Aspirin and heparin in the treatment of recurrent spontaneous abortion associated with antiphospholipid antibody syndrome: A systematic review and meta-analysis

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Abstract. The present study aimed to review relevant, randomized, controlled trials in order to determine the effects of aspirin and heparin treatment on recurrent spontaneous abortion (RSA) in women with antiphospholipid syndrome (APS). Previous relevant studies were identified using PubMed, Cochrane, Embase, CNKI, VANFUN and VIP by retrieving appropriate key words. Additionally, key relevant sources in the literature were reviewed and articles published before May 2019 were included. The 22 selected studies included 1,515 patients in the treatment group and 1,531 patients in the control group. These previous studies showed that heparin and aspirin significantly improved live birth rate when compared with treatments using intravenous immunoglobulin, aspirin alone or aspirin combined with prednisone. Moreover, heparin and aspirin greatly increased the birth weight compared with placebo and improved vaginal delivery relative to intravenous immunoglobulin. The gestational age at birth was significantly higher in the heparin and aspirin group compared with the placebo group and the incidence of intrauterine growth restriction was lower in the heparin and aspirin group compared with the placebo group. Furthermore, heparin and aspirin markedly reduced the incidence of miscarriage compared with the aspirin group and the placebo group, and the incidence of pre-eclampsia was lower in the heparin and aspirin group than the placebo group. Thus, heparin and aspirin could be further examined for the treatment of RSA in women with APS.

Introduction

Antiphospholipid syndrome (APS) is an autoimmune disease associated with arterial or venous thrombosis, recurrent fetal abortion or thrombocytopenia (1). The development of APS involves the production of antiphospholipid antibodies, such as anticardiolipin antibodies (ACL), lupus anticoagulant (LA) and anti-β2 glycoprotein I antibodies (2,3). The major pathological changes seen in APS caused by antibodies include villus microtubule embolism, placental infarction and fetal arterial embolism, which can result in embryo abortion and stillbirth (4,5). Termination of pregnancy at <28 weeks or fetal weight <1 kg is referred to as abortion and recurrent spontaneous abortion (RSA) is defined as continuous spontaneous abortion occurring more than twice (6). RSA is a common phenomenon with an incidence rate of 1-3% (7). Risk factors for RSA range from genetic, hormonal or metabolic factors, to uterine anatomy, autoimmune dysfunction, thrombosis tendency and infection (8). APS accounts for 7-25% of RSA and the rate of miscarriage can reach 90% in RSA without treatment (9-13).

In China, the positive rates of ACL and LA were 2.2 and 0.07-0.27%, while those with RSA history were 4.08 and 5.71% (2013), respectively, and in Western countries (USA, 1995; UK, 1996; Switzerland, 1987; Italy, 1997; Spain, 1994; The Netherlands, 1996), RSA pregnant women have ACL positive rates of 5-51% (14,15). For the past 30 years, several treatment options have been available, such as aspirin, heparin, plasma exchange, glucocorticoid, immunoglobulin and other combined or single applications for ACL (16,17), but the research conclusions about optimal treatment still remains controversial. At present, heparin combined with aspirin is a widely used treatment (18,19). The aim of the present study was to perform a meta-analysis to elucidate the effects of aspirin and heparin in the treatment of RSA in women with APS and to provide a basis for informed clinical treatment.

Materials and methods

Search strategy. Previous relevant studies published before May 2019 on the use of aspirin and heparin in the treatment of RSA in women with APS were obtained from the Cochrane (www.cochranelibrary.com), Pubmed (pubmed.ncbi.nlm.nih.gov), Embase (www.embase.com), CNKI (www.cnki.net), VANFUN (www.wanfangdata.com.cn/index.html) and VIP

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(www.cqvip.com) databases. The references of all identified articles were also reviewed to obtain additional studies. Search terms were as follows: 'Antiplatelet', 'anticoagulants', 'lupus', 'antiphospholipid syndrome', 'antiphospholipid antibody', 'recurrent miscarriage', 'recurrent abortion', 'spontaneous fetal loss', 'abortion', 'habitual', 'habitual abortion', 'treatment', 'heparin', 'aspirin', 'randomized', 'randomized controlled trial' and 'RCT'. These terms were used in combination with 'AND' or 'OR'. The present meta-analysis was performed independently by two investigators and disagreements were resolved by a third investigator. The main disagreement was whether one of the selected articles should be included or excluded in the meta-analysis. When the disagreement occurred, the three investigators read the article together and determined whether to incorporate the study.

Following the Participants, Interventions, Comparisons, Outcomes and Study design principle (20), the key search terms were: (P) female with RSA associated with APS; (I) patients in treatment group treated by aspirin and/or heparin; (C) placebo, aspirin and prednisone, intravenous immunoglobulin, prednisone or aspirin alone; (O) fertility outcome indexes, including live birth, pre-term delivery, miscarriage, birth weight, vaginal delivery, cesarean delivery, intrauterine death, gestational age at birth, intrauterine growth restriction (IUGR), gestational diabetes, thrombocytopenia and pre-eclampsia; and (S) randomized controlled trial.

Study selection criteria. All included studies met the following criteria: i) The study was a randomized controlled trial; ii) the research subjects were women with RSA associated with APS; iii) the treatment in the experimental group included aspirin and/or heparin, while the treatment in the control group was not limited; and iv) the study was written in English or Chinese. The exclusion criteria were as follows: i) Repeated articles or results; ii) clear data errors (including wrong index units, inconsistent data, results exceeding maximum values); iii) case reports, case-control studies, theoretical research, conference reports, systematic reviews, meta-analyses, or other forms of research or comments, which were not designed in a randomized controlled manner; and iv) irrelevant outcomes.

Data extraction. For each included study, two categories of information were extracted: Basic information and primary study outcomes. Basic information relevant to the current meta-analysis included authors' names, year of publication, sample size, patients' age and sex, results of the treatment of experimental and control groups, and Jadad score (21). Primary clinical outcomes relevant to the analysis included: Live birth, pre-term delivery, miscarriage, birth weight, vaginal delivery, cesarean delivery, intrauterine death, gestational age at birth, IUGR, gestational diabetes, thrombocytopenia and pre-eclampsia.

Quality assessment. Study quality was determined on the basis of Jadad scores, which were assigned according to the following criteria: i) Whether studies included a specific statement regarding randomization; ii) whether the method used to randomize patients was appropriate; iii) whether the study was conducted in a double-blinded manner; iv) whether the approach to double-blinding was described appropriately; and v) whether patient information was complete. A Jadad score <3 was indicative of low quality and therefore associated with a substantial risk of bias. Data extraction was performed independently by two investigators and disagreements were resolved by a third investigator. The main disagreements included: data extraction of primary clinical outcomes and the Jadad score of the included studies. When the data or scores were not consistent, the three investigators read the article together, analyzed and discussed data, and then extracted the data again until a consensus was reached.

Statistical analysis. STATA software (version 10.0; StataCorp LP) was used for all analyses. Heterogeneity in the study results was assessed using χ^2 and I^2 tests and appropriate analytical models (fixed effect or random effect) were determined accordingly. $P \leq 0.05$ and an $I^2 > 50\%$ indicated high heterogeneity and a random effect model was used in this case. $P > 0.05$ and an $I^2 \leq 50\%$ indicated acceptable heterogeneity and a fixed effect model was used instead. Results for continuous variables are presented as the mean ± standard deviation and were compared on the basis of weighted mean difference (WMD), while categorical data are presented as percentages and compared based on relative risk (RR) and odds ratio. WMD and 95% CI were used to analyze the birth weight and gestational age at birth, while RR and 95% CI were used to analyze live birth, pre-term delivery, miscarriage, vaginal delivery, cesarean delivery, intrauterine death, IUGR, gestational diabetes, thrombocytopenia and pre-eclampsia. Pooled data (WMD or RR with 95% CI) were analyzed to determine the effects of aspirin and heparin treatment on RSA in women with APS. Publication bias was evaluated using the funnel plot method. A symmetrical funnel plot that was narrow at the top and wide at the bottom indicated no publication bias in relation to the analyzed index. Begg's and Mazumdar's rank test was to analyze the direct correlation between standardized effect size and its variance. A value of 0 indicates that there is no direct correlation between effect size and accuracy; while a value higher than 0 indicates that there is a correlation, with an increasing value signifying a stronger correlation. Begg's rank correlation test and Egger's linear regression method were used to determine the possible publication bias through visually inspecting funnel plots. $P < 0.05$ was considered statistically significant.

Results

Overview of included studies. A total of 1,218 articles were identified, of which 1,147 were excluded by primary title and abstract review. The remaining 71 articles were subject to a complete full-text assessment, which further excluded 49 articles for failing to meet study inclusion criteria and the exclusion reasons were as follows: i) 5 articles with theoretical research; ii) 11 articles with no clinical outcomes, iii) 4 repeated articles; and iv) 29 non-randomized trials. Thus, a total of 22 studies (22-43) were ultimately identified that met the inclusion criteria for the present meta-analysis. These 22 studies involved 1,515 patients in the treatment group and 1,531 in the control group. The study selection process is outlined in Fig. 1.

Table I summarizes basic information for each study, including authors' names, year of publication, sample, age,

Table I. Basic characteristics of the included studies.

Author, year	No. of patients		Interventions		Jadad score	Refs.
	T	C	T	C		
Rai *et al*, 1997	45	45	Heparin and aspirin	Aspirin	3	(25)
Farquharson *et al*, 2002	51	47	Heparin and aspirin	Aspirin	5	(26)
Triolo *et al*, 2003	19	21	Heparin and aspirin	Intravenous immunoglobulin	3	(23)
Goel *et al*, 2006	33	39	Heparin and aspirin	Aspirin	4	(27)
Dendrinos *et al*, 2009	40	38	Heparin and aspirin	Intravenous immunoglobulin	3	(28)
Ismail *et al*, 2016	90	90	Heparin and aspirin	Placebo	3	(30)
Tulppala *et al*, 1997	33	33	Aspirin	Placebo	5	(32)
Pattison *et al*, 2000	20	20	Aspirin	Placebo	3	(22)
Cowchock *et al*, 1992	12	8	Heparin	Prednisone	3	(34)
Laskin *et al*, 2009	45	43	Heparin and aspirin	Aspirin	5	(29)
Zhou *et al*, 2012 a	30	31	Heparin and aspirin	Aspirin	3	(31)
Zhou *et al*, 2012 b	30	30	Heparin and aspirin	Placebo	3	(31)
Zhang *et al*, 2015	27	27	Heparin	Aspirin and prednisone	2	(33)
Bu Mingxiu *et al*, 2009	20	20	Heparin	Prednisone	2	(36)
Jinhua *et al*, 2003	24	24	Heparin	Aspirin and prednisone	2	(35)
Madani *et al*, 2019	30	30	Aspirin	Placebo	4	(37)
Blomqvist *et al*, 2018	200	200	Aspirin	Placebo	4	(38)
Bao *et al*, 2017	497	518	Heparin and aspirin	Aspirin	4	(39)
Maged *et al*, 2016	90	90	Heparin and aspirin	Placebo	5	(40)
Zhang *et al*, 2018	44	44	Heparin and aspirin	Aspirin	3	(41)
Zhaojuan *et al*, 2018	28	28	Heparin and aspirin	Aspirin	3	(42)
Tang *et al*, 2012	44	42	Heparin and aspirin	Aspirin and prednisone	3	(24)
Liang *et al*, 2015	63	63	Heparin	Aspirin and prednisone	3	(43)

T, treatment group; C, control group; Refs., reference.

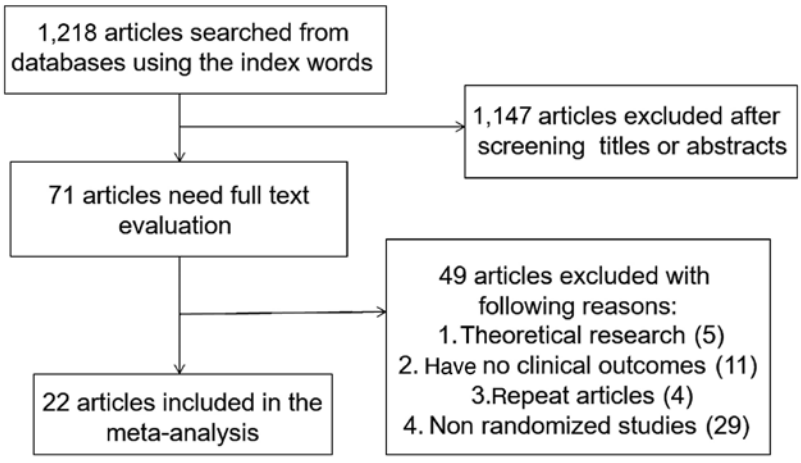

Figure 1. Literature search and selection strategy.

sex, treatment methods and Jadad score. The mean Jadad score for these selected studies was 3.39 (>3), indicating that, on average, these were of high quality.

All the indexes were divided into the following sub-groups for further analysis: Heparin and aspirin vs. aspirin alone, heparin and aspirin vs. intravenous immunoglobulin, heparin and aspirin vs. aspirin and prednisone, heparin and aspirin vs. placebo, aspirin vs. placebo, heparin vs. prednisone and heparin vs. aspirin and prednisone.

Live birth. A total of 20 studies, representing 1,427 patients in the treatment group and 1,442 patients in the control group, reported the live birth rates. Based on a χ^2 P<0.0001 and an I^2=70.9%, a random effect model was used to assess live birth. Overall, the

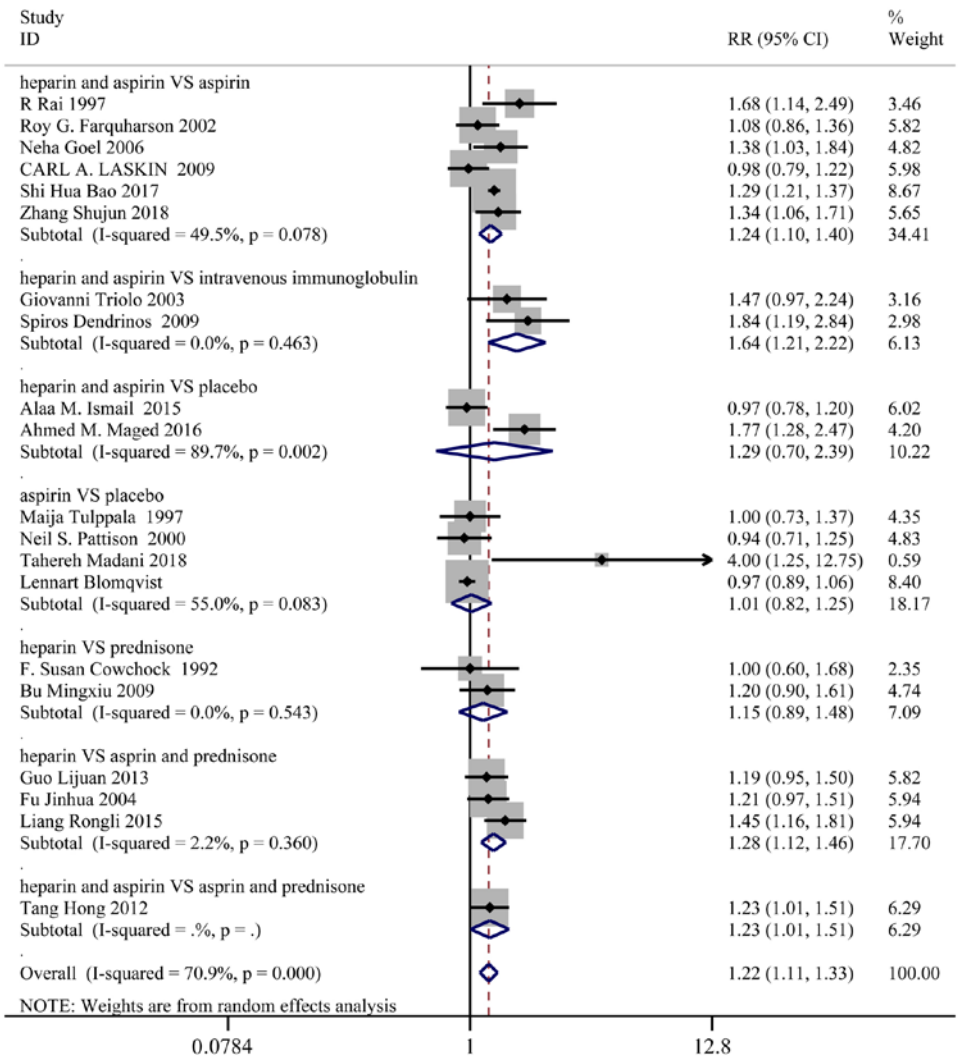

Figure 2. Forest plot for live birth incidence. Data are presented as 'treatment group vs. control group'. Where the RR (95% CI) of both groups was >1, the incidence of live birth was considered significantly higher in the treatment group than the control group. If the RR (95% CI) of both groups was <1, the incidence of live birth was considered significantly lower in the treatment group than the control group. In all other situations, no statistical difference could be inferred from the two groups. RR, relative risk.

live birth rate was significantly higher in the treatment group than the control group (RR: 1.22; 95% CI: 1.11-1.33). In the sub-group analysis, live birth was markedly improved in the following groups (Fig. 2): Heparin and aspirin vs. aspirin (RR: 1.24; 95% CI: 1.10-1.40), heparin and aspirin vs. intravenous immunoglobulin (RR: 1.64; 95% CI: 1.21-2.22), heparin and aspirin vs. aspirin and prednisone (RR: 1.23; 95% CI: 1.01-1.51), heparin vs. aspirin and prednisone (RR: 1.28; 95% CI: 1.12-1.46).

Birth weight. A total of 8 studies, with a total of 331 patients in the treatment group and 333 patients in the control group, reported the birth weights. Based on a χ^2 P<0.0001 and an I^2=93.4%, a random effect model was used to assess the birth weight (Fig. 3). No significant difference in birth weight was identified between the two groups [weighted MD (WMD): 154.65 g; 95% CI: -27.75-337.06]. In the sub-group analysis, birth weight was significantly higher in the heparin and aspirin group than the placebo group (WMD: 708.00; 95% CI: 531.06-884.94).

Pre-term delivery. A total of 11 studies, with 480 patients in the treatment group and 482 patients in the control group, reported the incidence of pre-term delivery. Based on a χ^2 P=0.007 and an I^2=59.0%, a random effect model was used to assess pre-term delivery (Fig. 4). No significant difference in pre-term delivery was observed between the two groups (RR: 0.72; 95% CI: 0.40-1.28). In the sub-group analysis, the incidence of pre-term delivery was higher in the heparin and aspirin group than the aspirin and prednisone group (RR: 1.39; 95% CI: 1.03-1.88).

Other results. No significant differences in the rates of cesarean delivery, intrauterine death, gestational diabetes and thrombocytopenia were identified between the two groups.

Vaginal delivery was significantly higher in the heparin and aspirin group than the intravenous immunoglobulin group (RR: 2.07; 95% CI: 1.19-3.62). The gestational age at birth was markedly higher in the heparin and aspirin group compared with the placebo group (WMD: 4.11 week; 95% CI: 3.68-4.53).

The incidence of IUGR was lower in the treatment group than the control group (RR: 0.42; 95% CI: 0.20-0.88). In the sub-group analysis, the incidence of IUGR was also lower in the heparin and aspirin group compared with the placebo group (RR: 0.33; 95% CI: 0.14-0.80).

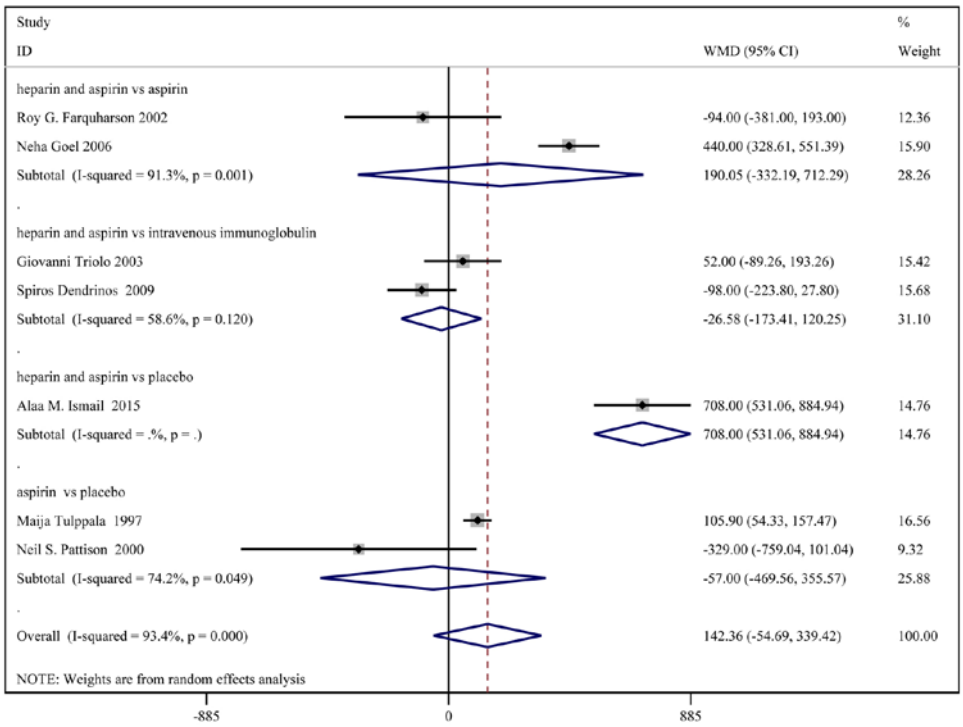

Figure 3. Forest plot for birth weight. Data are presented as 'treatment group vs. control group'. When the WMD (95% CI) of both groups was >0, birth weight was considered significantly higher in the treatment group compared with the control group. If the WMD (95% CI) of both groups was <0, birth weight was considered significantly lower in the treatment group compared with the control group. In all other situations, no statistical difference could be inferred from the 2 groups. WMD, weighted mean difference.

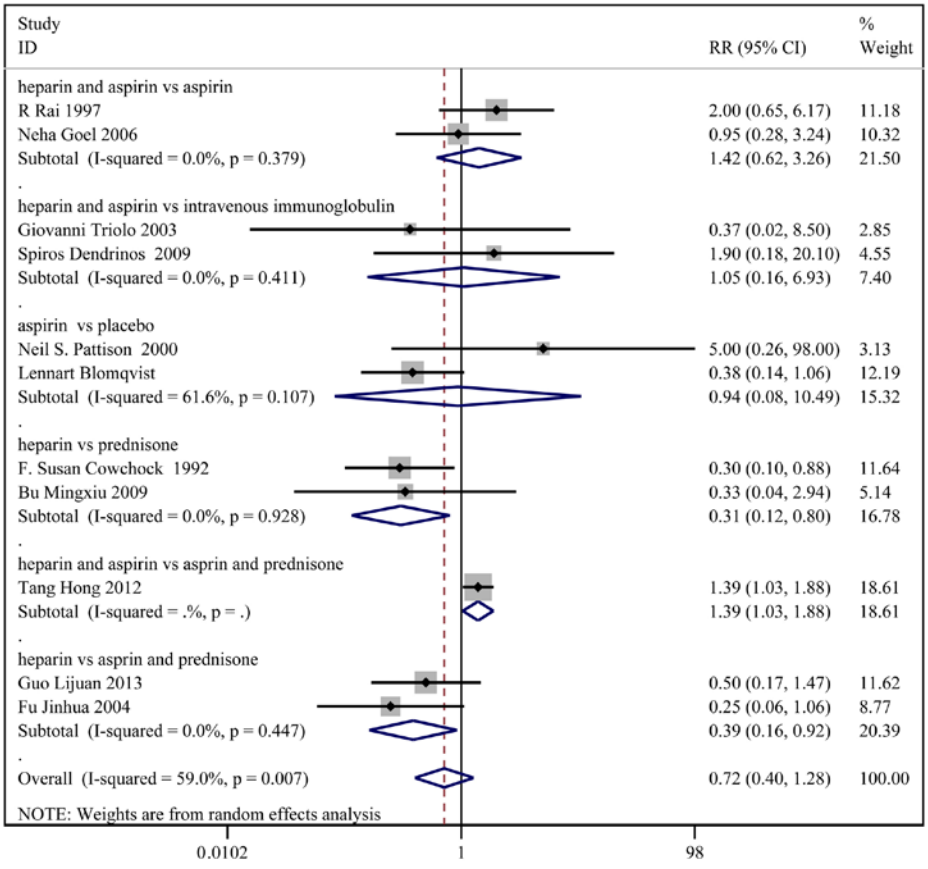

Figure 4. Forest plot for pre-term delivery. Data are presented as 'treatment group vs. control group'. When the RR (95% CI) of both groups was >1, the incidence of pre-term delivery was considered significantly higher in the treatment group compared with the control group. If the RR (95% CI) of both groups was <1, the incidence of pre-term delivery was considered significantly lower in the treatment group compared with the control group. In all other situations, no statistical difference could be inferred from the 2 groups. RR, relative risk.

Table II. The others results of meta-analysis.

Index	Interventions	RR (95% CI)	[b]P-value	I^2, %	[c]P-value	P-value	
						Begg's	Egger's
Vaginal delivery	Overall	1.37 (0.63-3.00)	0.022	80.9	0.432	1.000	-
	HA vs. II	2.07 (1.19-3.62)	-	-	0.011	-	-
	A vs. Pl	0.95 (0.64-1.42)	-	-	0.802	-	-
Cesarean delivery	Overall	1.09 (0.68-1.75)	0.346	10.5	0.729	0.462	0.574
	HA vs. A	0.75 (0.38-1.47)	-	-	0.402	-	-
	HA vs. II	2.39 (0.71-8.05)	0.187	42.6	0.159	0.317	-
	A vs. Pl	1.13 (0.48-2.65)	0.750	0.0	0.788	0.317	-
Intrauterine death	HA vs. II	0.44 (0.07-2.79)	0.387	0.0	0.382	1.000	-
Gestational age at birth	Overall	1.24 (-0.46-2.93)[a]	0.000	97.9	0.154	0.764	0.976
	HA vs. A	0.04 (-1.66-1.73)[a]	0.000	94.7	0.967	0.602	0.936
	HA vs. II	0.40 (-1.00-1.80)[a]	-	-	0.577	-	-
	HA vs. Pl	4.11 (3.68-4.53)[a]	0.925	0.0	<0.001	0.317	-
	A vs. Pl	0.00 (-0.49-0.49)[a]	-	-	1.000	-	-
IUGR	Overall	0.42 (0.20-0.88)	0.267	18.7	0.021	1.000	-
	HA vs. Pl	0.33 (0.14-0.80)	-	-	0.014	-	-
	A vs. Pl	0.89 (0.20-3.96)	-	-	0.873	-	-
Miscarriages	Overall	0.60 (0.49-0.73)	0.033	49.2	0.000	0.436	0.437
	HA vs. A	0.59 (0.40-0.87)	0.605	0.0	0.007	0.602	0.703
	A vs. Pl	1.20 (0.80-1.81)	0.862	0.0	0.382	0.317	-
	HA vs. Pl	0.47 (0.33-0.67)	0.946	0.0	<0.001	0.317	-
	HA vs. Apr	0.35 (0.12-1.01)	-	-	0.051	-	-
	H vs. Apr	0.32 (0.17-0.62)	0.962	0.0	0.001	0.317	-
	H vs. Pl	0.20 (0.03-1.56)	-	-	0.125	-	-
Gestational diabetes							
	Overall	0.26 (0.06-1.14)	0.966	0.0	0.073	1.000	-
	A vs. Pl	0.25 (0.03-2.07)	-	-	0.199	-	-
	H vs. Pl	0.27 (0.03-2.10)	-	-	0.209	-	
Thrombocytopenia							
	Overall	0.69 (0.30-1.57)	0.798	0.0	0.373	0.806	0.373
	HA vs. A	0.51 (0.16-1.63)	0.698	0.0	0.255	0.602	0.899
	HA vs. Pl	0.50 (0.05-5.22)	-	-	0.563	-	-
	HA vs. Apr	1.27 (0.30-5.35)	-	-	0.742	-	-
Pre-eclampsia							
	Overall	0.51 (0.31-0.87)	0.936	0.0	0.012	0.260	0.438
	HA vs. A	0.52 (0.05-5.40)	-	-	0.581	-	-
	HA vs. Pl	0.48 (0.25-0.93)	0.582	0.0	0.029	0.317	-
	A vs. Pl	0.58 (0.24-1.43)	0.666	0.0	0.240	0.602	0.643

[a]Analyzed by WMD (95% CI). [b]P-value of heterogeneity χ^2; [c]P-value of pooled statistic. H, heparin alone, A, aspirin alone; HA, heparin combined with aspirin; II, intravenous immunoglobulin; Pl, placebo; Pr, prednisone; APr, aspirin and prednisone; WMD, weighted mean difference; RR, relative risk; IUGR, intrauterine growth restriction.

Moreover, the incidence of miscarriages was lower in the treatment group compared with the control group (RR: 0.60; 95% CI: 0.49-0.73), as well as lower in the heparin and aspirin group than the aspirin (RR: 0.59; 95% CI: 0.40-0.87) and placebo groups (RR: 0.47; 95% CI: 0.33-0.67) and lower in the heparin group compared with the aspirin and prednisone groups (RR: 0.32; 95% CI: 0.17-0.62).

Furthermore, the incidence of pre-eclampsia was lower in the treatment group than the control group (RR: 0.51; 95% CI: 0.31-0.87) and the placebo group (RR: 0.48; 95% CI: 0.25-0.93). The aforementioned results are summarized in Table II.

Quality and bias assessment. An assessment of study quality and risk of bias was performed using multiple complementary

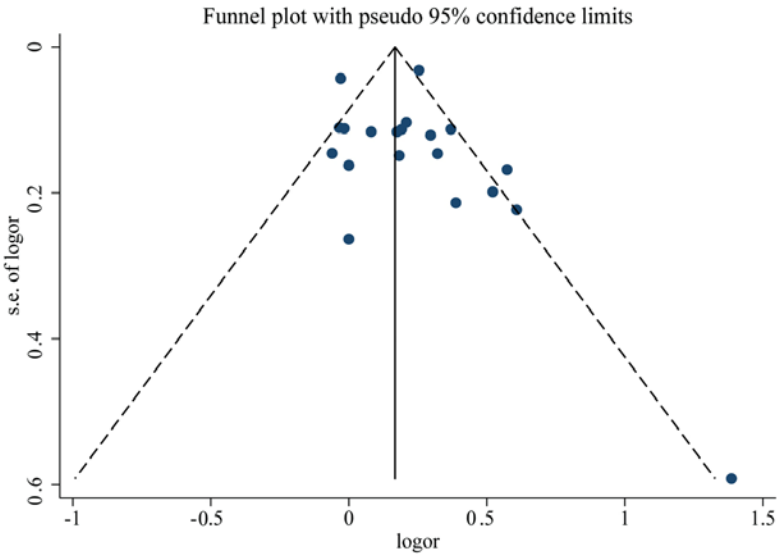

Figure 5. Funnel plot analysis of the included studies. OR, odds ratio.

methods, including funnel plots, Begg's and Mazumdar's rank test, and Egger's test. There was clear symmetry in the log RR funnel plot for included studies of live birth, suggesting a low publication bias risk (Fig. 5). The results of Begg's and Mazumdar's rank test (Z=1.52; P=0.127) and Egger's test (P=0.351) demonstrated that there was no significant risk of bias among the studied results.

Discussion

The mechanisms underlying the effects of heparin on RSA are unclear. However, several possibilities have been suggested in the literature. It has been demonstrated that the combination of heparin and heparin antithrombin III can exert direct anticoagulant effects (44). Alternatively, heparin can combine with antiphospholipid antibody (APA) and reduce its biological activity to protect the phospholipid components of blastocyst trophoblast cells from damage (45). APA can activate the complement system, especially C3 and C5, which in turn can promote inflammation and immune responses (46-48). In this respect, heparin can not only reduce inflammation, affect antigen processing, inhibit the formation of antibodies and complement-mediated abnormal immune responses, but also improve the implantation rate of embryos (49). Additionally, heparin can reduce the activity of aspartic acid caspase-3, inhibit the apoptosis of trophoblast cells and participate in the adhesion and invasion of blastocysts to endometrial epithelium, thereby promoting the proliferation of trophoblast cells and the formation of the placenta (50). As heparin has a relatively high molecular weight, it is difficult to pass through the placenta and has no teratogenic effects, thus is safe for the fetus and can be used in early pregnancy (51-53).

Anticoagulant therapy is mainly used for pregnant patients with a history of abortion and positive APA (54). The primary goal of this therapy is to protect the mother from thrombosis and reduce the risk of miscarriage (55). Aspirin can inhibit platelet aggregation, increase prostacyclin levels and has an anticoagulant effect (56,57). Hertz-Picciotto *et al* (58) observed that only high doses of aspirin (650-2, 600 mg/day) can lead to obvious fetal malformation, while low doses of aspirin (<150 mg/day) do not affect the quality of fetal birth or increase perinatal fetal mortality and therefore is safe to use. However, it should be noted that long-term use of aspirin may increase the risk of peptic ulcer disease (59). Therefore, aspirin should be used with caution when coagulation-related indicators are abnormal and APA is positive.

In the present study, it was observed that heparin and aspirin significantly improved live birth, compared with aspirin and prednisone. Compared with the placebo group, the heparin and aspirin group displayed markedly improved gestational age at birth, decreased the incidence of IUGR and miscarriage and a lower incidence of pre-eclampsia. Compared with the aspirin group, the heparin and aspirin group significantly improved live birth and decreased the incidence of miscarriages. Furthermore, heparin and aspirin significantly increased the birth weight relative to placebo. Heparin and aspirin markedly improved live birth and vaginal delivery, compared with intravenous immunoglobulin.

However, there were certain limitations in the present analysis. Indeed, only randomized studies were included and individual studies varied in their exclusion and inclusion criteria, as well as dosage. In addition, only a limited number of studies were included. Lastly, pooled data were analyzed, as individual patient data were not available; therefore, excluding the possibility of a more comprehensive analysis.

Overall, heparin and aspirin may be an optimal combination for treating RSA in women with APS. Nonetheless, the limited number of studies included in the present meta-analysis warrants further validation.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

XY made substantial contributions to the conception and design of the current study. XY drafted the article and critically revised the draft for important intellectual content. Data acquisition, analysis and interpretation were performed by LH. All authors read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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