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Review article

Evaluation of therapeutic efficacy of anticoagulant drugs for patients with venous thromboembolism during pregnancy: A systematic review and meta-analysis

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ABSTRACT

A meta-analysis based on published literature was undertaken to evaluate the efficacy of anticoagulant drugs for the treatment of venous thromboembolism during pregnancy. PubMed, Cochrane and Embase databases were searched from inception to September 2018 for relevant studies using indexed words, including qualified case–control and cohort studies. The meta-analysis used odds ratios (OR) and 95% confidence intervals (95% CI) to analyse the primary results. Nine studies were included in this meta-analysis, with a total of 834 cases and 3424 controls. There were no significant differences in the incidence of prenatal haemorrhage (OR 1.08, 95% CI 0.84–1.40), venous thromboembolism (OR 1.30, 95% CI 0.72–2.33) or caesarean section (OR 1.16, 95% CI 0.69–1.98) between the case group and the control group. The incidence of pulmonary embolism was significantly higher in the case group than in the control group (OR 3.90, 95% CI 1.23–12.34). However, there were a few limitations that may have influenced the results, so more randomized double-blind controlled studies of high quality are warranted to confirm the efficacy of anticoagulant therapy for venous thromboembolism in pregnancy.

Contents

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Introduction

During pregnancy, women are at higher risk of both arterial thrombosis and venous thrombosis (three to four times higher risk and four to five times higher risk, respectively). Moreover, the risk of postpartum thrombosis can be 20 times higher. It has been reported that the overall morbidity of thrombosis is approximately 0.2% (20% arterial thrombosis, 80% venous thrombosis). The mortality of venous thrombosis is approximately 1.1 per 10^5 cases, accounting for 10% of maternal deaths. In cases of venous thromboembolism (VTE), deep vein thrombosis (DVT) accounts for approximately 80% and pulmonary embolism (PE) accounts for the remaining 20% [1–4]. The main reason for the increased risk of thrombosis in pregnant women is hypercoagulability, which protects pregnant women from the risk of bleeding during miscarriage and childbirth. In Western Europe and the USA, where haemorrhage is often successfully treated and prevented, VTE is one of the leading causes of death. The reported mortality rate in the UK is 1.56 per 10^5 cases. Symptomatic VTE is estimated to occur in five to 12 cases per 10,000 pregnant women ante partum, and three to seven cases per 10,000 pregnant women post partum [5,6].

The health and safety of the mother and fetus can be influenced by anticoagulant therapy. Vitamin K antagonists and warfarin are often used for long-term anticoagulation in non-pregnant females, but as they can cross the placenta and may cause bleeding and teratogenicity in the fetus, heparin is the preferred anticoagulant during pregnancy. Normal heparin and low-molecular-weight heparin (LMWH) are unable to cross the placenta, and are safe for use during pregnancy. The characteristics of anticoagulation during pregnancy are included as follows: the enlargement of the maternal blood volume, the increased distribution volume and the glomerular filtration rate, increased removal rate of heparin through the kidney with the increased combination of heparin and protein. The half-life and peak concentration of normal heparin and LMWH in blood are reduced during pregnancy. Therefore, a higher dosage and more frequent adjustments are required. The disadvantages of using normal heparin are as follows: non-oral, bleeding complications, osteoporosis, vertebral fracture and heparin-induced thrombocytopenia (HIT). The incidence of HIT is lower in pregnant women than in non-pregnant women; more studies are needed to confirm the current findings for specific pathology. However, several comparative studies of pregnancy have been undertaken, and found that LMWH has fewer side effects than normal heparin in normal patients. The advantages of LMWH include low incidence of bleeding and secondary thrombocytopenia, less bone loss, long half-life and favourable outcomes [2,7,8].

This meta-analysis based on published literature was undertaken to evaluate the efficacy of anticoagulant drugs for the treatment of venous thromboembolism during pregnancy.

Methods

Search strategy

The following electronic databases were searched from their inception to September 2018 for all case–control and cohort studies on anticoagulant therapy during pregnancy: Cochrane, PubMed and Embase. Reference lists from identified papers were also checked, and internet searching was performed. Two investigators extracted data independently, and differences were settled by discussion with a third reviewer.

Study selection

Inclusion criteria were: (1) case–control or cohort study; (2) therapeutic therapy was used in the case group and prophylactic therapy was used in the control group; (3) outcomes included bleeding events, VTE, PE and CS; and (4) English-language publication.

Exclusion criteria were: (1) repeat publications or publications that shared content and results; (2) outcomes were not relevant for the analyses; and (3) case report, theoretical research, conference report, systematic review, meta-analysis or expert comment.

Data extraction and quality assessment

Two reviewers extracted data independently based on predefined criteria. Differences were settled by discussion with a third reviewer. Data were extracted from all included studies and consisted of two parts: basic information and main outcomes. Authors' names, design, detailed treatment for both groups, sample size and mean age were extracted as basic information. Clinical outcomes, including the incidence of bleeding events, VTE, PE and CS, were analysed for both groups.

Statistical analysis

All statistical analyses were performed using STATA 10.0 (Stata Corp., College Station, TX, USA). Chi-squared and I^2 tests were used to assess the statistical heterogeneity of clinical trial results, and to determine the analysis model (fixed-effects model or random-effects model). Heterogeneity was acceptable when $p < 0.05$ on Chi-squared test and $I^2 > 50\%$ on random-effects model. Data were defined as homogeneous when $p > 0.05$ on Chi-squared test and $I^2 < 50\%$ on fixed-effects model. Continuous variables were expressed as mean ± standard deviation and analysed by mean difference, and categorical data were calculated as percentages and analysed by relative risk or odds ratio (OR). All results were analysed by OR and 95% confidence intervals (CI).

Results

Literature search and study characteristics

In total, 1173 articles were identified. Of these, 1127 articles were excluded during the preliminary screening of titles or abstracts, leaving 46 articles for further selection. After full-text screening, 37 articles were excluded for the following reasons: no clinical outcomes ($n = 21$), unqualified grouping ($n = 9$) and theoretical research ($n = 7$). Nine studies [9–17] were included in the meta-analysis, with a total of 834 cases and 3424 controls. The selection process is presented in Fig. 1. The main characteristics of all included studies are summarized in Table 1. Of the nine studies included in this review, eight had a case–control design and one was a cohort study. LMWH was used in five studies, tinzaparin was

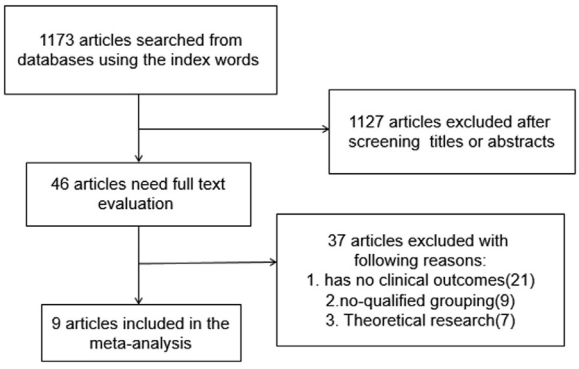

Fig. 1. Flow diagram of the literature search and selection process.

Table 1
Basic characteristics of included studies.

Study	Design	Treatment		No. of patients		Age (years)	
		Case group	Control group	Case group	Control group	Case group	Control group
Aburahma [9]	Case–control	Conventional full-dose intravenous heparin therapy for 5–10 days, followed by subcutaneous low-dose heparin until labour, continued for 6 weeks post partum	Same low-dose subcutaneous heparin regimen	15	11	24	
Blanco-Molina [10]	Case–control	LMWH, initial therapy 187 IU/kg/day, long-term therapy 173 IU/kg/day for 3 months	LMWH, initial therapy 185 IU/kg/day, long-term therapy 180 IU/kg/day for 3 months	154	693	31	32
Blanco-Molina [10]	Case–control	LMWH, initial therapy 181 IU/kg/day, long-term therapy 171 IU/kg/day for 3 months	LMWH, initial therapy 185 IU/kg/day, long-term therapy 180 IU/kg/day for 3 months	119	693	32	32
Donnelly [11]	Case–control	Therapeutic LMWH, 175 IU/kg	Prophylactic LMWH, 75 IU/kg	38	85	30.4	31.7
Nelson-Piercy [13]	Case–control	Tinzaparin as treatment, median dose 13,000 IU/day, median duration 72 days	Tinzaparin as prophylaxis, median dose 4500 IU/day, median duration 183 days	254	1013	30.1	31
Roshani [14]	Retrospective cohort study	LMWH treatment during pregnancy, dose based on body weight	Did not use LMWH during pregnancy	95	524	32	31
Rowan [15]	Case–control	Subcutaneous enoxaparin, 1 mg/kg twice daily	Subcutaneous enoxaparin, 40 mg daily	32	26	30.1	
Ulander [16]	Case–control	LMWH for 2 weeks, dose was gradually decreased and kept at a high dose until delivery	Unfractionated heparin (25,430 IU/day, mean) for 7 days	21	10	31.6	31
Narin [12]	Case–control	Enoxaparin therapy, 1 mg/kg twice per day	Enoxaparin therapy, 1.5 mg/kg once per day	18	17	28.4	30
Knol [17]	Case–control	Nadroparin, 175 IU/kg/day	Did not use LMWH or another anticoagulant during pregnancy	88	352	30	32

LMWH, low-molecular-weight heparin.

used in one study, enoxaparin was used in two studies and nadroparin was used in one study.

Antepartum bleeding events

Seven studies with a total of 4042 participants (case group = 746, control group = 3296) reported the incidence of all antepartum bleeding events. Based on the *p*-value from Chi-squared test of 0.412 and I^2 of 1.7%, a fixed-effects model was used to analyse the results. The pooled results showed that there was no significant difference in the incidence of antepartum bleeding events between the two groups (OR 1.08, 95% CI 0.84–1.40, Fig. 2).

Venous thromboembolism

Eight studies with a total of 3485 participants (case group = 680, control group = 2805) reported the incidence of VTE. Based on the *p*-value from Chi-squared test of 0.225 and I^2 of 26.7%, a random-effects model was used to analyse the results. The pooled results showed that there was no significant difference in the incidence of VTE between the two groups (OR 1.30, 95% CI 0.72–2.33, Fig. 3).

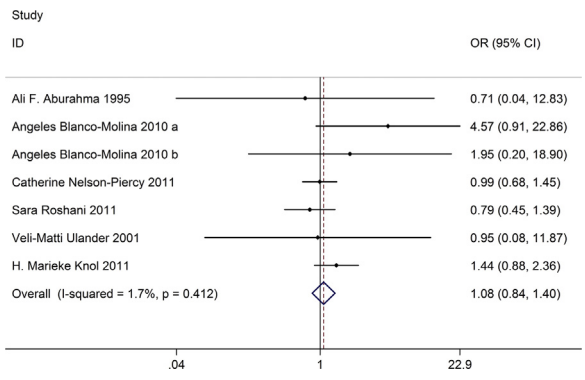

Fig. 2. Forest plot showing the incidence of all antepartum bleeding events. OR, odds ratio; CI, confidence interval.

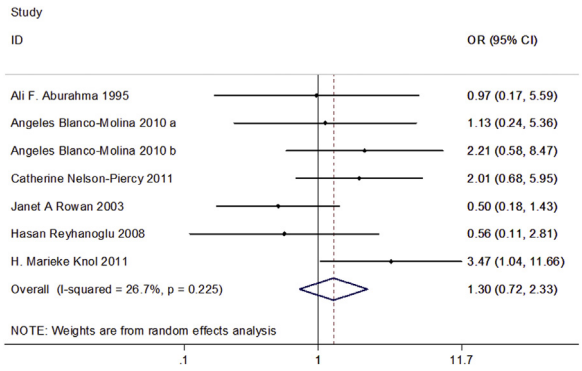

Fig. 3. Forest plot showing the incidence of venous thromboembolism during pregnancy. OR, odds ratio; CI, confidence interval.

Pulmonary embolism

Three studies with a total of 2926 participants (case group = 527, control group = 2399) reported an association between VTE exposure and risk of PE incidence. Based on the *p*-value from Chi-squared test of 0.436 and I^2 of 0.0%, a fixed-effects model was used to analyse the results. The pooled results showed that the incidence of PE was significantly higher in the case group compared with the control group (OR 3.90, 95% CI 1.23–12.34, Fig. 4).

Caesarean section

Seven studies with a total of 2573 participants (case group = 546, control group = 2027) reported an association between VTE exposure and risk of PE incidence. Based on the *p*-value from Chi-squared test of 0.010 and I^2 of 64.2%, a random-effects model was

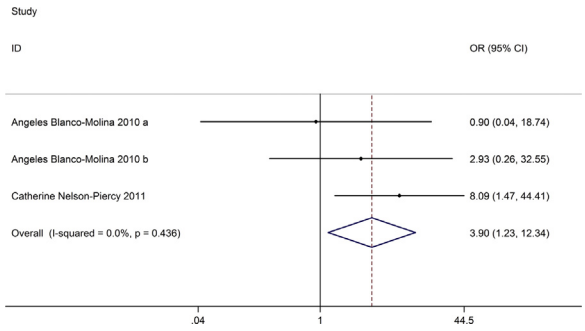

Fig. 4. Forest plot showing the incidence of pulmonary embolism during pregnancy. OR, odds ratio; CI, confidence interval.

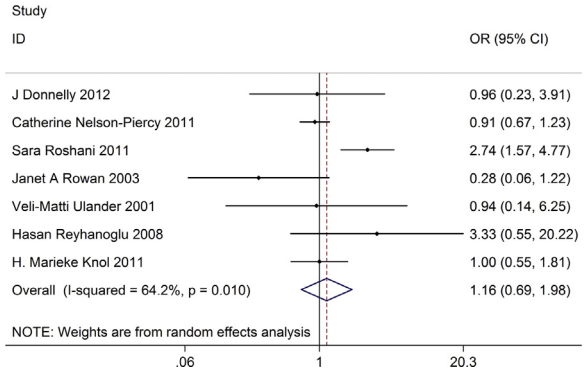

Fig. 5. Forest plot showing the incidence of caesarean section. OR, odds ratio; CI, confidence interval.

used to analyse the results. The pooled results showed that there was no significant difference in the incidence of CS between the two groups (OR 1.16, 95% CI 0.69–1.98, Fig. 5).

Quality assessment and potential bias

Based on the mentioned criteria, 21 articles were included in the meta-analysis. Study quality and potential bias were assessed using funnel plots, Begg and Mazumdar's rank test and Egger's test. The funnel plot for log OR in traffic density of included studies was notably symmetrical, suggesting no significant publication bias (Fig. 6). Furthermore, significant symmetry was found using Begg and Mazumdar's rank test ($Z = 0.90$, $p = 0.368$). Egger's test also showed that there was no significant publication bias ($p = 0.058$).

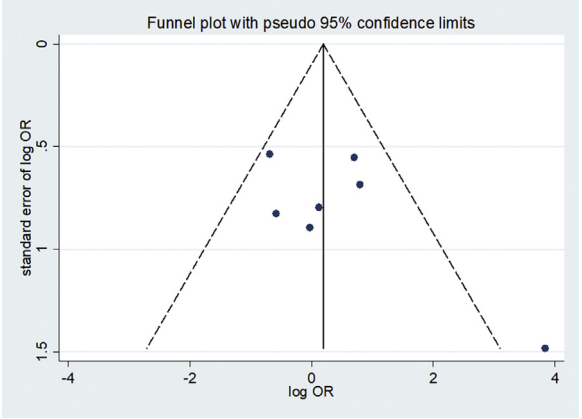

Fig. 6. Funnel plot of studies included in the meta-analysis. OR, odds ratio.

Discussion

Many studies have shown similar meta-analyses. Romualdi et al. [18] reported on eight studies with a total of 981 patients with acute VTE in pregnancy. Of these, 822 patients were treated with LMWH, and the remaining patients received unfractionated heparin therapy. Anticoagulant therapy was associated with 1.41% and 1.90% of white matter injury (WMI) within 24 h of postpartum haemorrhage. The estimated WMI for recurrent VTE during pregnancy was 1.97%. Anticoagulant therapy may be a safe and effective treatment for pregnancy-related VTE, but the optimal dosing regimen remains uncertain. Greer and Nelson-Piercy [19] evaluated the safety and efficacy of LMWH for thromboprophylaxis and VTE treatment during pregnancy. VTE and arterial thrombosis (associated with antiphospholipid syndrome) were reported in 0.86% and 0.50% of pregnancies, respectively. The incidence of significant bleeding associated with obstetric causes was 1.98%, the allergic skin reaction was 1.80%, and the incidence of heparin-induced thrombocytopenia was 1.98%, and 0.04% for osteoporotic fracture. Overall, 94.7% of pregnant women reported having live births, including 85.4% of those who received LMWH for repeated pregnancy loss. LMWH is safe and effective in preventing VTE during pregnanacy.

Evaluating the effect of treating DVT during pregnancy may be problematic, especially in cases of PE. Pulmonary and spiral computed tomography scans of asymptomatic women are considered to be unethical, and the use of D-dimer measurements during pregnancy gives unreliable results [20]. Clinical suspicion of PE during pregnancy is rarely confirmed radiologically, unlike ectopic pregnancy. However, considering that PE is the most common cause of maternal death in pregnant women [21,22], radiology should be used to examine all clinically suspected cases. In this study, PE was suspected in three patients, but lung scans showed negative results. Most cases of DVT in this study were proximal and left, and the area was more prone to embolism. The therapeutic effect can be assessed based on the patient's post-thrombotic symptoms and the patency of thrombosis. DVT during pregnancy is often large and proximal, so the risk of chronic venous insufficiency or post-thrombotic syndrome may be higher than in non-pregnant women [23,24].

This study had a few limitations, as follows. Only case–control and cohort studies were included, and there were differences in the inclusion criteria and exclusion criteria for these studies. The pregnant women included in these studies had various VTE histories and health conditions. All of the studies included in this review were published in English, which may represent a source of bias. The studies used different types and doses of anticoagulant therapy drugs. Finally, pooled data were used for analysis, and data for individual patients were unavailable. Considering all of these limitations, more high-quality studies are needed to confirm the current findings.

In conclusion, this systematic review and meta-analysis was performed to estimate the efficacy of anticoagulants for VTE therapy during pregnancy. The results suggested that there was no significant difference in the incidence of antepartum bleeding events, VTE and CS between cases and controls, but there were a few limitations that may have influenced the results. Thus, more randomized double-blind controlled studies of high quality are warranted to confirm the efficacy of anticoagulant therapy for VTE in pregnancy.

Conflict of interest

None declared.

Funding

None.

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