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A scoping review of venous thromboembolism and antithrombotic therapy in pregnancy

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***Abstract*---**Introduction: Venous thromboembolism (VTE) is a known factor implicated in maternal mortality. Low molecular weight heparin (LMWH) and unfractionated heparin (UFH) are being widely used in cases of VTE. However, the efficiency of both of these drugs in the treatment of VTE is limited. Hence, a scoping review was conducted to understand the role of these drugs in the case of VTE. Methodology: The studies that included either the VTE or pulmonary embolism (PE) or both, and the studies that used the intervention of either the LMWH or UHF or both were selected. Case-control or cohort studies were included. The studies that were case-reports or with a sample of <10 were excluded. Results: Fifteen studies included 819 subjects with acute VTE. A total of 506 deep venous thrombosis (DVTs) and 127 PEs were reported in these studies. A total of 656 individuals received LMWH and 150 received UFH. There were 21 cases of antenatal bleeding and 259 cases of peri and post-delivery bleeding. UFH was given intravenously and subcutaneously in accordance with activated partial thromboplastin time results. Fifteen recurrent VTEs: four were DVTs and 11 were PEs (one death). Conclusion: The

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anticoagulant medication has an acceptable safety profile and is helpful in preventing recurrent VTE in pregnant women. Most problems, including bleeding, occur during the first week of treatment. Anticoagulant drugs appear to be both effective and safe for treating VTE caused by pregnancy, but the best dosage regimens are still unknown.

***Keywords*---**venous thromboembolism, pregnancy, anticoagulants, fetal death, thrombolytic.

Introduction

Around 5–12 women per 10,000 antepartum pregnancies and three to seven women per 10,000 postpartum deliveries experience symptomatic "venous thromboembolism (VTE)." VTE risk increases five times during pregnancy and puerperium compared to the general female population of childbearing age (Jullien, 2021; Potgieter, Becker, & Suleman, 2022; "Saving Mothers' Lives: Reviewing Maternal Deaths to Make Motherhood Safer: 2006-2008," 2011; Shahrook, Hanada, Sawada, Ota, & Mori, 2014; Skeith, 2021). Due to the need to consider the safety of the chosen medications for both the mother and the fetus, treating VTE in pregnant women presents some unique complications. Vitamin K antagonists can result in fetal haemorrhage and teratogenicity because they pass through the placenta (Shahrook, Ota, Hanada, Sawada, & Mori, 2018). "Heparin-associated osteoporosis" and "heparin-induced thrombocytopenia (HIT)" are the chief maternal safety concerns that may be linked to the use of "unfractionated heparin (UFH)." This drug is commonly used for the treatment of VTE, which does not cross the placenta and does not result in fetal teratogenicity (Blondon & Skeith, 2022; Gates, Brocklehurst, & Davis, 2002; Greer, 2005; Huang, Li, Li, & Liao, 2022). Additionally, "activated partial thromboplastin time (APTT)" should be monitored when UFH is administered. "Low molecular weight heparin (LMWH)" has similar actions to that of UFH and is as safe as it (Gassmann et al., 2021; Papadakis et al., 2019; Solari & Varacallo, 2022). LMWH is considered superior with regard to the UHF in many features, like predictable dosage response, greater plasma half-life, and better bioavailability. LMWH is therefore being widely used in cases of acute VTE (Lowry et al., 2019; Papadakis et al., 2019; Raia-Barjat, Edebiri, & Chauleur, 2022; Solari & Varacallo, 2022; Stanciakova et al., 2022; Wu et al., 2022). However, the efficiency of both of these drugs in the treatment of VTE is from studies that have limitations. A few are case studies, while a few are case-control series. Some have described the implications of these drugs in specific conditions, like precious pregnancies. There is a scarcity of data on the choice of the treatment or drug for the cases of the VTE. Hence, a scoping review was conducted to understand the role of these drugs in the case of VTE.

Methodology

Prior definitions were made for the specific goals, selection criteria, methodology, outcomes, and statistical methodologies.

Literature search

Electronic databases were used to select studies like “PubMed”, “Medline”, “Google Scholar”, “Embase”, and “Scopus”. The following keywords were used in the search strategy: "Venous Thrombosis," "Pulmonary Embolism," "Pregnancy," "Therapy," and "Treatment."

Selection of the studies

The studies that were published between the years 2010 and 2022 were selected. English as well as other languages were also selected for inclusion criteria (Higgins, 2011). These were translated using the translation applications. Studies were included if they provided information about the episodes of VTE in the antepartum or after delivery. Two independent reviewers were chosen for the selection of the studies, and any disputes were settled by discussion. The studies that included either the VTE or pulmonary embolism (PE) or both, and the studies that used the intervention of either the LMWH or UHF or both were selected. Case-control or cohort studies were incorporated. The studies that were case-reports or with a sample of <10 were excluded. The studies that included subjects with any specific medical conditions were also excluded.

Extraction of data

The following parameters were studied in all the included studies: “demographics; type of the study design; study characteristics (year of publication, design, and study centre); number of study subjects; number of deep venous thrombosis (DVT) and PE events; medications and treatment regimens used for acute treatment; medications and treatment regimens used for long-term treatment; hemorrhagic events occurring both antepartum and postpartum; and recurrent VTE events occurring both antepartum and postpartum.” The first week of anticoagulant treatment was referred to as the acute treatment phase, and the remaining treatment time was referred to as the long-term treatment time. The data that was collected is represented in tabular form for interpretation.

Results

Article screening

Initially, 1150 articles were found using the search approach, of which 550 articles were excluded as duplicates. Following that, 450 items were discarded based on the selection criteria, leaving only 150 articles. A total of 15 studies (Aburahma & Boland, 1999; Bahlmann et al., 2000; Blanco-Molina et al., 2010; Clark, Delate, Witt, Parker, & McDuffie, 2009; Daskalakis, Antsaklis, Papageorgiou, & Michalas, 1997; Donnelly, Byrne, Murphy, & McAuliffe, 2012; Jacobsen, 2003; Narin et al., 2008; Nelson-Piercy et al., 2011; O’Connor et al., 2011; Rodie, 2002; Roshani et al., 2011; Rowan, McLintock, Taylor, & North, 2003; Ulander, Stenqvist, & Kaaja, 2002; Voke, Keidan, Pavord, Spencer, & Hunt, 2007) were included in this review. Figure 1 depicts the research flowchart and the identification process schematically.

Observations made in the finalised studies

There were a total of 819 subjects that were included in these studies. Their ages ranged from 17 to 43 years old. There were 506 DVTs and 127 PEs in total among the 13 studies that were chosen, which included a total of 632 patients (Aburahma & Boland, 1999; Bahlmann et al., 2000; Blanco-Molina et al., 2010; Daskalakis et al., 1997; Donnelly et al., 2012; Jacobsen, 2003; Narin et al., 2008; Rodie, 2002; Roshani et al., 2011; Ulander et al., 2002; Voke et al., 2007) (Table 1). In some studies, the start of VTE during pregnancy was not mentioned. This covered the seventh through the 38th week of gestation, depending on what was available. For the acute phase of VTE treatment, 656 individuals received LMWH and 150 received UFH. None of the articles describing the use of fondaparinux in patients matched our selection criteria. The dosage schedules of LMWH varied between studies. Most of the time, but not always, UFH was given intravenously and subcutaneously in accordance with APTT results (Table 2).

The long-term treatment phase summary is depicted in Table 3. LMWH replaced UFH in all the studies. Subjects were initially kept on UFH, typically administered subcutaneously. In one study, four individuals who had been receiving LMWH were transferred to UFH in the final trimester (Voke et al., 2007). The studies' follow-up periods varied in length, and in other cases they weren't even mentioned. In one study, the first three months following a VTE diagnosis were the only time period for follow-up in one study (Blanco-Molina et al., 2010). The length of the treatment period was inconclusive in the studies.

Bleeding complications during pregnancy

In total, 21 bleeding incidents involving a total of 819 patients during the antepartum period were documented. Overall, the authors classified 16 occurrences as minor, six as unclassified, one as clinically significant non-major, and five as major (Nelson-Piercy et al., 2011; O'Connor et al., 2011). Four of the five large bleeds occurred during the acute period of treatment, whereas there was only one clinically relevant non-major haemorrhage that occurred after two weeks of treatment (Narin et al., 2008). Patients who got LMWH experienced two of the four significant bleeds that occurred during the acute period of treatment, whereas patients who received UFH experienced the other two.

Bleeding complications after delivery

In 10 studies (Clark et al., 2009; Daskalakis et al., 1997; Donnelly et al., 2012; Jacobsen, 2003; Narin et al., 2008; Nelson-Piercy et al., 2011; Rodie, 2002; Roshani et al., 2011; Ulander et al., 2002; Voke et al., 2007), 259 peri and post-delivery bleeding were observed. A total of 205 postpartum haemorrhages (PPHs) were classified as minor, 40 clinically relevant non-major PPHs, and 14 serious PPHs (Table 4).

Thromboembolic side effects

In 15 studies with a total of 819 patients, data on recurrent VTEs that occurred during the antepartum interval was available. There were 15 recurrent VTEs: four were DVTs and 11 were PEs (one death) (Table 4).

Discussion

The findings of this scoping review of the literature strongly support the effectiveness and safety of the therapeutic approaches currently being used to treat VTE associated with pregnancy, but they also indicate that more work needs to be done to enhance their efficacy and safety profile, particularly during the times of greatest risk. In actuality, the rates of serious bleeding issues, again during the first week of therapy and in the first 24 hours following birth, remain high throughout the first week of treatment, as does the predicted incidence of recurrent episodes during pregnancy (Barillari et al., 2007; Jacobsen, 2003; Narin et al., 2008; Nelson-Piercy et al., 2011; O'Connor et al., 2011; Rodie, 2002; Roshani et al., 2011; Rowan et al., 2003; Ulander et al., 2002; Voke et al., 2007). The use of adjusted-dose LMWH for the treatment of VTE during pregnancy is advised by the revised recommendations of the American College of Chest Physicians' (ACCP), 2012 (Shahrook et al., 2018). Due to its improved safety profile and higher bioavailability, LMWH is regarded as the best alternative. Also, it is recommended that the anticoagulant therapy be continued at the same dose for the duration of pregnancy and for at least six weeks following birth (Shahrook et al., 2018).

With an acceptable incidence of serious bleeding events during the acute phase of treatment, the majority of patients received weight-adjusted, full-dose LMWH. However, during the long-term treatment phase, most patients had their doses empirically reduced. It is important to highlight that the major bleeding event rates published in studies conducted in non-pregnant patients treated for acute VTE with conventional anticoagulant medication are consistent with the major bleeding event rates reported in our study (Girona, Säly, Makaloski, Baumgartner, & Schindewolf, 2022; Jullien, 2021). In contrast, the estimated rates of bleeding and recurrent VTE episodes in our analysis are somewhat different than those found in a prior systematic review that Greer et al. (2005) published in 2005. In this study, patients treated for pregnancy-related DVT or PE (n = 146) as well as those taking antithrombotic prophylaxis were included in order to evaluate the safety and effectiveness of LMWH during pregnancy. Patients using LMWH for the treatment of acute VTE had a 1.72% PPH rate. These rates are lower than those observed in this review, most likely because patients receiving therapeutic doses of anticoagulants and those receiving UFH were included, though it's also possible that it's because of varied definitions of the bleeding. Additionally, the observed rates of recurrent VTE were higher than those in the evaluation of Greer et al. (2005).

There were a few limitations to this scoping review. Studies with various outcomes and follow-up times were included that may have created a bias. Furthermore, different substances with various dose schedules were used, and the therapy approaches used in research varied greatly. Another drawback is that different

studies may not use uniform definitions of how severe bleeding is, which necessitates some care in how the reported numbers are understood. This is especially true with the PPH definition. PPH is typically described as any blood loss from the vaginal canal that exceeds 500 ML during delivery (Papadakis et al., 2019; Wu et al., 2022). Furthermore, data covering the full puerperium was not included due to two factors: first, the considerable variation in follow-up times amongst the research chosen; and second, the lack of information on anticoagulant usage and postpartum problems in most studies. Similar to the diagnosis of recurrent VTE, the adjudication criteria employed in most trials were not disclosed, and it is likely that some variation exists in these criteria.

Conclusion

Within the limitations of this scoping review, it can be stated that anticoagulant therapy is useful in preventing recurrent VTE among pregnant women and has a tolerable safety profile. The majority of incidents, including bleeding, happened in the first week of therapy. Hence, caution has to be advised when these medications are given in the early stages of pregnancy. Further studies with the optimal estimation of the dosages to prevent episodes of VTE are suggested.

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Conflict of interest

No competing interests were present.

Data Availability

Data sharing does not apply to this article as no datasets were generated or analysed during the current study.

Authorship

Named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work, and have given their approval for this version to be published.

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Figure 1: A flow chart of the selection of the studies.

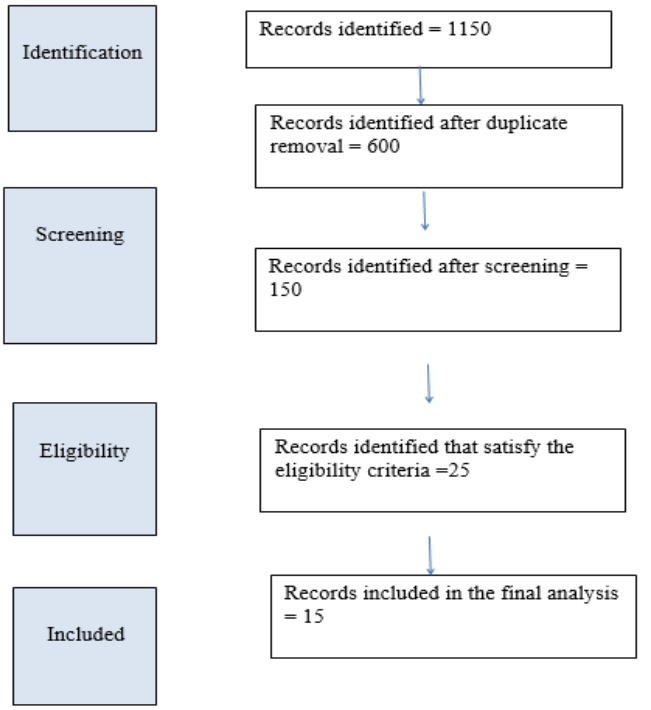

Table 1: Baseline characteristics of the study populations

Author	Type of study	Patients (no.)	Age (years)	Gestational age	DVT	PE
Voke *et al.*[33]	Cohort	126	Median 32 (16–42)	31 first trimester 37 second trimester 58 third trimester	78	48
Ulander *et al.*[32]	Case–control	31 (10, group I 21, group II)	31.0 ± 5.7, group I 31.6 ± 4.3, group II	27 ± 8.5 weeks, group I 21 ± 9.8 weeks, group II	31	0
Rowan *et al.*[31]	Cohort	13	NR	NR	NR	NR
Roshani *et al.*[30]	Cohort	13	Mean 32	NR	8	5
Rodie *et al.*[29]	Case series	29	NR	NR	23	6
O'Connor *et al.*[28]	Case series	34	NR	NR	NR	NR
Nelson-Piercy *et al.*[27]	Cohort	247	Mean 30.1	NR	NR	NR
Narin *et al.*[26]	Case–control	35 (18, group I17, group II)	Mean 28.4 ± 3.5, group I Mean 30.0 ± 5.2, group II	Mean 29.3 ± 4.4 weeks, group I Mean 26.5 ± 6.5 weeks, group II	35	0
Jacobsen *et al.*[25]	Cohort	20	Mean 31.8 ± 5.19	4 first trimester; 6 second trimester, 11 third trimester	19	2
Donnelly *et al.*[24]	Cohort	25	NR	NR	21	4
Daskalakis*et al.*[23]	Case series	18	27–43	7–38 weeks	18	0
Clark *et al.*[22]	Cohort	17	NR	Median 19 weeks	NR	NR
Blanco-Molina *et al.*[21]	Cohort	173	Mean 31 ± 6	NR	135	38
Bahlmann*et al.*[20]	Cohort	12	NR	26.1 ± 6.2 weeks	12	0
Aburahma and Boland[19]	Case–control	24	Mean 24 (17–39)	1 first trimester 5 second trimester 18 third trimester	24	NR

APTT, activated partial thromboplastin time; i.v, intravenous; IU, International Units; LMWH, low molecular weight heparin; NR, not reported; s.c., subcutaneous; UFH, unfractionated heparin; DVT, deep venous thrombosis; PE, pulmonary embolism

Table 2: Treatment regimens for the acute phase of venous thromboembolism

Author	LMWH	Dose of LMWH	UFH	Dose of UFH	Warfarin
Voke *et al.*[33]	115	83 patients once daily,	11	NR	0
Ulander*et al.*[32]	21 dalteparin	Based on anti-FXa (target: 1–1.5 U mL^{-1})	10	According to APTT (70–100 s)	0
Rowan *et al.*[31]	13 enoxaparin	1 mg kg^{-1} twice daily	0	–	0
Roshani*et al.*[30]	9 nadroparin, 2 dalteparin	100 IU kg^{-1} twice daily or 200 IU kg^{-1} once daily	1	NR	0
Rodie*et al.*[29]	29 enoxaparin	1 mg kg^{-1} twice daily	0	–	0
O'Connor *et al.*[28]	23	NR	11	NR	0
Nelson-Piercy *et al.*[27]	247 tinzaparin	Median 13 000 IU(3500–28 000)	0	–	0
Narin*et al.*[26]	0	–	35	According to APTT (target 1.5–2.5 times normal)	0
Jacobsen *et al.*[25]	20 dalteparin	Initially 100 IU kg^{-1} twice daily, then according to anti-FXa levels (0.5–1.0 U mL^{-1})	0	–	0
Donnelly *et al.*[24]	25	NR	0	–	0
Daskalakis*et al.*[23]	0	–	18	According to APTT (target 2.0 times normal)	0
Clark *et al.*[22]	2 enoxaparin	100–110 mg kg^{-1} twice daily	15	6 patients s.c.	0
Blanco-Molina *et al.*[21]	154	Mean 187 ± 51 IU kg^{-1} daily	16	NR	0
Bahlmann*et al.*[20]	1 dalteparin	5000 IU s.c. three times daily	11	According to APTT (target	0
Aburahma and Boland[19]	0	–	24	11 patients i.v. according to APTT (target 1.5–2.5 times normal); 13 patients i.v. bolus then 5000–10 000 U s.c. every 8–12 h	0

APTT, activated partial thromboplastin time; i.v, intravenous; IU, International Units; LMWH, low molecular weight heparin; NR, not reported; s.c., subcutaneous; UFH

Table 3: Treatment regimens for the long-term treatment period

Author	LMWH	Dose	UFH	Dose	Warfarin	Duration of therapy
Voke *et al.*[33]	118	Some patients according to anti-FXa levels	4	NR	0	NR
Rowan *et al.*[31]	13	Some patients according to anti-FXa levels	0	–	0	NR
Rodie*et al.*[29]	29	According to anti-FXa levels (0.4–1.0 U mL^{-1})	0	–	0	Median 6 weeks
O'Connor *et al.*[28]	23	NR	11	NR	NR	NR
Nelson-Piercy *et al.*[27]	247	Median 13 000 IU (3500–23 100)†	0	–	0	NR
Narin*et al.*[26]	35	1 mg kg^{-1} twice daily, group I 1.5 mg kg^{-1} once daily, group II	0	–	0	nr
Jacobsen *et al.*[25]	20	According to anti-FXa levels (0.5–1.0 U mL^{-1})	0	–	0	NR
Donnelly *et al.*[24]	25	NR	0	–	0	NR
Daskalakis *et al.*[23]	18	6150 anti-FXa IU once daily	0	–	0	1 month after delivery
Clark *et al.*[22]	3	70 mg Kg^{-1} twice daily, 17 000 IU once daily	14 s.c.	9000–13 000 IU every 8–12 h	0	NR
Bahlmann *et al.*[20]	2	500–600 IU h^{-1} i.v.	108 pts.c.,	every 8–12 h 5000–7000 U · 3 s.c.	0	after delivery NR
Aburahma and Boland[19]	0	–	24	5000–10 000 U s.c.	0	6–8 weeks
Blanco-Molina *et al.*[21]	133	Mean 173 ± 59 IU kg^{-} daily	0	–	36	after delivery NR
Roshani *et al.*[30]	9 nadroparin, 2 dalteparin	100 IU kg^{-1} twice daily or 200 IU kg^{-1} once daily	1	NR	0	(1–33 weeks) NR
Ulander *et al.*[32]	31	100 UI kg^{-1} twice daily for 2 weeks,	0	–	0	NR

		then once daily according to anti-FXa levels (0.7 U mL)[1] and 0.5–0.6 U mL^{-1} at the end of pregnancy)				

i.v, intravenous; IU, International Units; LMWH, low molecular weight heparin; NR, not reported; s.c., subcutaneous; UFH, unfractionated heparin

Table 4: Adverse events

Author	Antepartum bleeding	Antepartum recurrent VTE	Other antepartum adverse events	Peripartum bleeding (first 24 h after delivery)	Other postpartum bleeding	Other postpartum adverse events	Follow-up
Rodie*et al.*[29]	0	0	2 skin reactions (on enoxaparin)	3 atonic postpartum bleeds, 1 wound hematoma	NR	0	NR
O'Connor *et al.*[28]	2 unspecified	NR	NR	NR	4 unspecified	NR	NR
Nelson-Piercy *et al.*[27]	4 unspecified†	5 (4 PEs)‡	NR	196 bleeds < 500 mL, 31 bleeds > 500 mL, and < 1000 mL, 3 bleeds > 1000 mL§	NR	2 stillbirths, 1 termination	NR
Narin*et al.*[26]	1 vaginal bleed, 1 hematuria and1 clinically relevant vaginal bleed on LMWH	0	1 abortion	0	0	0	4–8 weeks after delivery in 57% of patients
Jacobsen *et al.*[25]	0	0	1 intrauterine death	1 atonic postpartum bleed, 1 wound hematoma	NR	0	NR
Donnelly *et al.*[24]	NR	NR	NR	0 bleeds > 1500 mL	NR	NR	NR
Daskalakis *et al.*[23]	0	0	1 abortion	0	NR	0	NR
Clark *et al.*[22]	0	1 PE in acute phase on LMWH	NR	1 wound hematoma1 minor bleed	1 major bleeding	NR	NR
Blanco-Molina *et al.*[21]	3 major bleeds in acute phase: 2 on UFH; 1 on LMWH*	2 PEs during LMWH after acute phase	NR	NR	NR	NR	3 months after VTE
Bahlmann *et al.*[20]	NR	4 (2 PEs): 3 in acute phase on UFH	NR	NR	NR	NR	NR
Aburahma and Boland[19]	1 retroperitoneal bleed in acute phase	2 PEs, one fatal, in acute phase on UFH*	NR	NR	NR	NR	61 months

LMWH, low molecular weight heparin; NR, not reported; PE, pulmonary embolism; VTE, venous thromboembolism