13:795–813.
- [8] Hamulyák EN, Scheres LJ, Marijnen MC, et al. 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:CD012852.
- [9] Otero A, Lena A, Lisa E, et al. Use of D-dimer in biological control of pregnancy. *J Thromb Haemost* 2015;13:280.
- [10] Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials* 1996;17:1–12.
- [11] Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Clin Res Ed)* 2011;343:d5928.
- [12] Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005;5:13.
- [13] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ (Clin Res Ed)* 2003;327:557–60.
- [14] Moher D, Liberati A, Tetzlaff J, et al. PRISMA Group Preferred Reporting Items for Systematic Reviews and Meta-Analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
- [15] Bao SH, Frempong ST, Ruan JL. D-dimer assay may guide LMWH treatment in repeated biochemical pregnancy losses in women with positive antiphospholipid antibody. *Clin Lab* 2020;66DOI: 10.7754/Clin.Lab.2019.190637.
- [16] Deng X, Pan SY, Lin YY. Therapeutic effect of 50 pregnancy patients with antiphospholipid syndrome. *J Gannan Med Coll* 2012;32:374–5. (in Chinese).
- [17] Jiang JH. Clinical Analysis of 48 Cases of Pregnancy Complicated With Antiphospholipid Syndrome. 2016; Wenzhou Medical University, (in Chinese).
- [18] Yanli W. Clinical efficacy of aspirin combined with LMWH in the treatment of recurrent abortion induced by anti-phospholipid antibodies. *J Qingdao Med Health Sci* 2020;52:27–9. (in Chinese).
- [19] Yongqin Z. The effect of low molecular weight heparin on the treatment of recurrent abortion caused by anti-phospholipid antibody syndrome. *J Contemp Med* 2016;14:139–40. (in Chinese).

- [20] Linchun Z, Meisong G. Clinical study on the treatment of recurrent abortion caused by anti-phospholipid antibody syndrome with aspirin and low molecular weight heparin. *Doctors* 2020;10:369–70. (in Chinese).
- [21] Wang Y, Zhang Y, Zhang Y, et al. Aspirin and low molecular weight heparin in the treatment of chronic abortion and antiphospholipid syndrome. *China Mod Phys* 2012;50:60–2. (in Chinese).
- [22] Bao SH, Sheng SL, Liao H, et al. Use of D-dimer measurement to guide anticoagulant treatment in recurrent pregnancy loss associated with antiphospholipid syndrome. *Am J Reprod Immunol* 2017;78:e12770.
- [23] Granger KA, Farquharson RG. Obstetric outcome in antiphospholipid syndrome. *Lupus* 1997;6:509–13.
- [24] Laskin CA, Spitzer KA, Clark CA, et al. Low molecular weight heparin and aspirin for recurrent pregnancy loss: results from the randomized, controlled HepASA Trial. *J Rheumatol* 2009;36:279–87.
- [25] Mohamed KAA, Saad AS. Enoxaparin and aspirin therapy for recurrent pregnancy loss due to anti-phospholipid syndrome (APS). *Middle East Fertil Soc J* 2014;19:176–82.
- [26] Gaspoz JM, Coxson PG, Goldman PA, et al. Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease. *N Engl J Med* 2002;346:1800–6.
- [27] Dugalic S, Petronijevic M, Stefanovic A, et al. Comparison of 2 approaches in management of pregnant women with inherited thrombophilias: prospective analytical cohort study. *Medicine (Baltimore)* 2019;98:e16883.
- [28] Gojnic MG, Dugalic SV, Stefanovic AO, et al. Combined hereditary thrombophilias are responsible for poor placental vascularization development and low molecular weight heparins (LMWH) prevent adverse pregnancy outcomes in these patients. *J Matern Fetal Neonatal Med* 2020;18:1–8.
- [29] Atallah A, Lecarpentier E, Goffinet F, et al. Aspirin for prevention of preeclampsia. *Drugs* 2017;77:1819–31.
- [30] Empson M, Lassere M, Craig J, et al. Prevention of recurrent miscarriage for women with antiphospholipid antibody or lupus anticoagulant. *Cochrane Database Syst Rev* 2005;18:CD002859.
- [31] Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: a randomized, controlled trial of treatment. *Obstet Gynecol* 2002;100:408–13.
- [32] Ziakas PD, Pavlou M, Voulgarelis M. Heparin treatment in antiphospholipid syndrome with recurrent pregnancy loss: a systematic review and meta-analysis. *Obstet Gynecol* 2010;115:1256–62.
- [33] Kaandorp SP, Goddijn M, Post JA, et al. Aspirin and aspirin combined with low-molecular-weight heparin in women with unexplained recurrent miscarriage: a randomized controlled multicenter trial (ALIFE study). *Blood* 2009;114:488–1488.
- [34] Lu X, Liu Z, Zhang X, et al. Prothrombotic state of patients with unexplained recurrent spontaneous abortion. *Int J Gynaecol Obstet* 2015;131:161–5.
- [35] Donohoe S, Quenby S, Mackie I, et al. Fluctuations in levels of antiphospholipid antibodies and increased coagulation activation markers in normal and heparin-treated antiphospholipid syndrome pregnancies. *Lupus* 2002;11:11–20.