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REVIEW ARTICLE

Thromboprophylaxis in pregnancy, delivery and puerperium: a review of literature and current guidelines

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ABSTRACT

Introduction. Venous thromboembolism is one of the leading causes of maternal morbidity and mortality. Pregnancy induces a hypercoagulable state as an adaptive mechanism to prevent hemorrhage during childbirth. These physiological changes significantly increase the risk of venous thromboembolism – by up to six-fold during pregnancy and up to 10-fold during the postpartum period compared to the non-pregnant population. Given these risks, proper identification of patients who may benefit from thromboprophylaxis is essential to improve maternal outcomes.

Material and methods. This manuscript reviews medical articles and current clinical guidelines on thromboprophylaxis in pregnancy and the puerperium, highlighting similarities, differences, and practical considerations in the management of at-risk patients. International guidelines developed to aid clinicians in venous thromboembolism risk stratification and prevention, including the Royal College of Obstetricians and Gynecologists, the American College of Obstetricians and Gynecologists, the American Society of Hematology, and the National Institute for Health and Care Excellence were analyzed.

Results. The incidence of Venous thromboembolism ranges from 1 to 2 per 1,000, with up to 80% attributed to deep vein thrombosis cases occurring during the antepartum period, and 20%-25% being pulmonary embolism cases. In contrast, the incidence of pulmonary embolism is significantly higher after childbirth, with 40% to 60% of all pulmonary embolism cases occurring during the postpartum period. The impact of venous thromboembolism is not limited to mortality. Acute venous thromboembolism and the need for long-term anticoagulant therapy are associated with a significant clinical and psychological burden, while potential long-term sequelae, such as pulmonary hypertension and post-thrombotic syndrome, can have lifelong consequences. Ensuring thromboprophylaxis is essential, and the primary responsibility lies with the obstetrician. Ultimately, effective thromboprophylaxis is about balancing efficacy and safety between the need to prevent a potentially life-threatening event and the cost of an increased risk of bleeding.

Conclusions. Effective thromboprophylaxis during pregnancy and the puerperium remains a critical component of maternal care. The national protocol aims to assist healthcare professionals in identifying women at increased risk of venous thromboembolism during pregnancy, childbirth, and the postpartum period, and in making evidence-based decisions regarding the use of thromboprophylaxis and anticoagulant agents.

Keywords: thromboprophylaxis, deep vein thrombosis (DVT), pulmonary embolism (PE), venous thromboembolism (VTE), pregnancy, puerperium, low molecular weight heparin.

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Key messages

What is not yet known on the issue addressed in the submitted manuscript

While thromboprophylaxis in pregnancy has advanced, significant knowledge gaps persist, particularly regarding personalized risk stratification, dosing, timing, and long-term outcomes. Addressing these issues will optimize care, reduce venous thromboembolism incidence, and minimize harm.

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The research hypothesis
Strengthening early detection of women at risk for venous thromboembolism in pregnancy or the postpartum period and prevention policies by effective thromboprophylaxis can reduce maternal morbidity and associated healthcare costs.

The novelty added by the manuscript to the already published scientific literature
The article systematically compares multiple international guidelines, highlights areas of consensus and points of divergence, especially around thresholds, dosing, and postpartum duration, and provides a side-by-side interpretation of risk stratification tools and their practical consequences. This comparative format helps clinicians working across borders or in multicultural health systems harmonize their decision-making, a rarely emphasized but clinically important angle.

Introduction

Venous thrombosis and pulmonary embolism remain the leading direct causes of maternal death during pregnancy or within the first six weeks postpartum [1]. Venous thromboembolism (VTE) complicates 1-2 per 1,000 pregnancies, and pregnancy increases the relative risk of VTE by 6 to 10 times compared to non-pregnant individuals.

Normal pregnancy is associated with major changes in hemostasis – specifically, hypercoagulability and hypofibrinolysis – with the purpose of maintaining placental function throughout pregnancy and preventing excessive bleeding during delivery [2]. While these hemostatic changes protect the mother from hemorrhage at birth, they also predispose her to thromboembolism during both pregnancy and the postpartum period.

Due to the prothrombotic state – characterized by hypercoagulability and venous stasis – pregnancy is associated with a fivefold increase in the risk of VTE compared to non-pregnant women, and with a 20-fold increase in VTE risk during the first three months postpartum [3].

The adaptive changes in hemostasis during pregnancy are primarily attributed to elevated estrogen levels and affect all components involved in coagulation: vascular capacity, vessel wall integrity, plasma levels of coagulation factors and fibrinolytic activity, platelet function, and plasma proteins [4, 5]. Anatomical changes related to the gravid uterus play a central role by causing venous stasis in the lower extremities.

The concentration of most coagulation factors increases, while levels of endogenous anticoagulant factors and fibrinolytic activity decrease [5, 6]. This imbalance in hemostasis can lead to fibrin deposition, resulting in placental ischemia and hypoxia, preeclampsia, intrauterine growth restriction, or miscarriage.

Physiological pregnancy is characterized by a progressive increase in the levels of coagulation factors VII, VIII, IX, X, and XII, as well as von Willebrand factor, fibrinogen, and tissue factor. The rise in factors VII and X, which can reach 120-180% of baseline levels, contributes to the shortened prothrombin time (PT) observed from mid-gestation through term [7].

Fibrinogen, a plasma glycoprotein, is a key component of the coagulation cascade and is involved in both primary and secondary hemostasis. In non-pregnant women, normal plasma fibrinogen levels range from 2.0 to 4.5 g/L [8, 9]. In pregnancy, fibrinogen levels increase progressively from the first trimester, reaching an average of 5 g/L by term. This suggests that fibrinogen values considered normal in the non-pregnant population may signal an underlying coagulopathy in pregnant women [8, 10].

During pregnancy, the braking mechanisms of coagulation are attenuated due to decreased levels of inhibitory coagulation factors.

Antithrombin (AT). AT levels remain unaffected by estrogen or progesterone; however, a moderate ~15% decline in AT III is observed in the late gestation and immediate postpartum periods. This is believed to reflect physiological activation of coagulation through intervillous placental thrombosis. Additional factors include hemodilution, altered synthesis, increased clearance, or consumption. James et al. reported a ~30% drop in AT levels at delivery, reaching a nadir 12 hours postpartum and normalizing by 72 hours [3].

Protein S (PS) and Protein C (PC). Total PS and PC levels remain stable during pregnancy and postpartum, but *free* PS and PS activity progressively decrease, accompanied by rising resistance to activated ***Protein C***, which also enhances von Willebrand factor. Free PS can drop by ~50% at term and remain low for two months postpartum, particularly during lactation. Therefore, PS quantification during pregnancy, even in early stages, is not recommended.

Protein C activity increases in the first and second trimesters, possibly offsetting decreased PS activity and increased thrombin generation to support fetal circulation. PC activity then declines in the third trimester, rebounding in the immediate postpartum period.

Pregnancy also elevates thrombomodulin, tissue factor pathway inhibitor, and heparin cofactor II. Concurrently, prothrombin fragments 1+2 and thrombin–antithrombin complexes rise, cumulatively heightening thrombotic risk.

Fibrinolytic activity progressively decreases throughout pregnancy, reaching its lowest point in the third trimester [11]. This hypofibrinolytic state contributes to the prevention of bleeding at the time of placental separation.

Fibrinolysis is suppressed due to increased synthesis of plasminogen activator inhibitor type 1 (PAI-1) by endothelial cells and substantial production of plasminogen activator inhibitor type 2 (PAI-2) by the placenta [12]. Tissue plasminogen activator (tPA) levels decrease significantly towards term, and this reduction persists for 6-8 weeks postpartum.

D-dimers are recognized as the most sensitive markers of secondary fibrinolytic activation. Paradoxically, despite elevated levels of PAI-1 and PAI-2 – which would be expected to lower D-dimer levels due to hypofibrinolysis – plasma concentrations of D-dimer increase progressively by two- to fourfold during pregnancy, reaching values of up to 198-266 ng/mL at delivery (compared to ~80 mg/L in non-pregnant women) [13]. A strong positive correlation exists between gestational age and D-dimer concentration. This progressive increase complicates the use of D-dimer levels in ruling out VTE in pregnant women with clinical suspicion [2, 14-17].

Fibrin degradation products also increase progressively, resulting from enhanced fibrin formation (through intravascular coagulation) and subsequent intensified fibrinolysis due to placental release of thromboplastic factors.

The hemostatic and coagulation changes described above develop gradually during normal pregnancy, reaching a peak state of hypercoagulability in the third trimester and resolving slowly during the postpartum period [7]. These changes represent an adaptive physiological mechanism to protect the pregnant woman from hemorrhage during delivery and typically do not carry clinical consequences. However, the risk of VTE and pulmonary embolism is known to be four to six times higher in pregnant women compared to non-pregnant women of similar age [18].

Blood flow changes in pregnancy. Endothelial trauma and venous stasis contribute to the increased thrombotic risk during pregnancy. Blood stasis is mediated by venous dilation, decreased venous tone, reduced venous flow, and compression of the iliac veins by the pregnant uterus, particularly the left common iliac vein. Additionally, vascular injury occurs following delivery [1, 19].

In conclusion, pregnancy represents a complex interaction of thrombosis-predisposing factors, aimed at achieving postpartum hemostasis. However, pregnancy simultaneously represents a condition that triggers the initiation of the pathological cascade of coagulation disorders and thrombotic events [20].

A proper understanding of the physiological changes in hemostasis during pregnancy is essential for recognizing coagulation-related pathologies and, consequently, for selecting the most appropriate therapeutic strategies [21].

Material and methods

A comprehensive literature search was conducted to identify current articles and clinical guidelines on thromboprophylaxis during pregnancy and the puerperium. The search was performed using electronic databases including PubMed, MEDLINE, the Cochrane Library, as well as professional society websites such as those of the American College of Obstetricians and Gynecologists (ACOG), Royal College of Obstetricians and Gynecologists (RCOG), American Society of Hematology (ASH), and the International Society on Thrombosis and Haemostasias (ISTH). Keywords and Medical Subject Headings (MeSH) used included combinations of "thromboprophylaxis," "pregnancy," "puerperium," "postpartum," "venous thromboembolism," "clinical guidelines," "anticoagulation," and "deep vein thrombosis." Inclusion criteria were: published medical articles, clinical guidelines, consensus statements, or position papers focusing on thromboprophylaxis in pregnant and postpartum women; Guidelines addressing risk assessment, pharmacological and non-pharmacological prophylaxis, and management strategies. Exclusion criteria included: guidelines not specifically addressing pregnancy or postpartum periods; primary research studies, case reports, or reviews not offering guideline-level recommendations. Relevant data were extracted systematically, including recommendations on risk stratification, types and doses of anticoagulants, timing and duration of thromboprophylaxis, and considerations for special populations. The findings were synthesized qualitatively to compare and contrast the approaches recommended by various professional bodies.

Results

All major guidelines agree on the importance of systematic VTE risk assessment. This should occur at multiple stages:

- At the first prenatal visit
- During any hospital admission
- At the onset of labor or before cesarean section
- Immediately postpartum

Key Risk Factors. The risk factors commonly identified include:

- Personal history of VTE
- Known thrombophilia (e.g., Factor V Leiden, antithrombin deficiency)
- Obesity (BMI ≥30)
- Age >35 years
- Multiparity
- Preeclampsia
- Assisted reproductive technology
- Prolonged immobilization
- Cesarean section, especially in emergency settings
- Smoking

RCOG employs a point-based scoring system to determine the necessity and duration of prophylaxis, while ACOG and ASH promote individualized approaches based on clinical judgment and shared decision-making.

RCOG developed a risk-scoring system [22], enabling individualized estimation of thrombotic risk during pregnancy, and permitting implementation of a risk-adapted strategy for antithrombotic prophylaxis during pregnancy and the puerperium (Table 1).

Table 1. Risk factors for VTE, [23].

Pre-existing risk factors	Score
Previous VTE (except a single event related to major surgery	4
Previous VTE provoked by major surgery	3
Known high-risk thrombophilia	3
Medical comorbidities e.g. cancer, heart failure; active systemic lupus erythematosus, inflammatory polyarthropathy or inflammatory bowel disease; nephrotic syndrome; type I diabetes mellitus with nephropathy; sickle cell disease; current intravenous drug user	3
Family history of unprovoked or estrogen-related VTE in first-degree relative	1
Known low-risk thrombophilia (no VTE)	1a
Age (> 35 years)	1
Obesity	1 or 2b
Parity ≥ 3	1
Smoker	1
Gross varicose veins	1
Obstetric risk factors	
Pre-eclampsia in current pregnancy	1
ART/IVF (antenatal only)	1
Multiple pregnancy	1
Caesarean section in labor	2
Elective caesarean section	1
Mid-cavity or rotational operative delivery	1
Prolonged labor (> 24 hours)	1
PPH (> 1 liter or transfusion)	1
Preterm birth < 37+0 weeks in current pregnancy	1
Stillbirth in current pregnancy	1
Transient risk factors	
Any surgical procedure in pregnancy or puerperium except immediate repair of the perineum, e.g. appendicectomy, postpartum sterilization	3
Hyperemesis	3
OHSS (first trimester only)	4
Current systemic infection	1
Immobility, dehydration	1
Covid -19	
Total:	

Note: *ART assisted reproductive technology; IVF in vitro fertilization; OHSS ovarian hyperstimulation syndrome; VTE venous thromboembolism.*
If the known low-risk thrombophilia is in a woman with a family history of VTE in a first-degree relative postpartum thromboprophylaxis should be continued for 6 weeks.
b. BMI ≥ 30 = 1; BMI ≥ 40 = 2

Risk assessment for venous thromboembolism (VTE), RCOG 2015, [22]:

- If total score ≥ 4 antenatally, consider thromboprophylaxis from the first trimester.
- If total score is 3 antenatally, consider thromboprophylaxis from 28 weeks.
- If total score ≥ 2 postnatally, consider thromboprophylaxis for at least 10 days.
- If admitted to hospital antenatally, consider thromboprophylaxis.
- If prolonged admission (≥ 3 days) or readmission to hospital within the puerperium, consider thromboprophylaxis.
- For patients with an identified bleeding risk, the balance of risks of bleeding and thrombosis should be discussed in consultation with a haematologist with expertise in thrombosis and bleeding in pregnancy.

Previous thromboembolic episode. Women with a history of venous thromboembolism (VTE) have an increased risk of recurrence during pregnancy and the postpartum period, with reported recurrence rates of 2-11%. The risk of recurrence appears to remain constant throughout the entire pregnancy [18, 22, 23]. Women with a history of VTE should receive pre-pregnancy counseling and have an individualized prospective management plan for thromboprophylaxis during pregnancy. Women who become pregnant before receiving such counseling should be referred as early as possible during pregnancy to a physician with expertise in thrombosis in pregnancy.

Prevention of VTE in pregnant women with thrombophilia and no previous VTE. Thrombophilias are conditions associated with an increased risk of thrombosis and can be either inherited or acquired. Most studies assessing the risk of VTE in pregnancy have focused on inherited thrombophilias. Although about 50% of pregnancy-associated VTE cases are linked to inherited thrombophilias, these abnormalities are quite common and are collectively present in at least 15% of the general population [24].

Inherited thrombophilias that have the potential to increase thrombotic risk, according to the Romanian Society of Obstetrics and Gynecology, include: factor V Leiden mutation, the G20210A mutation in the prothrombin gene, protein S deficiency, protein C deficiency, and antithrombin III deficiency. Screening for these mutations is recommended for all pregnant women with a history of venous thromboembolism [25].

Factor V Leiden mutation is the most common form of inherited thrombophilia, transmitted in an autosomal dominant manner with incomplete penetrance, and with variable prevalence ranging from 2-3% up to 10-15% across Europe [25, 26]. Data from reviews evaluating the association between thrombophilia and pregnancy-associated VTE show that the highest risks are associated with homozygosity for factor V Leiden or the prothrombin G20210A variant [24, 27]. Pregnant women who are heterozygous for factor V Leiden or the prothrombinG20210A variant have lower risks. Thrombosis due to the prothrombin gene mutation may present as deep vein thrombosis in the lower limbs or as pulmonary embolism. The prothrombin gene mutation is autosomal dominant and is responsible for up to 17% of venous thromboembolism events during pregnancy [28]. Deficiencies of antithrombin, protein C, and protein S have been associated with moderate increases in VTE risk. Antithrombin deficiency is a rare condition but

has a high thrombogenic potential [29, 30]. Nearly all types of antithrombin deficiency are heterozygous; the homozygous form is incompatible with life or results in a severe thrombotic phenotype. Protein C, together with protein S, contributes to the natural anticoagulation process by inactivating factors Va and VIIIa, thereby controlling thrombin generation. Protein S deficiency is inherited in an autosomal dominant pattern. Moderate protein S deficiency seems to affect about 1 in 500 people, while severe deficiency is extremely rare [29]. The prevalnce of severe protein C deficiency is rare (0.2%) [29]. The thrombotic risk of protein C deficiency increases if combined with factor V Leiden mutation. Estimated absolute VTE risks suggest a low thrombotic risk (0.5-1.2% of affected pregnancies) for most inherited thrombophilias, except possibly for homozygous carriers of factor V Leiden or prothrombin mutations, where the estimated risk is around 4%.

Classification of thrombophilias by risk

Low-risk thrombophilias:

- Heterozygous factor V Leiden mutation
- Heterozygous prothrombin gene mutation G20210A
- Activated Protein C Resistance
- Activated Protein S Resistance
- Hyperhomocysteinemia
- PAI (plasminogen activator inhibitor) abnormalities
- MTHFR mutations

High-risk thrombophilias:

- Homozygous factor V Leiden mutation
- Homozygous prothrombin gene mutation G20210A
- Compound heterozygosity for factor V Leiden and prothrombin mutation G20210A
- Protein C deficiency
- Protein S deficiency
- Antithrombin deficiency
- Antiphospholipid syndrome [31]

Based on recent studies, patients with low-risk thrombophilias are not routinely prescribed thromboprophylaxis but rather are closely monitored during pregnancy. The presence of low-risk thrombophilias, combined with other possible risk factors, may be sufficient to initiate thromboprophylaxis.

There is considerable disagreement among current guidelines regarding thromboprophylaxis during pregnancy in women with antithrombin, protein C, or protein S deficiencies. According to ACOG [29], anticoagulant prophylactic treatment should be started in patients with high-risk thrombophilias, specifically those with antithrombin, protein S, or protein C deficiency, and homozygous factor V mutation [23, 32, 33]. The RCOG recommends prophylactic anticoagulation for women with a history of venous thromboembolism and antithrombin deficiency during pregnancy and the puerperium [22]. The Society of Obstetricians and Gynaecologists of Canada advises testing for thrombophilia mutations after a venous thromboembolism episode [34].

The inconsistencies in recommendations likely stem from different risk thresholds for initiating prophylaxis and concerns raised by older studies suggesting these are high-risk thrombophilias (studies now considered to have methodological limitations).

The Royal College of Obstetricians and Gynaecologists recommends that the interpretation of hereditary thrombophilia test results be carried out by a clinician with specific expertise in this area. Generally, testing for hereditary thrombophilias is recommended in the presence of a medical history indicating previous venous thromboembolism (VTE).

Testing for thrombophilias should also be considered in pregnant women without a personal history or risk factors for VTE, but who have a first-degree relative with a history of unprovoked or estrogen-related VTE before the age of 50. Thrombophilia testing is especially indicated if a first-degree relative of the pregnant woman has a known thrombophilia (D) [22].

Acquired thrombophilias. The most common acquired thrombophilias during pregnancy are antiphospholipid syndrome (APS) and hyperhomocysteinemia. APS is associated with an increased risk of venous thromboembolism (VTE) [24] and obstetric complications such as preterm birth, recurrent pregnancy loss, fetal death in utero, premature placental abruption of normally implanted placenta, intrauterine growth restriction, severe early-onset preeclampsia, and HELLP syndrome. Approximately 1% of patients develop the catastrophic form of APS, characterized by multiorgan thrombotic complications during pregnancy or the postpartum period [35].

In general, primary thromboprophylaxis is not recommended for pregnant women who test positive for antiphospholipid antibodies but have no prior clinical history of thrombosis, due to limited data on the protective effects of low-dose aspirin or anticoagulants in this population. There are no strict treatment guidelines in this situation, and treatment options may include:

- no treatment,
- low-dose aspirin (around 150 mg/day),
- low-dose aspirin combined with a prophylactic dose of low molecular weight heparin.

However, most guidelines recommend low-dose aspirin therapy for pregnant women with positive antiphospholipid antibodies, especially those at high risk for preeclampsia. Treatment decisions should be individualized based on a careful risk-benefit assessment for each patient [36-38]. Long-term anticoagulant treatment, starting from the beginning of pregnancy, is essential for pregnant women with APS and thrombotic events diagnosed prior to pregnancy. Oral anticoagulant therapy should be switched to therapeutic doses of enoxaparin throughout the pregnancy, with a subsequent transition back to oral anticoagulants in the postpartum period [36].

Hyperhomocysteinemia. MTHFR mutations are a common cause of elevated homocysteine levels, which were previously considered a risk factor for venous thromboembolism (VTE). However, recent data suggest that it represents a weak risk factor, and MTHFR mutations have not been shown to increase the risk of VTE [39]. A meta-analysis

conducted by Robertson L. and colleagues failed to demonstrate an association between MTHFR mutations, hyperhomocysteinemia, and VTE during pregnancy [23]. Currently, ACOG recommends against screening for MTHFR mutations or measuring fasting homocysteine for thrombophilia evaluation and VTE risk assessment during pregnancy [29].

Age as a risk factor for VTE. Data on age are contradictory, but a modestly increased relative risk of less than twofold is suggested for women over 35 years old. In a large population cohort study from the United Kingdom, outside of pregnancy, women aged 35-44 years had a 50% higher rate of VTE compared to women aged 25-34 years. The VTE rate did not increase with age during the antepartum period; however, during the postpartum period, women aged ≥35 years had a 70% increased risk of VTE compared to women aged 25-34 years (corresponding to an absolute excess risk of 1.6 per 1000 person-years). The RCOG maintains age over 35 years as a thrombotic risk factor both antenatally and postpartum [22].

Obesity. The WHO defines obesity as an abnormal or excessive accumulation of fat that may be detrimental to health, operationally defined as a body mass index (BMI) ≥ 30 kg/m^2. The risk of VTE increases as BMI rises above 25 kg/m^2. This is the threshold defining overweight (BMI 25 to 29.9 kg/m^2), meaning the risk increases even at BMI values lower than those defining obesity. The association between obesity and VTE becomes stronger as BMI increases. Morbid obesity (BMI ≥ 40 kg/m^2) is associated with a fourfold higher incidence of VTE [41-43].

Obesity is a risk factor for VTE during pregnancy, with risk increasing alongside the degree of obesity. Obesity is linked to a higher risk of pulmonary embolism (adjusted odds ratio [aOR] 14.9, 95% CI 3.0-74.8) than deep vein thrombosis (aOR 4.4, 95% CI 1.6-11.9). Overweight status (BMI 25-29.9) represents a weak risk factor for VTE in pregnancy, with a prevalence of nearly 50% in the fertile population (Level of evidence 2++). All women with class 3 obesity (BMI ≥ 40 kg/m^2), even in the absence of other risk factors, should receive LMWH prophylaxis at doses appropriate to their weight for 10 days postpartum (Grade of recommendation D) [22].

Immobility and long-distance travel. Data on the pregnancy-related risk of immobility and long-distance travel are limited and there is a lack of adequate study data. Some studies have shown that the interaction between various risk factors, such as a body mass index (BMI) over 25 kg/m^2 and prolonged antepartum immobilization (defined as strict bed rest for one week or more before delivery), has a multiplicative effect on the risk of antepartum VTE (adjusted odds ratio [aOR] 62.3, 95% confidence interval [CI] 11.5-337.7) and postpartum VTE (aOR 40.1, 95% CI 8.0-201.5), respectively, and thus requires thromboprophylaxis according to Table 1 [22]. The NICE guideline on prenatal care and the RCOG scientific impact document regarding air travel during pregnancy state that long-distance air travel increases the risk of venous thromboembolism; this guideline considers all long-distance travel (more than 4 hours), not exclusively air travel, as a risk factor for VTE during pregnancy and recommends thromboprophylaxis.

Intrapartum management of women receiving thromboprophylaxis. At this stage, the main concern is the risk of hemorrhagic complications from pharmacological thromboprophylaxis. In planned delivery, prophylactic doses of LMWH are stopped at least 12 hours before delivery and can be resumed at least 4-6 hours after delivery if there is no significant bleeding risk (if bleeding risk is high, management should be individualized) [44]. During operative delivery, regional anesthesia (epidural, spinal, combined spinal-epidural) is currently used in 70-90% of cases. To prevent a serious complication such as epidural hematoma, strict adherence to timing intervals between anticoagulant administration and performing regional anesthesia or removal of the epidural catheter is necessary.

Cesarean delivery carries a fourfold increased risk of venous thromboembolism compared to vaginal delivery (approximately 3 per 1000 patients). Given this increased risk and extrapolating from perioperative data, the use of compression stockings before cesarean delivery is recommended for all women, and early mobilization is recommended for all women after cesarean birth [44]. When labor induction or delivery is planned, LMWH is usually stopped 24 hours beforehand. A plan should be made with the obstetric team, balancing the risk of hemorrhage from continued anticoagulation and the risk of thromboembolic events. Active management of the third stage of labor is recommended in all settings for women on antenatal thromboprophylaxis.

Thromboprophylaxis in the postpartum period. The risk of venous thromboembolism increases with gestational age, reaching a peak immediately after delivery. The relative postpartum risk is five times higher compared to the antepartum period. According to the recommendations of ACOG – American College of Chest Physicians (2012), in the absence of risk factors, pharmacologic thromboprophylaxis is not necessary; early mobilization of patients is sufficient (Grade of recommendation IB). Regardless of the mode of delivery and anesthesia, the patient should be mobilized as soon as possible – within a few hours after delivery or surgery [44].

Key points for administering thromboprophylaxis during the postpartum period:

- The risk of VTE must be reassessed for all women after delivery [22].
- Thromboprophylaxis should be started or resumed as soon as the immediate risk of bleeding is reduced.
- To minimize the risk of postpartum hemorrhage, doses of LMWH thromboprophylaxis should be resumed at least 4-6 hours after vaginal delivery or between 6-12 hours after operative delivery or cesarean section.
- A postnatal plan for thromboprophylaxis should be documented by an obstetrician in the medical record for women who received antenatal LMWH. All women require immediate reassessment after delivery, and the risk score must be documented in the medical record.

- For all women who need LMWH, any delay in administration should be avoided.
- Risk factors should be reassessed if complications develop, such as secondary postpartum hemorrhage, postnatal preeclampsia, infection, or increased immobility [40, 45].

Women with two or more intermediate risk factors for postpartum VTE should receive weight-adjusted prophylactic doses of LMWH for at least 10 days after delivery (Grade of recommendation C) [22]. Additional relevant risk factors for postpartum thromboprophylaxis after delivery include prolonged labor, immobility, infection, hemorrhage, and blood transfusion. Recent evidence supporting these obstetric complications as risk factors for VTE comes from several large population studies. Since the risk of VTE is higher in the postpartum period than antenatally, all women with a previous VTE should continue prophylaxis with LMWH for 6 weeks postpartum. Those with recurrent VTE who are on long-term oral anticoagulant treatment should continue LMWH until they switch back to warfarin or another oral anticoagulant agent [22, 40]. All women who have delivered by cesarean section should receive LMWH thromboprophylaxis for 10 days postpartum, except for those who had an elective cesarean section. For the latter, LMWH thromboprophylaxis for 10 days postpartum should be considered only if additional risk factors are present [23]. Thromboprophylaxis should be continued for 6 weeks in high-risk women and for 10 days in intermediate-risk women. (Grade of recommendation B) [23]. In women with persistent additional risk factors (lasting more than 10 days postpartum), such as prolonged hospitalization, wound infection, or surgery during the puerperium, thromboprophylaxis should be extended up to 6 weeks or until the additional risk factors are no longer present (Grade of recommendation C) [22].

Early mobilization of patients. It is well established that immobilization is an important risk factor for VTE and can increase its incidence up to 10-fold. Regardless of the mode of delivery and anesthesia, the patient should be mobilized as soon as possible – within a few hours after delivery or surgery, (Grade of recommendation B) [22].

Pharmacological thromboprophylaxis. anticoagulants. Low Molecular Weight Heparins (LMWHs) are, by consensus, the first-choice medications recommended for pharmacological thromboprophylaxis during pregnancy and postpartum. LMWHs are animal-derived polysaccharides (porcine origin), administered subcutaneously, which act on the coagulation cascade by activating antithrombin, thereby accelerating the inhibition of both Factor Xa and thrombin by antithrombin. Due to their large molecular size, LMWHs cannot cross the placental barrier and therefore can be safely used during pregnancy. LMWH is safe during pregnancy and lactation and has not been associated with fetal hemorrhage or teratogenic effects on the developing fetus [31]. It is the treatment of choice for pregnant and breastfeeding women due to good tolerability and a convenient dosing profile that does not require routine monitoring [24, 45]. Compared with unfractionated heparin, LMWH is superior in reducing thrombotic complications, major bleeding, and mortality. It has similar efficacy in reducing VTE recurrence, higher anti-Xa activity, more predictable pharmacokinetics, an equal risk of bleeding from any cause, and a lower risk of heparin-induced thrombocytopenia [46]. Therefore, it is the preferred anticoagulant for pregnant women with a glomerular filtration rate (GFR) > 30 ml/min [19]. In cases of severe renal dysfunction (creatinine clearance <30 mL/min), the effect of these medications may accumulate, increasing the risk of bleeding. To prevent these situations, renal function should be evaluated before prescribing renally cleared antithrombotic drugs, especially in patients with diabetes and those at high risk of bleeding [31]. Unfractionated heparins are preferred in pregnant women with severe renal dysfunction (GFR < 30 ml/min). They can be administered intravenously or subcutaneously, and dosing requires adjustment according to body weight [24]. Unfractionated heparins may also be considered as transitional therapy before delivery or prior to surgery, as they offer better management of the heparin half-life and rapid reversal of anticoagulant effects.

Oral anticoagulants. Vitamin K antagonists (warfarin, acenocoumarol) cross the placenta and are associated with fetal defects, especially if administered between the 6th and 12th weeks of pregnancy, when the fetus is most vulnerable to vitamin K deficiency [47]. Vitamin K antagonists reduce the synthesis of vitamin K-dependent proteins, which are essential for normal fetal development, increasing the risk of fetal malformations such as bone abnormalities, central nervous system defects, and ocular anomalies [48]. In addition, their use in the first trimester is associated with a potential increased risk of spontaneous abortion. Vitamin K antagonists (warfarin) are safe during the postpartum period for breastfeeding mothers and can be prescribed if needed from the first day after birth.

Direct oral anticoagulants (DOACs) (Dabigatran, Rivaroxaban, Apixaban, Edoxaban) have largely replaced vitamin K antagonists in the treatment and prevention of VTE. However, during pregnancy, their safety profile has not been studied in detail, and there is no evidence of the safety of DOACs in pregnant women. Animal studies have documented their placental transfer and presence in breast milk. Therefore, the use of DOACs in pregnant women and women attempting to conceive is currently contraindicated. Nevertheless, the American College of Obstetricians and Gynecologists suggests that DOACs may be considered for thromboprophylaxis in the postpartum period in non-breastfeeding women [31].

Aspirin is not recommended as a method of thromboprophylaxis in obstetric patients, but it may be necessary for pregnant women at moderate or high risk of preeclampsia [22, 31]. Treatment with antiplatelet agents (e.g., aspirin) is *not* a contraindication for thromboprophylaxis with heparin.

Dosage of anticoagulants used for thromboprophylaxis. The calculation of LMWH doses should be based on the patient's body weight in kilograms, not on body mass

index (BMI). For thromboprophylaxis dosing, the pre-pregnancy weight (in kg) should be used, or if unknown, the most recent weight. Recent guidelines recommend the use of fixed prophylactic doses of LMWH, rather than high or weight-adjusted doses during pregnancy. LMWH is renally excreted, so dose adjustment may be necessary for women with renal insufficiency [22, 23]. Table 2 provides a cross-guideline comparison (RCOG/ACOG/ASH/NICE) of VTE risk assessment and thromboprophylaxis, with emphasis on LMWH dosing and postpartum prophylaxis length.

Table 2. Comparative Recommendations for VTE Prophylaxis in Pregnancy, Delivery, and the Puerperium (RCOG, ACOG, ASH, NICE)

Guideline (year)	Risk assessment tool	Antepartum prophylaxis – who & when	Postpartum prophylaxis – duration & who	Cesarean-specific	Agent & dose (prophylaxis)	Notes
RCOG Green-top 37a (2015)	Point-based score Thresholds: ≥4 → from 1st trimester; 3 → from 28 weeks; ≥2 postpartum → ≥10 days.	Start LMWH by thresholds above; weight-based dosing. Consider hematology input for thrombophilia.	High risk: 6 weeks. Intermediate risk: 10 days. Extend to 6 weeks if persistent factors >10 days (e.g., wound infection, prolonged admission).	All cesareans: consider LMWH 10 days; elective cesarean: 10 days only if additional risk factors.	LMWH = first-line, dose by weight; safe in breastfeeding.	Prior VTE: continue prophylaxis 6 weeks regardless of delivery mode.
ACOG PB No.196 (2018)	No validated score endorsed; individualized based on clinical risk factors.	Consider prophylaxis in women at increased risk; management individualized.	Prior VTE / selected thrombophilias: typically, 6 weeks; if >6 weeks needed, bridge to oral anticoagulant postpartum as appropriate.	All cesareans: pneumatic compression before surgery + early mobilization; add LMWH if additional risk factors.	LMWH prophylaxis when indicated; dosing per local protocol.	Framing emphasizes individualized risk over fixed scoring; aligns with US practice patterns.
ASH (2018; pocket guide 2019/2023)	Uses risk thresholds (≈2% antepartum, 1% postpartum) to decide on prophylaxis.	If prophylaxis needed: standard-dose LMWH preferred over intermediate dose antenatally.	If prophylaxis needed postpartum: standard or intermediate LMWH acceptable; many high-risk groups continue to 6 weeks.	Not a cesarean-universal LMWH stance; apply risk threshold approach.	Ex:(prophylaxis): enoxaparin 40 mg once daily (standard) or 40 mg q12h / 80 mg qd (intermediate);	Clear dosing table & neuraxial timing in pocket guide; LMWH preferred agent.
NICE NG89 (2018)	Adopts RCOG obstetric risk tool (Appendix with the RCOG score/thresholds).	Risk assessment at booking/admission; follow RCOG thresholds for starting LMWH.	Postnatal score ≥2 → ≥10 days LMWH; longer in high-risk scenarios per RCOG.	Follows RCOG stance on cesarean categories and duration.	LMWH as per RCOG/ Trust protocols; weight-based.	NICE is a cross-specialty guideline; obstetric specifics point back to RCOG tool.

Duration of thromboprophylaxis. The duration of thromboprophylaxis is a crucial factor determining its effectiveness. Prophylaxis for VTE should be continued until the embolic risk is reduced (becomes low) or disappears.

Discussion

Venous thromboembolism represents one of the leading preventable causes of maternal morbidity and mortality in both developed and developing countries. This comprehensive literature review emphasizes the complexity of VTE prevention during pregnancy and the postpartum period and the need for individualized, evidence-based thromboprophylaxis strategies.

Consistent with previous studies, our review confirms that pregnancy and the puerperium are prothrombotic states, driven by hormonal, vascular, and hematological changes. These changes are compounded by the presence of individual risk factors, including a history of VTE, thrombophilia, obesity, advanced maternal age, preeclampsia, cesarean section, and immobility. All major clinical guidelines (RCOG, ACOG, ASH, ISTH) emphasize the importance of systematic risk assessment at multiple time points: at booking, during hospitalization, around delivery, and postpartum.

One of the main contributions of this review is the detailed comparison of thromboprophylaxis approaches across guidelines, particularly the point-based scoring system recommended by the RCOG, which contrasts with the more flexible, judgment-based approaches endorsed by ACOG and ASH. The RCOG model provides a structured framework that can be easily integrated into clinical workflows, promoting consistent and timely initiation of prophylaxis. However, its application may require local adaptation to account for population-specific risk distributions and resource availability.

A notable finding is the divergence in thromboprophylaxis recommendations for women with thrombophilia, especially in those without a prior history of VTE. Although high-risk thrombophilias (e.g., homozygous Factor V Leiden, antithrombin deficiency, APS) are generally considered indications for antenatal and postpartum LMWH, the role of low-risk thrombophilias remains contentious. This variability likely reflects both the heterogeneity in study designs and the lack of robust prospective trials assessing thrombosis risk stratified by specific genetic mutations. Thus, the clinical decision to initiate thromboprophylaxis in these patients should involve shared decision-making and consultation with a hematologist.

The postpartum period remains the time of highest thrombotic risk, with a VTE incidence up to five times higher than during pregnancy. Cesarean delivery, especially emergency procedures, is consistently associated with higher VTE rates. All reviewed guidelines recommend thromboprophylaxis with LMWH for at least 10 days postpartum in women with significant risk factors, with longer durations (up to 6 weeks) advised for those at highest risk, such as women with prior VTE, ongoing immobility, or multiple thrombophilias.

Low Molecular Weight Heparins are universally endorsed as the pharmacologic agent of choice during pregnancy and lactation due to their safety profile, lack of placental transfer, and predictable pharmacokinetics. Warfarin, while effective, is contraindicated in pregnancy due to its teratogenicity but can be resumed postpartum in breastfeeding women. Conversely, direct oral anticoagulants (DOACs) are currently not recommended in pregnancy or lactation due to the absence of safety data and evidence of placental and breast milk passage.

Non-pharmacological strategies, particularly early mobilization, play a crucial adjunctive role and are emphasized in all guidelines. Early ambulation following delivery or surgery, combined with mechanical prophylaxis where appropriate (e.g., compression stockings during cesarean section), significantly reduces the risk of postpartum VTE.

Our review also highlighted important knowledge gaps and inconsistencies across guidelines, particularly regarding:

- Optimal LMWH dosing in women with obesity or renal impairment
- Management of borderline thrombophilia profiles
- The role of emerging biomarkers or genetic panels for risk stratification
- Standardization of postpartum risk reassessment tools

The lack of uniform criteria for thrombophilia testing and variation in definitions of high vs. low risk complicates guideline adherence and may lead to under- or overtreatment. Furthermore, risk factors such as age, obesity, and immobility often interact synergistically, necessitating a multifactorial approach rather than isolated risk estimation.

Lastly, the importance of interdisciplinary care, patient education, and clear documentation cannot be overstated. Given the potentially catastrophic outcomes of missed VTE prevention, consistent implementation of protocols and real-time risk assessment – supported by electronic medical records and clinical checklists – can greatly enhance maternal safety.

Practical implications for the Republic of Moldova

Integrating RCOG, ACOG, ASH, and NICE recommendations into national standards should follow a resource-sensitive, locally tailored approach. We propose:

- **National risk-assessment tool:** adopt/adapt the RCOG scoring system as the core instrument, with four mandatory assessment time points (first prenatal visit, any hospital admission, at onset of labour/before cesarean delivery, and at postpartum discharge), documented in the obstetric record and registry.
- **Unified clinical algorithm:** set clear thresholds for prophylaxis (antepartum prophylaxis for score ≥4, or ≥3 after 28 weeks; postpartum score ≥2 → at least 10 days; 6 weeks for high-risk/previous VTE), while allowing individualization per ACOG/ASH for atypical cases (e.g., class III obesity, combined thrombophilias, renal impairment).
- **Standardized pharmacologic regimens:** LMWH as first-line; fixed or weight-adjusted prophylactic doses (e.g., enoxaparin 40 mg once daily; intermediate dose 40 mg every 12 h in severe obesity), switch to unfractionated heparin when eGFR < 30 mL/min, and respect neuraxial anesthesia intervals (hold ≥12 h for prophylactic dosing; resume 4–6 h after vaginal birth and 6–12 h after cesarean if hemostasis is secure).
- **Minimum resource set:** ensure uninterrupted LMWH availability in maternity units (including prefilled syringes for discharge), compression stockings for cesarean/immobility, and standardized risk-assessment forms. Reserve anti-Xa monitoring for selected scenarios (extreme body weight, renal impairment).
- **Cesarean and postpartum care:** perioperative pneumatic/elastic compression and early mobilization; LMWH for 10 days after any cesarean with additional risk factors; 6 weeks in high-risk or prior-VTE patients.
- **Education and discharge continuity:** provide patient information (VTE warning signs, injection adherence) and a written postnatal plan (duration, dosing, reassessment points).
- **Governance and audit:** track simple indicators (proportion assessed at all 4 time points, appropriate LMWH initiation, adherence to recommended duration), with annual audit and feedback to maternity services.

Key Practice Messages

- VTE risk assessment should be performed at four key time points: first prenatal visit, any hospital admission, onset of labour/before cesarean delivery, and at postpartum discharge.
- LMWH remains the first-line agent for thromboprophylaxis during pregnancy and the puerperium.
- Postpartum prophylaxis duration should be tailored to individual risk: 10 days for intermediate risk and 6 weeks for high risk (e.g., prior VTE or major thrombophilia).

Conclusions

This review underscores the importance of individualized, evidence-based thromboprophylaxis during pregnancy and postpartum. While clinical guidelines provide robust frameworks for identifying and managing VTE risk, variability in recommendations – particularly for women with thrombophilia or multiple intermediate risk factors – highlights the need for further research and guideline harmonization.

Following the review of international guidelines, the national protocol „Thromboprophylaxis in pregnancy, childbirth, and puerperium" was formulated to align with current evidence-based practices. Implementation of consistent risk assessments, adherence to LMWH protocols, and multidisciplinary collaboration remain essential pillars in reducing maternal VTE morbidity and mortality.

Competing interests

None declared.

Authors' contributions

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