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Review Article

The role of low molecular weight heparin on recurrent pregnancy loss: A systematic review and meta-analysis

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ABSTRACT

To assess the roles of the low molecular weight heparin (LMWH) on recurrent pregnancy loss (RPL). The relevant studies of all randomized controlled trials (RCTs) were retrieved, and the systematic evaluation was conducted. PubMed, Embase, and Cochrane library databases were searched by using keywords, including low-molecular-weight heparin or LMWH, and recurrent miscarriage or recurrent pregnancy loss in pregnant women from their earliest data to February 2020. Two investigators independently evaluated eligibility. Risk ratios (RRs) and their corresponding 95% confidence interval (CI) were determined. To pool the results, this meta-analysis was performed using random-effect model due to the high heterogeneity among these eight studies. A total of eight RCTs involving 1854 participants were included in the meta-analysis involving 963 patients with RPL who were prescribed LMWH (enoxaparin, tinzaparin, or dalteparin) alone and 891 patients who were treated with no LMWH interventions (placebo, folic acid or non-treatment) were compared. Pooled data from the remaining eight RCTs showed the differences between intervention groups and control groups. Compared with control groups, LMWH had significantly improved live births (RR,1.19; 95%CI, 1.03 to 1.38; $P = 0.02$), and reduced miscarriage rates (RR, 0.62; 95%CI, 0.43 to 0.91; $P = 0.01$). The study suggested that LMWH could improve the live births and reduce the miscarriage rates of RPL. Therefore, LMWH might be a good treatment choice for women with unexplained PRL.

Introduction

Recurrent pregnancy loss (RPL), affecting in 0.8%–1.4% of fertile couple [1], is defined as more than three spontaneous losses of pregnancies before 20 weeks of gestation [2]. However, many experts consider that the rate of 2 spontaneous losses is close to that of more than 3 spontaneous losses [3].

Despite a small part of RPL is associated with known abnormalities in the fetus or the parent, the causes of recurrent pregnancy losses (~50%) have not been explained yet [4].

At present, a number of etiologies of RPL have been identified, including the abnormal parental chromosome, infections, genetic factors, hormonal abnormalities, environment factors, immunologic abnormalities, and heritable or acquired thrombophilias [5]. Although most researches have focused more on the effect of male factors now, maternal factors are commonly considered in RPL due to the important roles of the healthy utero-placental circulation in developing embryo. Jaffe et al. reported that the successful pregnancy was based on the development and conservation of a suitable utero-placental circulation [6]. Previous studies showed that the defective placental function and development might lead to arterial thrombosis that result in pregnancy losses [7]. Furthermore, the venous thromboembolism (VTE) in pregnancy is more common than arterial thrombosis [8]. The blood in the maternal body starts flowing within the intervillous spaces of the placenta at around ten weeks of gestation, which could ensure that the transport of nutrition from blood of the maternal body to the fetal tissue [9]. The thrombophilias with pregnancy cause the RPL, placental damage, and fetal death. Particularly, in the last century, the relation between RPL and antiphospholipid antibodies (APAs) has been found. The presence of

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APAs is defined as antiphospholipid syndrome, and RPL is a feature of this symptom [10]. Farquharson et al. reported that antiphospholipid syndrome (APS) would increase thrombin generation, which led to thrombotic placental damage [11]. In this case, prevention and treatment of the thrombosis in pregnancy are important. It has been conclusively showed that pregnancy loss in APS could be prevented by antithrombotic treatment [12]. Low-molecular-weight heparins (LMWHs), such as dalteparin and enoxaparin, are generally clinical and practical drugs that used to treat the acute VTE [13]. Despite no strong and direct evidence suggests LMWHs could improve live birth rates in women with PRL. And women with 2 or more successive pregnancy losses are prescribed with LMWHs due to no effective treatments in unexplained PRL. Recently, some randomized controlled trials (RCTs) found that LMWHs were useful to prevent PRL and increase live birth rates [14,15], while other papers suggested that LMWHs had no significant difference between LMWHs treatment and no pharmacologic intervention [16,17]. According to these controversies, this systematic review and meta-analysis aimed to evaluate the roles of LMWHs on women with unexplained RPL.

Materials and methods

For this is a systematic review and meta-analysis of using the data of previously published studies, ethical approval and patient consent are not required.

Search strategy and selection criteria

A systematic search of the potential literature, we conducted on several database by using MEDLINE (1946—2020), Cochrane CENTRAL database (1994—2020), and Embase (1947—2020), using the following keywords (low-molecular-weight heparin or LMWH, and recurrent miscarriage or recurrent pregnancy loss), which is the PICOS (P: participants, I: intervention, C: comparison, O: outcome measure, S: study design) Cochrane approach. Besides, the references were also hand-searched through all potentially relevant journals. All researches were included with no restrictions on languages, type of researches, or the time of researches. The searches were updated in February 2020, and no additional relevant publications were found. Randomized controlled trials (RCTs) were included if they were with eligibility criteria as follows: (1) RCTs comparing patients were given LMWH (enoxaparin, dalteparin, or tinzaparin) alone, while patients in control groups received placebo, folic acid or without any treatment. (2) population: pregnant women with PRL. (3) reported the primary outcome of live births. The exclusion criteria was as follows: (1) non-RCTs. (2) LMWHs were used in both experimental groups and control groups, or LMWHs combined with other treatments (eg. aspirin). (3) duplicated publications, case studies, non-clinical trails, observational studies, letters and comments.

Intervention methods

The intervention of any types of LMWH mono-therapy was included with no limitations of the dosage, the frequency, forms and the route of administration. The comparison therapy could not be any forms of LMWH mono-therapy.

Selection of the articles

All relevant literature including abstracts and the full text were reviewed by two investigators independently for further scrutiny. The references of all relevant literature were checked to identify other potentially eligible studies. The inclusion or exclusion of each literature was determined by discussion between two investigators. None of the relevant literature could be rejected by any investigators. When there was any disagreement, the third investigator carried out the inclusion or exclusion of literatures.

Data extraction management

The data extraction was conducted from two authors independently. The data extraction included the general publication information (first author, and year of publication), the type of study design, the sample size, the mean age, intervention details (drug, dosages, frequencies and duration of interventions), and outcomes (primary and secondary outcomes). All extraction data was inputted into RevMan 5.3 (Cochrane Community, London, UK) software for further assessing.

Outcome measure

The primary outcomes of this study were characterized as live birth rates and miscarriage rates, and the secondary outcomes were defined as birth weight and gestational age. The adverse events including skin reactions at the injection site, thrombocytopenia, bleeding episodes and pre-eclampsia were also regards as the secondary outcomes.

Quality evaluation

The quality of these eight studies was assessed by RevMan5.3. The risk of bias was evaluated by Cochrane Handbook criteria.

Statistical analysis

We evaluated standard Mean differences with 95% confidence intervals (CIs) for continuous outcomes (birth weight and gestational age), and risk ratios (RRs) with 95% Cls using a random-effects model for dichotomous outcomes (live births, miscarriage rates, the skin reactions at the injection site, thrombocytopenia, bleeding episodes and pre-eclampsia), with a $P < 0.05$ considered statistically significant. All statistical measures were conducted using the Review Manager (RevMan, version 5.3, The Cochrane Collaboration, Copenhagen, Denmark) software. The chi-square and I^2 were used to assess visual inspection of forest plots. Besides, the Cochrane Q test is the classical method to evaluate the clinical design of heterogeneity. In the test, the weighted sum of squared differences between individual study effects and the pooled effects in studies were calculated to do the evaluation. The Cochrane I^2 statistic described the percentage of total variation among studies caused by the heterogeneity instead of chance. A high I^2 (>75%) value implied high degree of heterogeneity, and an $I^2 < 25\%$ suggested low-level heterogeneity. Publication bias was not assessed due to the limited number (<10) of included studies [18]. Because of considerable heterogeneity among different studies, the random-effects model was assumed in our study. Finally, considering the heterogeneity among studies, a sensitivity analysis was performed to assess the influence of individual data set on the overall effect by the leave-one out principle.

Results

Study selection

There were 319 relevant articles identified through electronic databases. A detail flowchart of the literature search and selection results that were summarized below is shown in Fig. 1. All titles and abstracts were screened for the exclusion criteria. After duplicates

were removed, 285 entries were screened further. Further 46 records including reviews, summaries, case reports, the meta-analysis, not available articles, or topics not relevant to this review were excluded. 239 full article records of potentially relevant studies were retrieved by our strategy, of which 17 publications available for qualitative analysis. In the end, only eight randomized controlled trials [15–17,19–23], and 1854 participants met all eligibility criteria and had data available for quantitative extraction for meta-analysis.

Risk of bias of included studies

Two authors evaluated these studies independently. The risk of bias assessment was shown in Fig. 2 and the quality of these eight studies was determined as good quality [15–17,19–23].

Study characteristics

A total of 963 participants with RPL received LMWH (enoxaparin, tinzaparin, dalteparin) alone. Recruited patients in five included studies were given with enoxaparin [19–23], one with tinzaparin [15], one with dalteparin [17], and one study did not mention what forms of LMWHs they used [16]. And 861 participants in the control groups included trails with a placebo, folic acid tablet, or no treatment. Among the 861 patients in control groups, 543 participants received the folic acid, 239 participants were assigned for placebo interventions, and 109 participants did not accept any treatment. The age of participants were all ≥18 years, with varying mean ages among the eight studies (Table 1). Also, all participants had at least two or more miscarriages. Live birth rates and miscarriage rates were reported in all eight included RCT studies [15–17,19–23]. Four studies noted the gestational age, and the birth weight [19–22]. Four studies reported the skin reactions at the injection site [15,19–21]. Moreover, four studies showed thrombocytopenia, and bleeding episodes [15,19,20,22]. Pre-eclampsia was mentioned in five studies [15,19–22].

Synthesis of results

The combined results of the eight studies with the random-effect model for the two main outcomes (live births and miscarriage rates) were shown in Fig. 3 and Fig. 4. In addition, secondary outcomes including skin reactions at the injection site, birth weight, gestational age, thrombocytopenia, bleeding episodes and pre-eclampsia were presented respectively in Figs. 5–10.

Main findings

Primary outcomes: live births, and miscarriage rates

Eight studies reported live births. The results of pooling the eight studies showed significant difference in live births with the use of LMWH group when compared with control groups (RR = 1.19; 95%CI, 1.03 to 1.38; $P = 0.02$), with significant heterogeneity that was observed among eight studies ($I^2 = 86\%$, $P < 0.00001$; Fig. 3). The live births were higher in patients treated with LMWH. Consistently, there was a statistical difference of miscarriage rates between the use of LMWH and without LMWH. Statistical heterogeneity was showed between the studies ($I^2 = 73\%$, $P = 0.0006$) by using a random effects model. The result indicates that the patients treated with LMWH had significant lower miscarriage rates than those from normal controls (RR = 0.62; 95%CI, 0.43 to 0.91; $P = 0.01$; Fig. 4).

Secondary outcomes

By comparison with control groups, skin reaction at the injection site was increased in women with RPL who received LMWHs (RR = 13.96; 95% CI = 1.36 to 143.44; $P = 0.03$; Fig. 5). Receiving LMWHs had no substantial impact on birth weight (Std. MD = 0.28; 95% CI = −0.13 to 0.68; $P = 0.18$; Fig. 6), gestational age (Std. MD = 0.06; 95% CI = −0.29 to 0.40; $P = 0.75$; Fig. 7), thrombocytopenia (RR = 2.72; 95% CI = 0.74 to 6.99; $P = 0.15$; Fig. 8), bleeding episodes (RR = 6.07; 95% CI = 0.24 to 152.23; $P = 0.27$; Fig. 9), and pre-eclampsia (RR = 1.24; 95% CI = 0.80 to 1.94; $P = 0.34$; Fig. 10).

Table 1
Characteristics of studies included in the meta-analysis.

NO.	Author	LMWH group					Control group				
		Number	Age	Previous live birth	Numbers of previous miscarriage	Methods	Number	Age	Previous live birth	Numbers of previous miscarriage	Methods
1	Shaaban et al. (2017)	150	26.61 ± 3.23	NA	3	500ug folic acid tablet daily together with tinzaparin sodium 0.4 mg/kg	150	26.63 ± 3.64	NA	3	500 mg folic acid tablet
2	Schleussner et al. (2015)	226	31.9	115	2.6	Self-administered subcutaneous injections of dalteparin-sodium, 5000 IU daily, plus multivitamins with folic acid	223	32.3	110	2.6	Plus multivitamins with folic acid
3	Pasquier et al. (2015)	138	32.7 ± 5.2	66	3	Receive one daily subcutaneous injection of enoxaparin 40 mg	118	32.1 ± 5.4	50	3	Placebo
4	Fawzy et al. (2008)	57	28.7 ± 5.4	NA	3.2 ± 1.3	Received daily enoxaparin	59	29.4 ± 7.1	NA	3.7 ± 2.4	Non-treatment
5	Badawy et al. (2009)	170	26.2 ± 2.6	NA	4.2 ± 1.3	Daily subcutaneously enoxaparin sodium 0,2 ml and folic acid tablets 0.5 mg	170	28.7 ± 3.1	NA	4.5 ± 1.6	Folic acid tablets 0.5 mg daily until 13 weeks' gestation
6	Qublan et al. (2008)	42	29 ± 6.3	NA	NA	Daily received enoxaparin 40 mg	41	29.2 ± 6.1	NA	NA	Placebo
7	Khan et al. (2017)	80	25.9	NA	NA	Daily dose of 40 mg LMWH subcutaneously	80	26	NA	NA	Placebo
8	Yuksel et al. (2014)	100	28 ± 5	NA	3	Daily Self-inject subcutaneously either 4000 IU in enoxaparin group or 3500 IU	50	28.8 ± 6	NA	2	Non-treatment

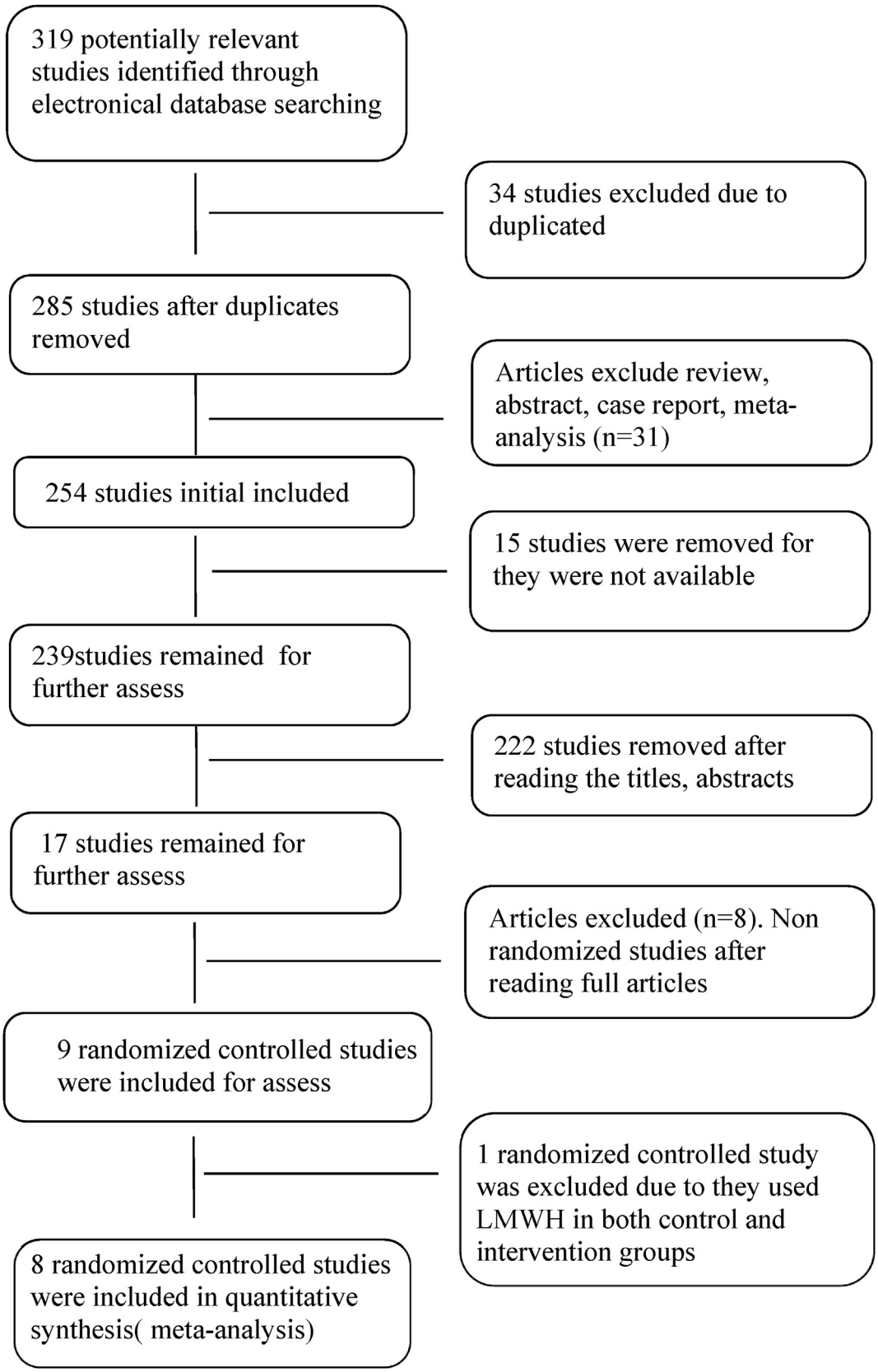

Fig. 1. Flow diagram of studies searching, selecting and including process.

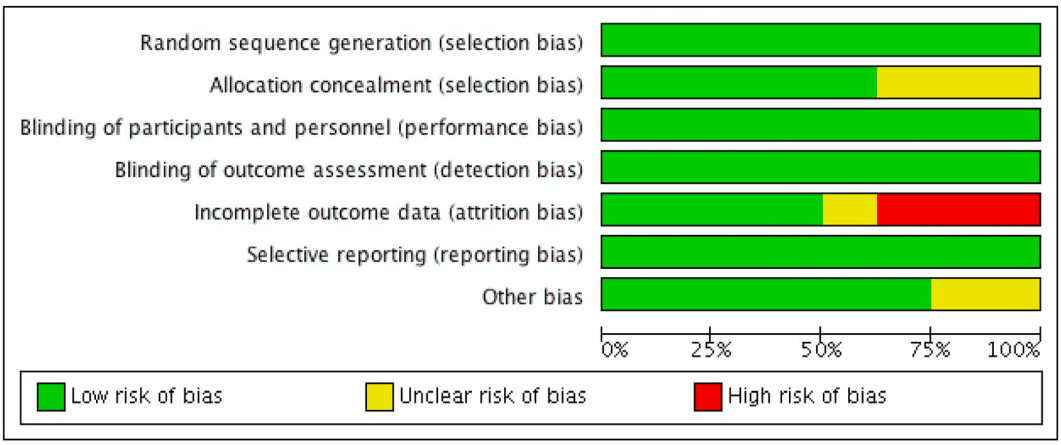

Fig. 2. Assessment of risk of bias of included studies according to the Cochrane handbook.

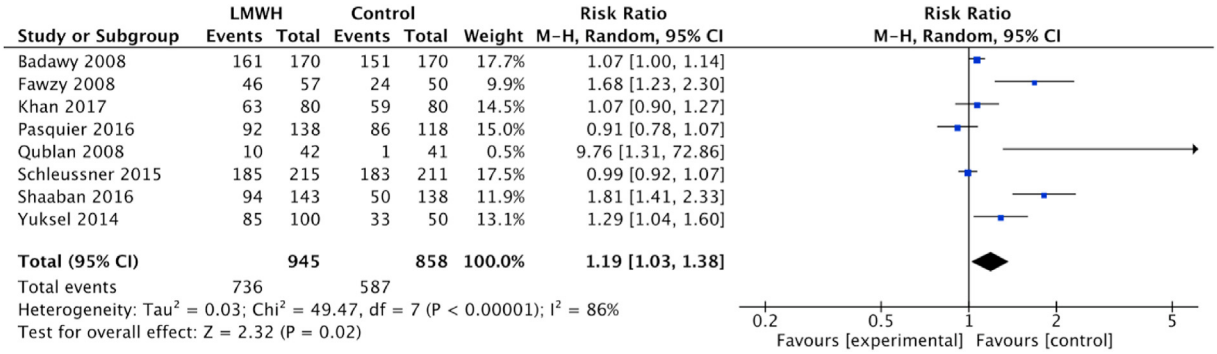

Fig. 3. Forest plots of eight studies selected from our literature search for meta-analysis of live births. CI: confidence interval; LMWH: low-molecular-weight heparin; M–H: Mantel–Haenszel risk ratios.

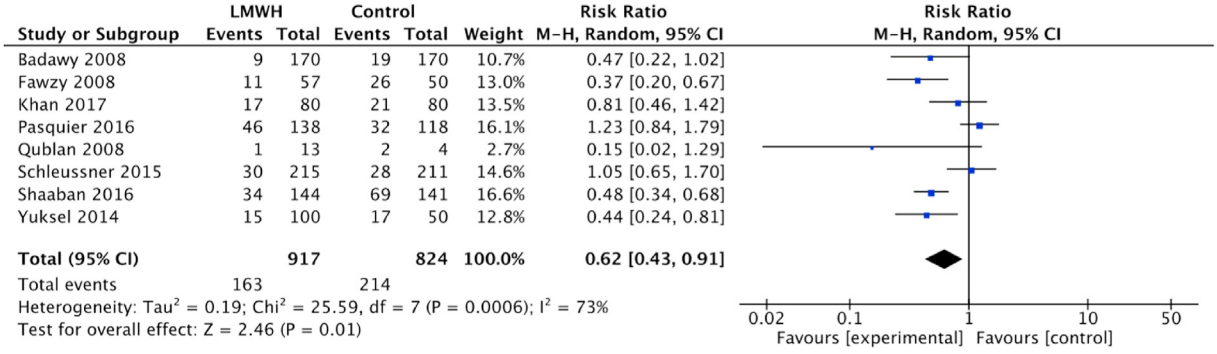

Fig. 4. Forest plots of eight studies selected from our literature search for meta-analysis of miscarriage rates.

Sensitivity analysis

The included studies showed significant heterogeneity for the primary outcomes (live births and miscarriage rates) and secondary outcomes (skin reactions at injection site, birth weight, gestational age, thrombocytopenia, bleeding episodes and pre-eclampsia). The leave-one-out approach was used to assess the influence of individual data on the overall outcome. When excluded individual study one-by-one, the results indicated that there was no significant alteration in any of the outcomes.

Discussion

RPL includes women who have greater than or equal to two failed clinical pregnancies tested by histopathological examination or ultrasonography or two or more consecutive pregnancy losses. Around 0.8%–1.4% women will suffer from RPL, but the causes of more than fifty percentage of women with PRL have not been explained yet. A variety of treatments have been provided to patients with unexplained RPL, such as preimplantation genetic diagnosis, lifestyle changes and human menopausal gonadotropin.

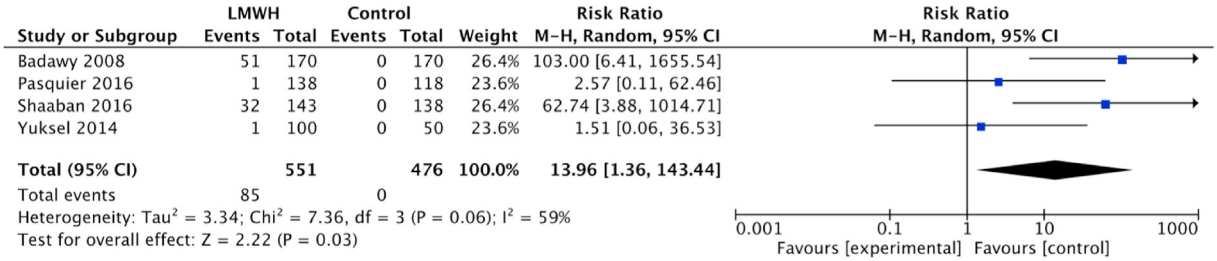

Fig. 5. Forget plots of four studies selected from our literature search for meta-analysis of skin reactions at the injection site.

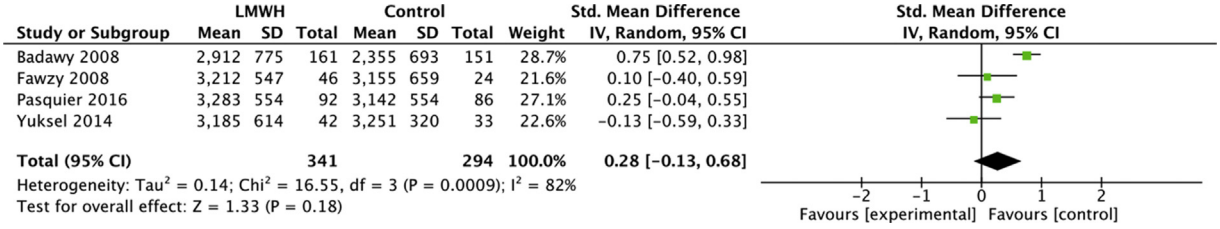

Fig. 6. Forget plots of four studies selected from our literature search for meta-analysis of birth weight.

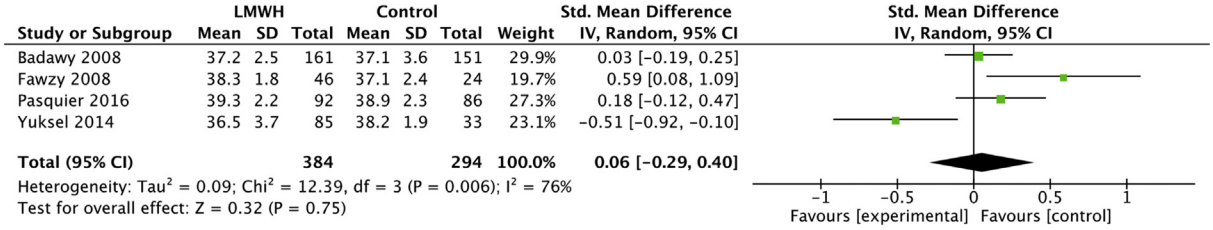

Fig. 7. Forget plots of four studies selected from our literature search for meta-analysis of gestational age.

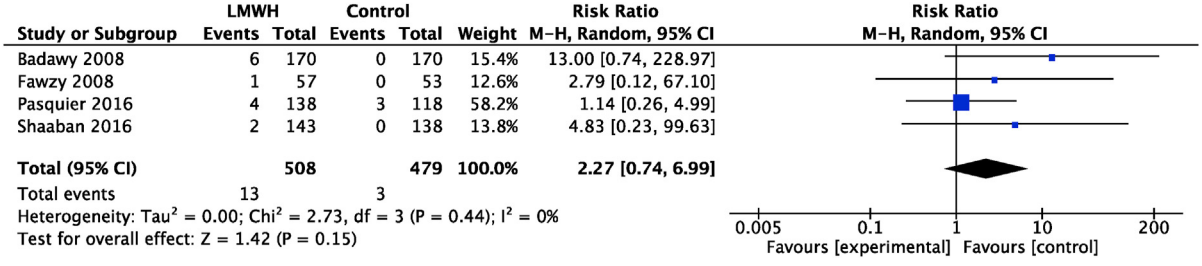

Fig. 8. Forget plots of four studies selected from our literature search for meta-analysis of thrombocytopenia.

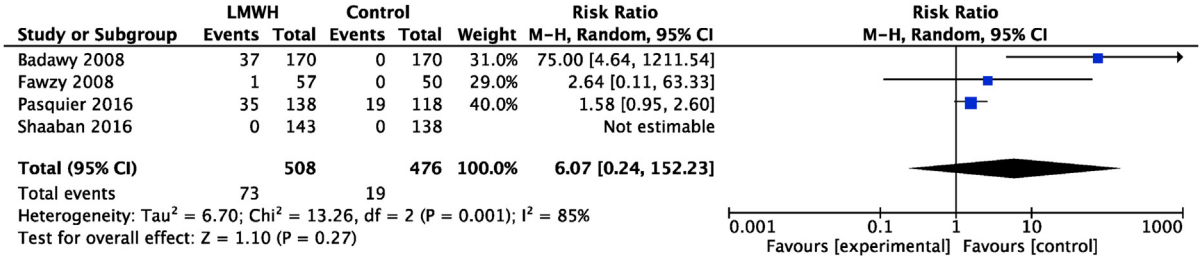

Fig. 9. Forget plots of four studies selected from our literature search for meta-analysis of the bleeding episodes.

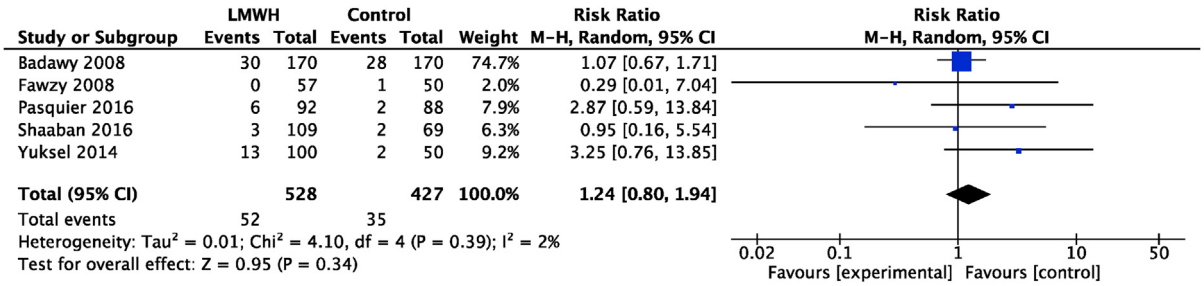

Fig. 10. Forget plots of five studies selected from our literature search for meta-analysis of the pre-eclampsia.

Recently, Brenner et al. and Dolitizky et al. showed anticoagulants and thromoboprophylaxis could be the preventive therapy for RPL [24,25]. Due to about 50% cases have no defined reasons, the anticoagulants and thromoboprophylaxis therapy has been recommended for patients [26].

Retrospective studies have a higher likelihood of selection bias and recall bias compare with RCT studies. This is the reason that only the type of RCT studies was included. But there are some significant heterogeneity for outcomes among studies. Several factors accounting for the high heterogeneity are as follows. Firstly, four studies evaluated the use of enoxaparin [19,20,22,23], two studies assessed tinzaparin [15] and dalteparin [17], respectively, one study evaluated tinzaparin or enoxaparin [21], and another study used the unknown type of LMWHs [16]. The various types of LMWHs (enoxaparin, tinzaparin and dalteparin) which may have different impact on inflammatory pathways and venous thromboembolism. Liu et al. hold the view that enoxaparin might be better in inhibiting the circulation of the antiphospholipid antibodies, inflammatory pathways and venous thromboembolism in antiphospholipid syndrome [27]. Secondly, there were some other differences between the evaluated studies, including the dosages of LMWHs, the beginning and duration time of using LMWHs. Rottenstreich et al. found that the patients with RPL receiving the LMWH continuously resulted in a high live births [28]. Thirdly, the complicated pathogenesis of RPL may cause women with RPL of different reasons were enrolled in RCTs. For example, The Factor V Leiden thrombophilia is the most common disorder in Europeans. However, the protein S, protein C deficiency are the major reasons of thrombophilias in East Asians [29]. They all may meet the criteria in this meta-analysis, which may lead to the heterogeneity. All of these factors may lead to significant heterogeneity between the studies. The sensitivity analysis of primary outcomes and six secondary outcomes (the skin reactions at the injection site, birth weight, gestational age, thrombocytopenia, bleeding episodes and pre-eclampsia) was assessed by omitting one study in each turn method, and the results did not show significant effects by any single study, the heterogeneity was acceptable.

In order to know whether LMWHs are safety for women with RPL, evaluating the adverse events is important as well. The present studies have been explored, most of them reported that thromboprophylaxis during pregnancy was safe for both the fetus and patients. Moreover, Bazzan et al. found that the LMWHs could not pass through the blood-placental barrier, providing the safety of using it for pregnant patients [30]. Also, in our study, there is no significant difference in maternal severe side effects (thrombocytopenia, bleeding episodes and pre-eclampsia) between LMWH groups and control groups. However, the increase in skin reactions at the injection site is observed after the LMWH treatment with RPL based on the result of three including studies. Shaman et al. reported that 78.7% showed no adverse events, while 21.3% had skin reactions at the site of injection [15]. These results are similar to the study that local skin reactions at the injection site appeared around 40% of patients [31]. Apart from that, Monien et al. have not seen the severe side effects of LMWH, either [32]. The results of these studies may reassure us about the safety of using LMWHs to prevent the RPL during the pregnancy.

Limitation of the study

There are several limitations in this meta-analysis. Firstly, our systematic review and meta-analysis was based on only eight RCTs, with different types of LMWHs, which may have different efficacies and safety profiles. Secondly, the ideal dosages have not known yet. There is a wide variation in the present publications for the ideal dosages of the different types of LMWHs, including fixed dosages, rising dosages as pregnancy progresses, or dosages according to the weight of women. Therefore, more RCTs with large sample sizes are needed to find out whether different dosages affect outcomes and the ideal dosages for women with RPL through subgroups. Thirdly, the characteristics of the participants enrolled into each study were different, such as age, the beginning and duration time of using LMWHs and the precious patients' medical histories. So far, the LMWH treatment which should be stopped at 24–48 h before delivery has been regarded as appropriate, although some reports suggested 36th week [33]. Further studies might investigate the exact time when LMWH treatment should be started and stopped. Fourthly, some studies were assessed as the unclear risk of the allocation concealment, because these studies did not mention it. However, the allocation concealment might exist in the actual situations in these studies, resulting in false high risk of bias.

Comparison with previous studies

LMWHs are noticed to have a stronger benefit for women with either congenital or acquired thrombophilias in accordance of live births, miscarriage rates and late obsterical complication rates, whereas two other trials reported it had no obviously positive effect on the prevention of RPL [34,35]. In 2019, Lin et al. published the results that the LMWH treatment had no benefits for women with RPL, which included three trials [36]. Also, another recent reports also supported that LMWH treatment had no substantial benefits in women with RPL [27]. However, in contrast to our systematic review and meta-analysis, the treatment with LMWHs has a significant improvement in the live births and reduction in the rate of miscarriages in compared with control groups.

As we know, this might be the first meta-analysis to conclude that LMWHs could improve the live births and reduce the miscarriage rates.

Conclusions

According to current evidences and results, it shows that the LMWH therapy may indeed increase the live births and decrease the miscarriage rates in patients with RPL compared with control groups. Also, most of the recent RCTs confirmed the safety and efficacies of the LMWH treatment in patients with RPL. In summary, our findings show LMWHs may have an advantage for pregnant women with RPL, and these results suggest that LMWH therapy might be a good treatment choice for women with unexplained RPL. However, because of the small sample sizes of currently available publications and the limitations in this study, further more high-quality studies including multiple centers and a larger number sample sizes are required to validate the efficacies and safety of LMWHs, and to confirm the ideal dosage and duration time of LMWH therapy for women with RPL.

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Conflict of interest

The authors report no conflict of interest.

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References

[1] Larsen EC, Christiansen OB, Kolte AM, Macklon N. New insights into mechanisms behind miscarriage [J]. BMC Med 2013;11:154.
[2] Ford HB, Schust DJ. Recurrent pregnancy loss: etiology, diagnosis, and therapy [J]. Rev Obstet Gynecol 2009;2(2):76–83.
[3] Branch DW, Gibson M, Silver RM. Clinical practice. Recurrent miscarriage [J]. N Engl J Med 2010;363(18):1740–7.
[4] Jeve YB, Davies W. Evidence-based management of recurrent miscarriages [J]. J Hum Reprod Sci 2014;7(3):159–69.
[5] El Hachem H, Crepaux V, May-Panloup P, Descamps P, Legendre G, Bouet P-E. Recurrent pregnancy loss: current perspectives [J]. Int J Wom Health 2017;ume 9:331–45.
[6] Jaffe R. First trimester utero-placental circulation: maternal-fetal interaction [J]. J Perinat Med 1998;26(3):168–74.
[7] Brenner B. Enoxaparin use in pregnancy: state of the art [J]. Womens Health (Lond) 2007;3(1):9–14.
[8] Walker ID. Arterial thromboembolism in pregnancy [J]. Best Pract Res Clin Haematol 2003;16(2):297–310.
[9] Gude NM, Roberts CT, Kalionis B, King RG. Growth and function of the normal human placenta [J]. Thromb Res 2004;114(5–6):397–407.
[10] Franklin RD, Kutteh WH. Antiphospholipid antibodies (APA) and recurrent pregnancy loss: treating a unique APA positive population [J]. Hum Reprod 2002;17(11):2981–5.
[11] Farquharson RG, Quenby S, Greaves M. Antiphospholipid syndrome in pregnancy: a randomized, controlled trial of treatment [J]. Obstet Gynecol 2002;100(3):408–13.
[12] Sugi T, Mcintyre JA. Antiphospholipid antibodies (APA) and recurrent pregnancy loss: treating a unique APA positive population [J]. Hum Reprod 2003;18(7):1553–4. author reply 4.
[13] Greer IA. Venous thromboembolism and anticoagulant therapy in pregnancy [J]. Gend Med 2005;2(Suppl A):S10–7.
[14] Fouda UM, Sayed AM, Abdou AM, Ramadan DI, Fouda IM, Zaki MM. Enoxaparin versus unfractionated heparin in the management of recurrent abortion secondary to antiphospholipid syndrome [J]. Int J Gynaecol Obstet 2011;112(3):211–5.
[15] Shaaban OM, Abbas AM, Zahran KM, Fathalla MM, Anan MA, Salman SA. Low-molecular-weight heparin for the treatment of unexplained recurrent miscarriage with negative antiphospholipid antibodies: a randomized controlled trial [J]. Clin Appl Thromb Hemost 2017;23(6):567–72.
[16] Khan ES, Basharat A, Jamil M, Ayub S, Khan MA. Preventive role of low-molecular-weight heparin in unexplained recurrent pregnancy loss [J]. S Afr J Obstet Gynaecol 2017;23(1):17.
[17] Schleussner E, Kamin G, Seliger G, Rogenhofer N, Ebner S, Toth B, et al. Low-molecular-weight heparin for women with unexplained recurrent pregnancy loss [J]. Ann Intern Med 2015;162(9):485.
[18] Dersimonian R, Laird N. Meta-analysis in clinical trials [J]. Contr Clin Trials 1986;7(3):177–88.
[19] Badawy AM, Khiary M, Sherif LS, Hassan M, Ragab A, Abdelall I. Low-molecular weight heparin in patients with recurrent early miscarriages of unknown aetiology [J]. J Obstet Gynaecol 2009;28(3):280–4.
[20] Pasquier E, Saint Martin L, Bohec C, Chauleur C, Bretelle F, Marhic G, et al. Enoxaparin for prevention of unexplained recurrent miscarriage: a multicenter randomized double-blind placebo-controlled trial [J]. Blood 2015;125(14):2200–5.
[21] Yuksel H, Kayatas S, Boza AT, Api M, Ertekin AA, Cam C. Low molecular weight heparin use in unexplained recurrent miscarriage [J]. Pak J Med Sci 2014;30(6):1232–7.
[22] Fawzy M, Shokeir T, El-Tatongy M, Warda O, El-Refaiey AA, Mosbah A. Treatment options and pregnancy outcome in women with idiopathic recurrent miscarriage: a randomized placebo-controlled study [J]. Arch Gynecol Obstet 2008;278(1):33–8.
[23] Qublan H, Amarin Z, Dabbas M, Farraj AE, Beni-Merei Z, Al-Akash H, et al. Low-molecular-weight heparin in the treatment of recurrent IVF-ET failure and thrombophilia: a prospective randomized placebo-controlled trial [J]. Hum Fertil (Camb) 2008;11(4):246–53.
[24] Brenner B, Hoffman R, Carp H, Dulitsky M, Younis J, Investigators L-E. Efficacy and safety of two doses of enoxaparin in women with thrombophilia and recurrent pregnancy loss: the LIVE-ENOX study [J]. J Thromb Haemostasis 2005;3(2):227–9.
[25] Dolitzky M, Inbal A, Segal Y, Weiss A, Brenner B, Carp H. A randomized study of thromboprophylaxis in women with unexplained consecutive recurrent miscarriages [J]. Fertil Steril 2006;86(2):362–6.
[26] Santos TDS, Ieque AL, Carvalho HC, Sell AM, Lonardoni MVC, Demarchi IG, et al. Antiphospholipid syndrome and recurrent miscarriage: a systematic review and meta-analysis [J]. J Reprod Immunol 2017;123:78–87.
[27] Liu Y, Shan N, Yuan Y, Tan B, Che P, Qi H. The efficacy of enoxaparin for recurrent abortion: a meta-analysis of randomized controlled studies [J]. J Matern Fetal Neonatal Med 2019:1–6.
[28] Rottenstreich A, Amsalem H, Kleinstern G, Kalish Y. Outcomes of threatened abortions after anticoagulation treatment to prevent recurrent pregnancy loss [J]. Reprod Biomed Online 2017;35(4):461–7.
[29] Miyata T, Maruyama K, Banno F, Neki R. Thrombophilia in East Asian countries: are there any genetic differences in these countries? [J]. Thromb J 2016;14(Suppl 1):25.
[30] Bazzan M, Donvito V. Low-molecular-weight heparin during pregnancy [J]. Thromb Res 2001;101(1):V175–86.
[31] De Jong PG, Kaandorp S, Di Nisio M, Goddijn M, Middeldorp S. Aspirin and/or heparin for women with unexplained recurrent miscarriage with or without inherited thrombophilia [J]. Cochrane Database Syst Rev 2014;7:CD004734.
[32] Monien S, Kadecki O, Baumgarten S, Salama A, Dorner T, Kiesewetter H. Use of heparin in women with early and late miscarriages with and without thrombophilia [J]. Clin Appl Thromb Hemost 2009;15(6):636–44.
[33] Martinelli I, Taioli E, Cetin I, Marinoni A, Gerosa S, Villa MV, et al. Mutations in coagulation factors in women with unexplained late fetal loss [J]. N Engl J Med 2000;343(14):1015–8.
[34] Fouda UM, Sayed AM, Abdou A-MA, Ramadan DI, Fouda IM, Zaki MM. Enoxaparin versus unfractionated heparin in the management of recurrent abortion secondary to antiphospholipid syndrome [J]. Int J Gynecol Obstet 2011;112(3):211–5.
[35] Dendrinos S, Kalogirou I, Makrakis E, Theodoridis T, Mahmound EA, Christopoulou-Cokkinou V, et al. Safety and effectiveness of tinzaparin sodium in the management of recurrent pregnancy loss [J]. Clin Exp Obstet Gynecol 2007;34(3):143–5.
[36] Lin T, Chen Y, Cheng X, Li N, Sheng X. Enoxaparin (or plus aspirin) for the prevention of recurrent miscarriage: a meta-analysis of randomized controlled studies [J]. Eur J Obstet Gynecol Reprod Biol 2019;234:53–7.