

Does low-molecular-weight heparin improve live birth rates in pregnant women with thrombophilic disorders? A systematic review

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INTRODUCTION Pregnancies in women with thrombophilia are associated with a higher risk of obstetric complications. We systematically reviewed the findings of relevant randomised controlled trials (RCTs) with the aim of investigating the effectiveness of low-molecular-weight heparins (LMWHs) in pregnant women with inherited thrombophilic disorders and its effect on the incidence of live births in these patients.

METHODS The MEDLINE-PubMed and Cochrane CENTRAL databases from 2000 to 2010 were searched using a combination of keywords, including low-molecular-weight heparin, enoxaparin, pregnancy, live birth and thrombophilia. Studies were included if they were RCTs assessing the effect of anticoagulant treatment on live birth rates in women with a history of miscarriage without apparent causes other than thrombophilic disorder. Interventions included LMWH, with or without aspirin, aspirin alone or placebo controlled for the prevention of adverse pregnancy outcome.

RESULTS 43 articles with seven RCTs were retrieved following the initial search, of which four studies had to be excluded as they assessed thromboembolic events as the final outcome (n = 1), focused on idiopathic recurrent miscarriages (n = 1), compared efficacy and safety of two doses of enoxaparin (n = 1), and examined patients with or without thrombophilic disorder (n = 1). Pooled data from the remaining three RCTs showed no significant difference in the improvement of live birth rates following LMWH interventions (p = 0.15).

CONCLUSION At present, the use of LMWH in women with inherited thrombophilia with recurrent pregnancy loss is not indicated. Large randomised placebo-controlled trials are further needed to prove the effectiveness of LMWH in these patients.

Keywords: enoxaparin, live birth, low-molecular-weight heparin, pregnancy, thrombophilia
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INTRODUCTION

Thrombophilic disorder is defined as a predisposition to thrombosis secondary to any persistent or identifiable hypercoagulable state. This can be inherited or acquired.⁽¹⁾ Thrombophilia is present in at least 15% of the population in western countries and can be identified in up to 50% of those with a history of venous thromboembolism (VTE). Protein C, protein S, factor V Leiden, antithrombin III and the prothrombin gene mutation 20210 are now the most common causes of hypercoagulability. Others include hyperhomocystinaemia, elevated factor VII and antiphospholipid syndrome (APS). There is a well-established association between antiphospholipid antibodies (aPLs) and pregnancy loss, but available data also suggests additional associations for other thrombophilias.^(2–4) At the moment, there is no strong implication that the use of low-molecular-weight heparin (LMWH) improves live birth rates in women with inherited thrombophilia.⁽⁵⁾

Systematic reviews are warranted whenever there is a substantive therapeutic question, several primary studies – perhaps with disparate findings – and substantial uncertainty. Systematic reviews supersede narrative reviews as a way of summarising research evidence that attempts to bring the same level of rigour to the review of research evidence, as should be exercised when producing that research evidence in the first place.⁽⁶⁾ In the present

systematic review, we aimed to assess whether the use of LMWH improved live birth rates in pregnant women with inherited thrombophilic disorders.

METHODS

We performed an electronic literature search using a combination of keywords, such as low-molecular-weight heparin, enoxaparin, pregnancy, live birth and thrombophilia. The MEDLINE-PubMed and Cochrane CENTRAL databases were searched from year 2000 to 2010. Using the PICOS (P: participants, I: intervention, C: comparison, O: outcome measure, S: study design) Cochrane approach, trials that randomly assigned patients to receive either a combination of LMWH with or without aspirin, aspirin alone, or placebo controlled interventions, where the final outcome was live birth rates, were included. Randomised controlled trials (RCTs) were included if they met the following criteria: (a) compared patients given LMWH, with or without aspirin, with those receiving aspirin alone or placebo; (b) inclusion criteria: women (aged ≥ 18 years), confirmed pregnancy with either two appropriately rising β -human chorionic gonadotropin 48 hours apart or positive foetal heart activity on ultrasonography, history of pregnancy loss, and at least one inherited

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thrombophilic defect (through laboratory evaluation); (c) exclusion criteria: antecedent VTE requiring anticoagulation, autoimmune diseases, pregnancy loss secondary to genetic, anatomic or hormonal aetiologies, lethal foetal defects, obstetric complications (such as pregnancy-induced hypertension, preeclampsia) and diabetes mellitus; and (d) live birth rate as the final outcome measure. The relevance of the studies retrieved from our literature searches was independently assessed by two investigators. Studies were eliminated if: (a) they were not RCTs; (b) the final outcome was not live birth rate; (c) they did not use expected comparators; or (d) they did not fulfill the inclusion and exclusion criteria. A statistician, who also provided statistical advice for the systematic review, carried out all statistical analyses.

Only one outcome measure was investigated, which was live birth rate. Secondary outcomes were not analysed, as our primary aim was to appraise the association of LMWH and live birth rates in pregnant women with inherited thrombophilias. The quality of each trial was assessed using the Cochrane review methodology.⁽⁷⁾ The assessment was based on whether there was: (a) adequate sequence generation; (b) allocation concealment; (c) blinding of the patients and outcome assessors; (d) any incomplete data reporting; and, (e) selective outcome reporting and other bias. Two assessors evaluated the risk of bias and conflicts, if any, and these were resolved by discussion. The proportion of patients who had live births was pooled for a combined relative risk (RR) assessment, which was expressed as RRs with corresponding 95% confidence interval (CI). All statistical measures were conducted using the RevMan5 software (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Visual inspection of forest plots and heterogeneity was assessed using the chi-square test and I^2 statistics. Heterogeneity of the clinical design was also assessed using the Cochrane Q test. It is likely that the result of heterogeneity yielded a low statistical power for our study due to the small number of trials included in our systematic review.⁽⁸⁾ I^2 statistics obtained described the percentage of total variation across studies caused by heterogeneity rather than chance. A high I^2 value suggested increased heterogeneity. The random effects model was assumed due to considerable heterogeneity among different trials.

RESULTS

A total of 43 articles were identified through electronic database searches. In stage 1, 36 clinical trials were excluded due to the following reasons: clinical trials not apparently assessing live birth rate ($n = 8$); trials assessing patients with APS ($n = 4$); observational studies ($n = 10$); irrelevant trials ($n = 12$); and other non-related reviews ($n = 2$). In stage 2, a further four RCTs were excluded as the final outcome assessed was thromboembolic event ($n = 1$),⁽⁹⁾ the outcomes of idiopathic recurrent miscarriages were investigated ($n = 1$),⁽¹⁰⁾ the efficacy and safety of two doses of enoxaparin in APS were compared ($n = 1$),⁽¹¹⁾ and patients with or without thrombophilic disorder were examined ($n = 1$).⁽¹²⁾ Finally, only three RCTs published between 2004 and 2009 were

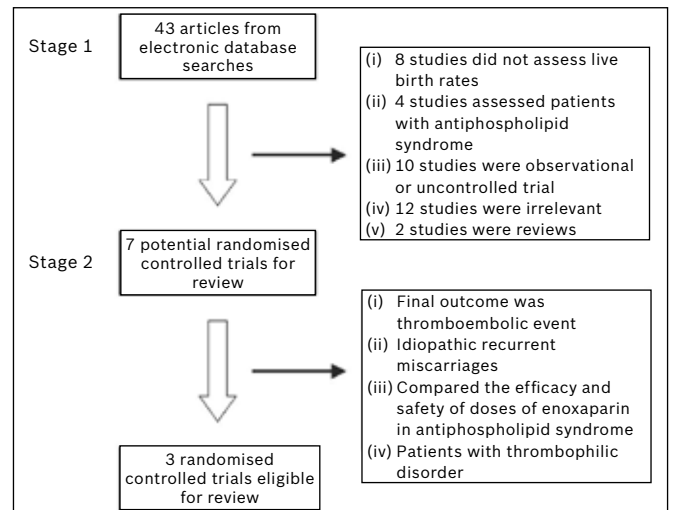


Fig. 1 Results of the literature search.

included in our final systematic review. The literature search is summarised in Fig. 1.

Among the 331 patients involved in these trials, 122 women received LMWH alone, 45 received LMWH and aspirin, 123 received aspirin alone, and 41 were assigned for placebo interventions. Participants were all aged ≥ 18 years, with varying mean ages (26 years⁽¹³⁾, 29 years⁽¹⁴⁾ and 33.8 years⁽¹⁵⁾) among the three studies (Table 1). All participants had at least one or more miscarriages, with a known thrombophilic disorder. An analysis was performed to show the low risk of bias in the assessment of these three RCTs (Fig. 2).

In the study by Qublan et al in 2008, which compared the use of LMWH ($n = 42$) with placebo ($n = 41$) in patients, the number of live births were ten (23.8%) and one (2.4%), respectively, in these two groups of patients, so that results were in favour of LMWH (RR 9.76, 95% CI 1.31–72.86) (Fig. 3). There was a statistically significant increase (21.4%) in live birth rates for patients who were given LMWH.⁽¹⁴⁾ Gris et al in 2004 compared the use of LMWH ($n = 80$) with aspirin ($n = 80$) in women with recurrent *in vitro* fertilisation (IVF) treatment failures and found that the live birth rates were 69 (86.3%) and 23 (28.8%), respectively, in these two groups of patients (RR 3.0, 95% CI 2.10–4.28), with a difference of 57.5%. The increase in live birth rates with the use of LMWH was statistically significant compared to aspirin ($p < 0.00001$).⁽¹³⁾ Interestingly, Laskin et al, in their study of 2009, found no statistically significant difference between two groups of patients receiving LMWH with aspirin ($n = 45$) and aspirin alone ($n = 44$). The number of live births achieved among patients given LMWH with aspirin was 35 (77.8%), while that in the group receiving aspirin alone was 34 (77.3%) (RR 1.01, 95% CI 0.80–1.26).⁽¹⁵⁾

In total, there were 114 (68.3%) live births among patients given LMWH ($n = 167$), and 58 (35.2%) live births in the control groups that did not involve the use of any LMWH ($n = 165$). An apparent increase of 33.1% in live births within the LMWH group was noticed when compared to the control group. However, analysis of the overall pooled data demonstrated no significant difference between the two groups of patients in terms of live birth

Table I. Clinical design of the three studies selected from our literature search.

Reference (yr)	Country/patient no./study design	Patient age (yr)*	Inclusion criteria	Exclusion criteria	Experimental/ eligible comparator	Controlled comparator	Primary outcome
Gris et al ⁽¹³⁾ (2004)	France/160/RCT	26.0 ± 6.4 (18–36)	One or more unexplained pregnancy loss and thrombophilic disorder	Autoimmune disease (immune thrombocytopenic purpura, foetomaternal alloimmune thrombocytopenia), genetic or anatomical anomaly, thyroid disease, thrombocytopenia, antecedent venous thromboembolism, any lethal foetal defect, pregnancy-induced hypertension, diabetes mellitus	Subcutaneous injection of 40 mg LMWH abdominally, administered daily at 8.00 pm, began at the eighth week of amenorrhoea	Aspirin ingestion 100 mg at 8.00 pm daily, began at the eighth week of amenorrhoea	Live birth rate
Qublan et al ⁽¹⁴⁾ (2008)	Jordan/83/RCT	29.0 ± 6.3 (19–35)	Three or more failed <i>in vitro</i> fertilisations, at least one thrombophilic defect	Chronic disease (liver, renal), thyroid disease, abnormal uterine cavity, thrombocytopenia, history of thrombosis, heparin therapy contraindication, polycystic ovary syndrome, endometriosis	Received LMWH 40 mg/day subcutaneous injection, started from the day of embryo transfer	Received placebo (equivalent volume of 0.9% sodium chloride) subcutaneous injection, started from the day of embryo transfer	Live birth rate
Laskin et al ⁽¹⁵⁾ (2009)	Canada/88/RCT	33.8 ± 4.1 (18–44)	Two or more unexplained consecutive pregnancy losses, presence of at least antinuclear antibody, antiphospholipid antibody or inherited thrombophilia	Systemic lupus erythematosus, sensitivity to aspirin/heparin, platelet dysfunction, previous thromboembolic event, genetic/anatomic or hormonal aetiologies	Subcutaneous once daily LMWH 5,000 IU/day and 81 mg enteric coated aspirin	81 mg enteric coated aspirin	Live birth rate

*Data is presented as mean ± SD (range).

LMWH: low-molecular-weight heparin; RCT: randomised controlled trial; SD: standard deviation



Fig. 2 Summary of risk of bias assessment.

rates, in spite of results favouring the LMWH group (RR 2.40, 95% CI 0.73–7.83).

DISCUSSION

The present standard of care for women with aPLs (including anticardiolipin and lupus anticoagulant), with recurrent pregnancy loss, is treatment with heparin and aspirin.^(16–20) This standard has evolved since the late 1990s based on a series of case-control

studies performed after an initial report by Sanson et al in 1996⁽²¹⁾ that thrombophilic disorders in pregnant women are associated with an increased risk of foetal loss before or after 22 weeks of gestation. The precise pathophysiological mechanism by which thrombophilic factors induce implantation failure with subsequent early pregnancy loss remains unclear, although various authors have put forward varying accounts over the years. Researchers have suggested that impaired initial vascularisation, which is characterised by the abnormal invasion of maternal blood vessels by the syncytiotrophoblast, may be influenced by microthrombosis at the site of implantation, leading to implantation failure and consequently, pregnancy loss in such women.^(22–25) Others have proposed that such thrombophilias may disrupt trophoblast functions, including invasion, cellular differentiation with proliferation as well as hormonal activity.^(26–28) Recently, Kwak-Kim et al have considered an immune-mediated response where these thrombophilic factors have a direct stimulatory effect on implantation in investigatory works on women with IVF and embryo transfer (IVF-ET) treatment failures.⁽²⁹⁾ These authors have suggested that intracellular T-helper 1 (Th1) cytokine expression is increased over the ratio

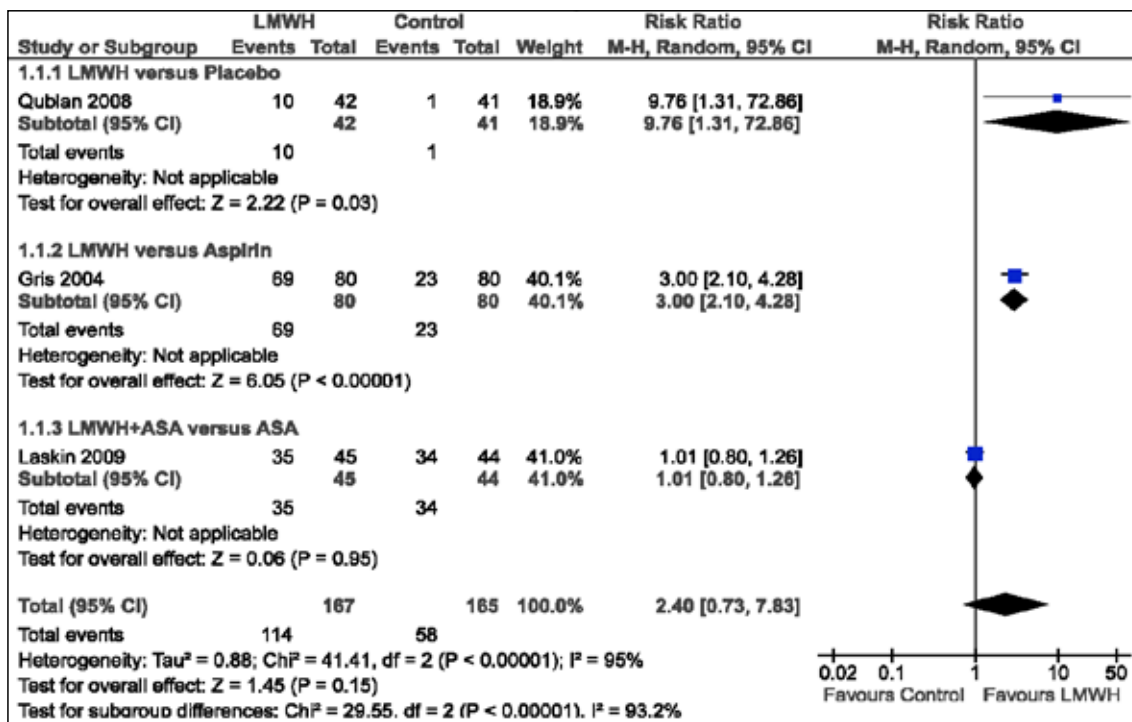


Fig. 3 Forest plots of the three studies selected from our literature search.

CI: confidence interval; LMWH: low-molecular-weight heparin; M-H: Mantel-Haenszel risk ratios

of T-helper 2 (Th2) cytokine expression in women with multiple implantation failures after IVF-ET treatment cycles.

In conjunction with the discovery of various possible pathophysiological mechanisms being involved in pregnant women with known thrombophilias, multiple modalities of treatment with variable success rates have evolved over the years, which have included glucocorticosteroids, aspirin and immunoglobulins.^(30,31) The use of LMWHs for thromboprophylaxis and the treatment of VTEs in pregnancy was reascertained to be safe and effective by Greer and Nelson-Piercy in 2005.⁽³²⁾ Nonetheless, despite the vast amount of information and evidence available on the benefits of LMWHs in pregnant women with acquired thrombophilias, the relationship between inherited thrombophilias and recurrent pregnancy loss remains elusive, and the limited evidence supporting the various treatments proposed, including the use of LMWHs, in these patients continues to be inadequate.⁽³³⁾

Our study therefore aimed to re-examine the data and evidence available in the literature on the potential benefits of using LMWHs in pregnant women with at least one inherited thrombophilia and a previous history of pregnancy loss. Women with known aPLs, genetic or anatomical defects, autoimmune conditions (such as systemic lupus erythematosus), and previous VTE events on anticoagulation were excluded from our study. Risk of bias and heterogeneity assessments were employed in our analysis to minimise any potential confounders. A systematic search was carried out using various pertinent keywords on MEDLINE and Cochrane CENTRAL databases, which elicited a total of 43 related studies. After a two-stage review, three relevant RCTs that adhered strictly to our eligibility criteria were selected for further detailed analysis.

RR, which was employed to gather summary statistics, revealed that the live birth rates in women given LMWH was 9.76 times higher than those on placebo in the Qublan study (RR 9.76, 95% CI 1.31–72.86; $p = 0.03$), which was indeed statistically significant.⁽¹⁴⁾ Gris et al also found that there was a statistically significant increase in the live birth rates of women on LMWH as compared to patients given aspirin alone (RR 3.0, 95% CI 2.10–4.28; $p < 0.00001$).⁽¹³⁾ Both these studies favoured the use of LMWH in pregnant women with inherited thrombophilias over control interventions (placebo and aspirin) for the purpose of achieving a higher live birth rate.

Laskin et al, on the other hand, found that the live birth rates in women given LMWH in combination with aspirin did not improve significantly when compared to women who received aspirin alone (RR 1.01, 95% CI 0.8–1.26; $p = 0.95$).⁽¹⁵⁾ Such a comparison was also aimed to indirectly measure the effect of LMWH. The findings of this study were consistent with those of two other reports by Spitzer et al⁽³⁴⁾ and Kovalevsky et al,⁽³⁵⁾ which also did not find any statistically valid difference in treatment efficacy.

Although the present literature suggests a much higher incidence of inherited thrombophilias in women with recurrent pregnancy loss than previously reported figures,⁽³⁴⁾ one of the commonest difficulties encountered by researchers was the recruitment of patients with recurrent pregnancy losses who had been diagnosed with inherited thrombophilias into individual clinical trials. Small sample sizes were also a weakness for many such studies, as it affected the generation of good quality statistical results. This was a factor impacting the fidelity of the pooled data in our study, too. Some investigators remained uncomfortable with the inclusion of an aspirin or placebo-only treatment arm in

their trials, as they felt it to be ethically inappropriate to withhold heparin treatment from these women, although evidence of the benefit of such treatment was limited.

Overall, out of a total of 332 women in the three RCTs selected, the live birth rates for patients given LMWH either alone or together with aspirin centred around 68.26% (114/167), whereas the pooled live birth in the control group (who were given only placebo or aspirin alone) was 35.15% (58/165). However, in spite of results favouring treatment with LMWH in these studies (RR 2.40, 95% CI 0.73–7.83), the difference in birth rates between the two patient groups was not statistically significant ($p = 0.15$). Our results highlight that there remains a dearth of conclusive evidence supporting the use of LMWH in pregnant women with inherited thrombophilias in terms of improved live birth rates from such an intervention, although there is convincing proof of the benefit of using LMWH in women with acquired thrombophilias (such as APS). Nevertheless, the findings of this study add to the growing body of research on the management of inherited thrombophilias in pregnancy.

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