E-ISSN 2250-0944
ISSN 2250-1150
doi: 10.31838/ijprt/16.02.124

Research Article

Thromboprophylaxis in Pregnancy and the Puerperium: Physiology, Evidence, Guideline Discordance and Research Gaps: A Narrative Review

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Received: 11.05.2026, Revised: 20.06.2026, Accepted: 01.07.2026

ABSTRACT
Venous thromboembolism (VTE) is a leading direct cause of maternal death and among the most preventable. Pregnancy satisfies every element of Virchow's triad-a progressive procoagulant shift with suppressed fibrinolysis, mechanical venous stasis, and endothelial injury at delivery-and risk peaks in the puerperium rather than during gestation. Yet the translation of this well-characterised physiology into prophylaxis policy has proved remarkably contentious. This narrative review synthesises the physiological basis of pregnancy-associated hypercoagulability, the epidemiology of obstetric VTE with particular attention to Indian data, the diagnostic approach to deep vein thrombosis and pulmonary embolism in pregnancy, and the pharmacology and safety of low-molecular-weight heparin (LMWH) and its alternatives. It then examines the substantial discordance between the recommendations of the Royal College of Obstetricians and Gynaecologists (RCOG), the American College of Obstetricians and Gynecologists (ACOG) and the American Society of Hematology (ASH). Applied to identical cohorts, these guidelines identify populations for prophylaxis that differ several-fold in size, with the estimated VTE incidence among those recommended for prophylaxis ranging from 2.5 to 35.2 per 1,000 deliveries depending solely on which guideline is used. The underlying trial evidence is thin: successive Cochrane reviews have concluded that the benefits and harms of thromboprophylaxis in pregnancy and the early postnatal period remain very uncertain. We argue that the field's central problem is not disagreement about physiology but the near-absence of adequately powered randomised data, and we set out a research agenda-including an Indian incidence registry-required to resolve it.

Keywords: Venous Thromboembolism, Pregnancy, Puerperium, Thromboprophylaxis, Heparin, Low-Molecular-Weight, Clinical Practice Guidelines, India.

INTRODUCTION
In 1271, Raoul, a twenty-year-old Norman cobbler, developed unilateral pain and swelling of the right calf that subsequently extended to the thigh. The account, preserved in Guillaume de Saint-Pathus's La vie et les miracles de Saint Louis, is generally regarded as the first recorded case of deep vein thrombosis.[1,2] For the next six centuries treatment consisted principally of enforced immobilisation-devices such as the gouttiere de Bonnet and the reclining iron bed were still in use in early twentieth-century France-a strategy now understood to aggravate the very stasis that produces the disease. Rudolf Virchow's articulation of the triad of hypercoagulability, vascular injury and stasis, and the introduction of heparin for the treatment of venous thrombosis in the 1940s,[3] transformed the field. Obstetric practice, however, still lacks the randomised evidence

that would allow the resulting prophylactic strategies to be applied with confidence.

The problem is not obscure. VTE remains one of the leading direct causes of maternal mortality in high-income countries and is disproportionately preventable relative to the other leading causes. The physiological rationale for prophylaxis is unambiguous. What is contested is which women should receive it, at what dose, for how long, and whether the aggregate benefit across a large, low-risk-per-individual population exceeds the aggregate harm. Different national bodies have reached materially different answers to these questions from substantially the same evidence base-a pattern that ordinarily signals that the evidence is insufficient to constrain the recommendation. This review synthesises the physiology, epidemiology, diagnosis and pharmacology relevant to obstetric thromboprophylaxis; sets out the areas of guideline agreement and disagreement; appraises the trial evidence underlying them; and identifies the gaps that a research agenda would need to close. Particular attention is given to the Indian context, where reported incidence is low, ascertainment is likely incomplete, cultural postpartum immobility is common, and guideline implementation is minimal.

SCOPE AND APPROACH

This is a narrative rather than systematic review. Literature was identified through PubMed, Cochrane Library and Google Scholar searches combining the terms venous thromboembolism, pregnancy, puerperium, postpartum, thromboprophylaxis, low molecular weight heparin, enoxaparin, guidelines and India, supplemented by the reference lists of retrieved articles and by the current guideline documents of the RCOG, ACOG and ASH. Priority was given to systematic reviews, randomised trials, large cohort studies and guideline documents. No formal quality appraisal or quantitative synthesis was undertaken, and the selection of studies reflects the authors' judgement of relevance; readers should interpret the review accordingly.

PHYSIOLOGY: WHY PREGNANCY IS PROTHROMBOTIC

NORMAL HAEMOSTASIS IN BRIEF

Haemostasis proceeds in two coordinated phases. In primary haemostasis, vascular injury exposes subendothelial extracellular matrix-chiefly collagen-and adhesive glycoproteins including von Willebrand factor. Platelets adhere, become activated with shape change, granule release and generation of thromboxane A_2, and then aggregate through fibrinogen bridges between GpIIb/IIIa receptors on adjacent platelets, forming the primary plug.[4] In secondary haemostasis, the coagulation cascade converts prothrombin to thrombin and fibrinogen to fibrin, stabilising the plug. The classical intrinsic and extrinsic pathways converge on a final common pathway at factor X, though the cell-based model-in which tissue factor-bearing cells initiate and activated platelet surfaces amplify and propagate thrombin generation-better represents *in vivo* events.[5,6] Counter-regulation is provided by antithrombin, the protein C/protein S system, tissue factor pathway inhibitor, and the fibrinolytic system centred on plasmin.

THE GESTATIONAL SHIFT

Pregnancy produces a coordinated, teleologically sensible shift towards a procoagulant state, presumably evolved to limit haemorrhage at placental separation-placental blood flow can reach 700 mL/min at term, and the consequences of failed haemostasis at that moment are immediate.

PROCOAGULANT FACTORS RISE: Factors VIII, X and XII, von Willebrand factor and ristocetin cofactor all increase. Factor VII rises progressively and may reach very high levels by term. Fibrinogen roughly doubles from pre-pregnancy concentrations by term.[7,8] Factor V rises early then plateaus. Factor XIII, which cross-links fibrin, increases in the first trimester but falls to approximately half of non-pregnant levels by term.[9] Prothrombin concentrations are essentially unchanged at term. Protein C is stable or modestly increased, while free protein S falls substantially-a functional acquired protein S deficiency.

FIBRINOLYSIS IS SUPPRESSED: Tissue plasminogen activator activity falls, driven by an approximately threefold rise in plasminogen activator inhibitor-1 (PAI-1) and by the appearance of placentally derived PAI-2, which reaches roughly 25-fold normal levels at term. Thrombin-activatable fibrinolysis inhibitor rises

in the third trimester. The net effect is that fibrin, once formed, is cleared less efficiently. D-dimer concentrations rise physiologically through pregnancy without indicating pathological intravascular coagulation-a fact of considerable diagnostic importance, discussed below.

RECOVERY IS INCOMPLETE FOR WEEKS: Tissue plasminogen activator activity returns towards normal within about an hour of delivery and PAI-1 falls, but PAI-2 remains elevated for several days. Coagulation and fibrinolysis generally return to the pre-pregnancy state over three to four weeks postpartum.[10] The platelet count declines through pregnancy, most markedly in the third trimester, through a combination of haemodilution and increased consumption.[11]

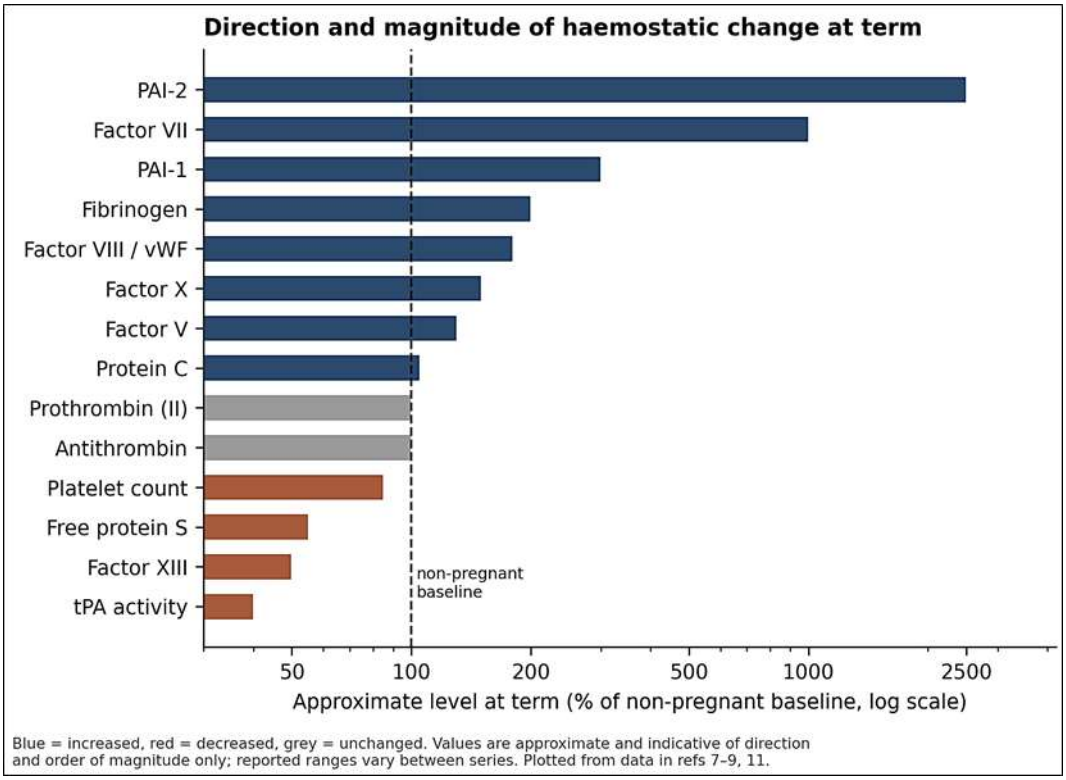

Figure No. 1: Direction and magnitude of haemostatic change at term relative to the non-pregnant baseline. The near-uniform shift is towards procoagulation: the largest increases are in placentally derived PAI-2 and in factor VII, while the principal decreases-free protein S, factor XIII and tPA activity-remove brakes rather than adding accelerators. Values are indicative of direction and order of magnitude; reported ranges vary between series. Original figure plotted from data in refs 7-9 and 11

Table No. 1: Direction of haemostatic change in normal pregnancy

Component	Change in pregnancy	Note
Fibrinogen	↑↑ (≈200% of baseline at term)	Principal contributor to raised ESR
Factor VII	↑↑↑	Marked, progressive
Factors VIII, X, XII, vWF	↑	
Factor V	↑ early, then plateau	
Factor XIII	↑ first trimester, ↓ to ≈50% at term	Fibrin cross-linking
Prothrombin (II)	↔ at term	
Protein C	↔ or slight ↑	
Free protein S	↓↓	Acquired functional deficiency
Antithrombin	↔	
PAI-1	↑ (≈3-fold)	

PAI-2	↑↑↑ (≈25-fold at term)	Placental origin
tPA activity	↓	Normalises ≈1 h postpartum
D-dimer	↑	Limits diagnostic utility
Platelet count	↓	Greatest fall in third trimester

↑ increased, ↓ decreased, ↔ unchanged. Compiled from refs 7-9 and 11.

VIRCHOW'S TRIAD IN THE OBSTETRIC PATIENT STASIS: Increased venous capacitance combines with mechanical outflow obstruction by the gravid uterus to reduce venous flow velocity in the legs by approximately 50% by weeks 25-29 of gestation, a reduction that persists until around six weeks postpartum.[12] Anatomy determines laterality: compression of the left common iliac vein by the overlying right common iliac artery, accentuated by the enlarging uterus, accounts for the striking predominance of left-sided DVT-approximately 82% of cases in pregnancy and the puerperium.[13] Pelvic vein thrombosis, uncommon outside pregnancy, accounts for 6-11% of obstetric DVT.

ENDOTHELIAL INJURY: Delivery-vaginal or operative-produces direct endothelial trauma in pelvic veins, compounded by venous hypertension. Caesarean section adds a surgical insult with procoagulant release and reduced tPA generation.

HYPERCOAGULABILITY: The gestational shift described above, superimposed in some women on inherited or acquired thrombophilia. An estimated 20-50% of women who sustain venous thrombosis in pregnancy have an identifiable underlying procoagulant genetic condition.[14]

The important corollary is that these three exposures do not peak simultaneously. Hypercoagulability is maximal at delivery and in the days immediately following; stasis is maximal in late pregnancy and early puerperium and is heavily modified by mobilisation practices; endothelial injury is an acute peripartum event. Their convergence explains why the puerperium, and specifically its first three weeks, carries the highest instantaneous risk of any period in a woman's reproductive life.

EPIDEMIOLOGY

GLOBAL ESTIMATES

The incidence of VTE in pregnancy is conventionally cited as approximately 1 in 1,200 pregnancies, with a strong age gradient-roughly 1 in 1,600 in women under 35 and 1 in 800 in women over 35.[15] Case fatality is of the order of 1-2%. DVT accounts for 75–80% of obstetric VTE and pulmonary embolism for the remainder,[16] and events divide approximately equally between the antenatal and postnatal periods-but because the puerperium is short, the instantaneous risk postpartum is several-fold higher than antenatally.

Large cohorts allow risk to be attached to specific exposures. In a Danish nationwide prospective cohort of 1.3 million pregnancies, incidence rates for postpartum VTE were 25.5 per 10,000 person-years with obesity, 23.2 with elective caesarean section, 34.0 with emergency caesarean section, 20.3 with major postpartum bleeding, 45.8 with pre-eclampsia and 18.3 with intrauterine growth restriction or fetal death; hospitalisation with infection in the puerperium carried a rate of 62.7 per 10,000 person-years.[17] A meta-analysis of caesarean section reported a pooled odds ratio for VTE of 3.7 (95% CI 3.0-4.6) versus vaginal delivery, largely independent of age and BMI, stronger for emergency than elective procedures, and corresponding to an absolute risk of approximately 3 per 1,000.[18]

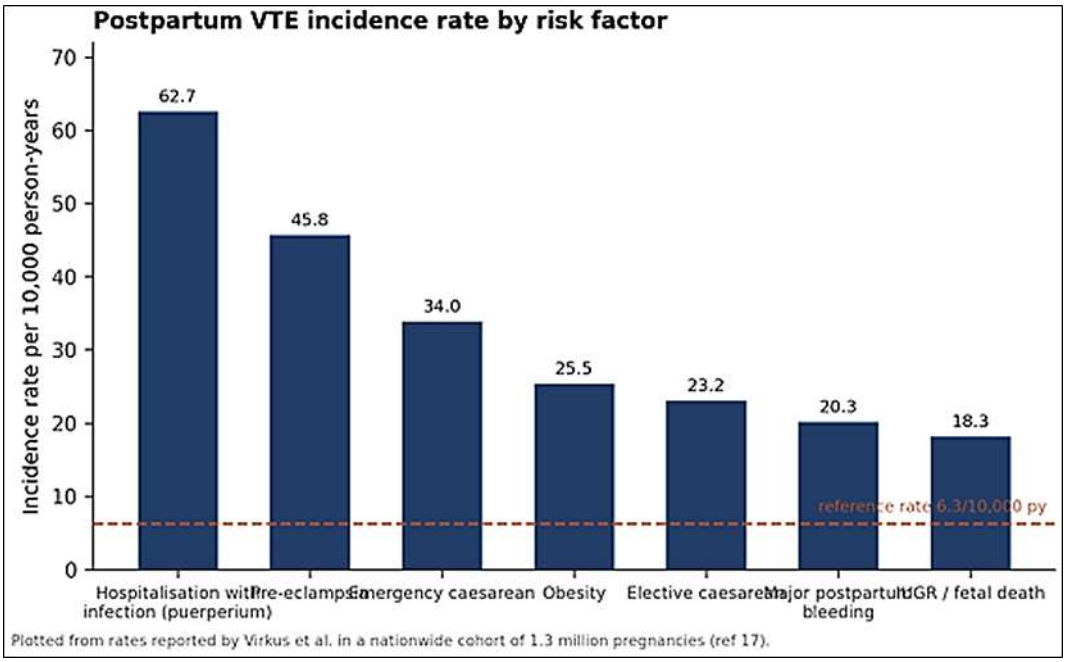

Figure No. 2: Postpartum VTE incidence rate by risk factor. Puerperal infection carries the highest rate, followed by pre-eclampsia and emergency caesarean section; each of the seven exposures shown carries at least a threefold elevation above the reference rate. Original figure plotted from rates reported by Virkus *et al.* in a nationwide cohort of 1.3 million pregnancies (ref 17).

THE INDIAN PICTURE

Indian data are limited and probably incomplete. Available figures suggest approximately 0.1% of Indian pregnant women present with symptomatic DVT,[19] and pulmonary embolism accounts for around 3.75% of maternal deaths-roughly one-third of the proportion reported in Western series.[20] Under-ascertainment is the likeliest explanation, given limited access to confirmatory imaging in many settings, competing causes of maternal death that dominate audit attention, and the diagnostic difficulty of PE in a population where breathlessness has many other causes.

Three considerations suggest that the Indian burden may increase. Maternal age at first birth is rising; obesity prevalence is rising; and assisted reproductive technology use is expanding, each of which independently elevates risk. A fourth consideration is specific to the region. Prolonged postpartum confinement is culturally normative across much of the Indian subcontinent: in a prospective cohort of 150 women who identified as being from the Indian subcontinent or as Chinese, 85% were confined to bed postpartum for cultural reasons and 51% rested in bed as much as possible, with an inverse correlation between number of children and degree of immobility.[21] Enforced bed rest is precisely the exposure that early twentieth-century practice mistakenly prescribed as treatment. Its prevalence in Indian postpartum women is a plausible risk amplifier that no existing risk-assessment model incorporates.

Implementation of prophylaxis in India is minimal. In a cross-sectional study of 1,652 postpartum women at a South Indian tertiary centre, RCOG stratification identified 3 women at high risk, 598 at intermediate risk and 254 at low risk; 601 women (36.4%) qualified for prophylaxis but only 5 (0.8%) received it.[22] The gap between guideline and practice is therefore close to total-and, importantly, it exists in the absence of local evidence that closing it would prevent events.

RISK FACTORS AND RISK ASSESSMENT

The single strongest individual risk factor is a personal history of thrombosis; recurrent events account for 15-25% of VTE occurring in pregnancy.[14] Inherited thrombophilia is the other major individual determinant. Calculated risk is approximately doubled by multifetal gestation, hyperemesis, haemorrhage, caesarean section, obesity, pre-eclampsia and postpartum infection; it is substantially higher after stillbirth and peripartum hysterectomy, and inflammatory bowel disease raises risk two- to threefold.

The RCOG approach (Green-top Guideline 37a) converts these into a cumulative score, with women stratified into high, intermediate and low risk and prophylaxis duration determined accordingly.[23] Intermediate-risk classification follows either from a single strong factor-BMI ≥40 kg/m², caesarean section in labour, non-routine perineal surgery, or a listed medical comorbidity-or from any two of a longer list including age >35, BMI ≥30 kg/m², parity ≥3, smoking, family history of VTE, gross varicose veins, systemic infection, immobility, pre-eclampsia, multiple pregnancy, preterm delivery, stillbirth, prolonged labour and major postpartum haemorrhage or transfusion. Ten days of postnatal LMWH is recommended for this group.

The critical weakness is that these models perform poorly on formal evaluation. A health technology assessment that systematically reviewed risk-assessment models concluded that in unselected postpartum women and following caesarean section, model performance is poor enough that offering prophylaxis on the basis of those models has unfavourable cost-effectiveness with relatively low decision uncertainty-that is, the analysis was fairly confident that model-based prophylaxis is not worthwhile in those groups.[24] Kotaska has made a related methodological criticism: prediction models draw on studies reporting asymptomatic DVT detected by screening, risk estimates are not adjusted for time of exposure, and the harms of heparin are systematically under-weighted, with numbers needed to treat and to harm universally absent from the guideline literature.[25]

CLINICAL FEATURES AND DIAGNOSIS

DEEP VEIN THROMBOSIS

The dominant symptoms are swelling and calf discomfort. Leg pain occurs in about half of patients but is non-specific; tenderness is present in around three-quarters.[26] Signs include oedema, dilated superficial veins, a stiff or tense calf, warmth and erythema. Advanced presentations include phlegmasia alba dolens and phlegmasia cerulea dolens, with venous gangrene in rare cases. Iliofemoral thrombosis may present atypically with abdominal pain, back pain and whole-leg oedema.

The classical eponymous signs are of limited value. Homans' sign-resistance or pain on forcible dorsiflexion-is non-specific and should not be elicited, since it carries a theoretical risk of dislodging thrombus. Bancroft's (Moses') sign is positive when pain is produced by compressing the calf anteroposteriorly against the tibia but not by side-to-side compression. Lowenberg's sign is pain elicited by inflating a blood-pressure cuff around the calf to 80 mmHg.

Clinical assessment alone is inadequate: up to 46% of patients with characteristic symptoms have negative venography, while up to 50% of those with imaging-documented thrombosis lack specific symptoms.[27] Compression ultrasonography is the first-line investigation in pregnancy. Where proximal compression ultrasonography is normal but iliac vein thrombosis is clinically suspected-whole-leg swelling, or pain in the back, buttock or flank-dedicated iliac vein imaging is required.[28] D-dimer is unhelpful in pregnancy because of the physiological rise described above; conventional thresholds generate unacceptable false-positive rates.[29]

Complications of untreated DVT include pulmonary embolism, post-thrombotic syndrome with chronic venous insufficiency, and recurrence.

PULMONARY EMBOLISM

Presentation ranges from mild dyspnoea to cardiac arrest. Dyspnoea, pleuritic chest pain, tachypnoea and tachycardia are the commonest features; haemoptysis, syncope, cyanosis and hypotension indicate more extensive obstruction. The differential in pregnancy is broad and includes pneumonia, amniotic fluid embolism, peripartum cardiomyopathy, pneumothorax, aortic dissection and anxiety.

Arterial blood gases classically show hypoxaemia with a widened alveolar-arterial gradient, respiratory alkalosis and hypocapnia; hypercapnia or lactic acidosis suggests massive PE with obstructive shock. Troponin and brain natriuretic peptide elevations reflect right ventricular strain and carry prognostic rather than diagnostic value.[30,31] Electrocardiography most often shows sinus tachycardia; the S1Q3T3 pattern is specific but insensitive.[32] Chest radiography is usually normal or non-specific, but may show Hampton's hump (a peripheral wedge-shaped opacity) or Westermark's sign (regional oligaemia).

Computed tomographic pulmonary angiography is the principal confirmatory investigation, with high sensitivity and specificity in the general population,[33] and is acceptable in pregnancy

with attention to fetal and maternal breast dose. Ventilation-perfusion scintigraphy remains an alternative, particularly where the chest radiograph is normal, and delivers a lower breast dose. Pulmonary angiography is now reserved for cases where non-invasive imaging is inconclusive or catheter-directed intervention is planned. Diagnostic algorithms for pregnancy generally begin with compression ultrasonography of the legs, since a positive result establishes an indication for anticoagulation without further thoracic imaging.

PHARMACOLOGY AND MANAGEMENT

LOW-MOLECULAR-WEIGHT HEPARIN

LMWH is the agent of choice for both prophylaxis and treatment of VTE in pregnancy and has largely displaced unfractionated heparin.[28] LMWHs are glycosaminoglycan chains of alternating D-glucosamine and uronic acid residues with a mean molecular weight of approximately 5,000 Da. They act by potentiating antithrombin, accelerating inactivation of factors IIa, IXa and Xa, with relatively greater activity against factor Xa than thrombin.[34] They do not cross the placenta.

Practical advantages over unfractionated heparin include once-or twice-daily subcutaneous administration, predictable dose-response permitting weight-based dosing without routine monitoring, and lower rates of heparin-induced thrombocytopenia and osteoporosis. Routine measurement of peak anti-Xa activity is not required except at extremes of body weight (<50 kg or ≥90 kg) or in the presence of complicating factors such as renal impairment. Routine platelet monitoring is not indicated for LMWH; it is recommended every two to three days from day 4 to day 14 for postoperative obstetric patients receiving unfractionated heparin.

Table No. 2: Adverse effects and contraindications of prophylactic enoxaparin

Adverse effects	Contraindications
Bleeding (commonest)	Known hypersensitivity to enoxaparin or heparins
Heparin-induced thrombocytopenia	Active major bleeding
Injection-site pain, bruising or bleeding	HIT within the past 100 days, or circulating antibodies
Nausea, headache, confusion	Hypersensitivity to benzyl alcohol (neonates; multi-dose vials)
Gastrointestinal bleeding; rectus sheath haematoma	
Osteoporosis (long exposure)	
Transaminitis (rarely clinically significant)	
Bullous haemorrhagic dermatosis; allergic skin reactions	

Compiled from product information and Greer & Nelson-Piercy (refs 35, 36).

The best safety data come from a systematic review of 61 studies comprising 2,603 pregnancies: significant bleeding, generally attributable to primary obstetric causes, occurred in 1.98%; allergic skin reactions in 1.80%; heparin-induced thrombocytopenia in 0%; thrombocytopenia unrelated to LMWH in 0.11%; and osteoporotic fracture in 0.04%, with no maternal deaths.[35]

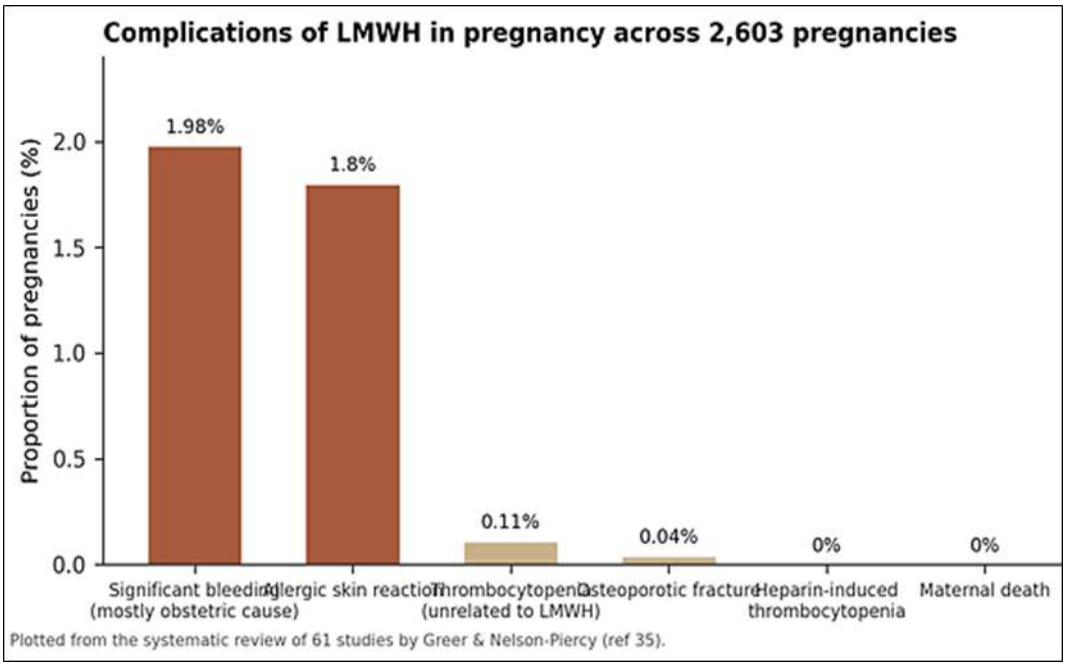

Figure No. 3: Complications of LMWH across 2,603 pregnancies. Every complication rate falls below 2%, and heparin-induced thrombocytopenia and maternal death were not observed. The practical implication is that the barrier to obstetric thromboprophylaxis is not short-term maternal toxicity. Original figure plotted from the systematic review of 61 studies by Greer & Nelson-Piercy (ref 35)

Dose selection is not fully settled. A randomised trial in obese post-caesarean women found that weight-based twice-daily dosing achieved prophylactic anti-Xa levels more reliably than fixed daily dosing without entering the therapeutic range.[37] In the higher-risk setting of previous VTE, the Highlow trial randomised 1,110 pregnant and postpartum women to weight-adjusted intermediate-dose versus fixed low-dose LMWH and found events in 11 (2%) versus 16 (3%)-a difference not reaching significance despite a sample two orders of magnitude larger than most obstetric prophylaxis studies.[38] Duration is similarly unresolved: a single trial comparing five- versus ten-day post-caesarean LMWH found no difference in maternal mortality or in symptomatic thromboembolic events.[39] Comparative work between agents has found bemiparin effective as postpartum prophylaxis with fewer wound complications than enoxaparin.[40]

OTHER ANTICOAGULANTS

Vitamin K antagonists cross the placenta and anticoagulate the fetus.[41] They are associated with miscarriage, prematurity, low birth weight, neurodevelopmental problems and fetal bleeding, with a risk of embryopathy on first-trimester exposure, and should be avoided antenatally.[42] They are compatible with breastfeeding.

Direct oral anticoagulants (rivaroxaban, apixaban, edoxaban, dabigatran) lack pregnancy safety data, are likely to cross the placenta, and should be avoided antenatally.

Alternative parenteral agents- fondaparinux, argatroban, danaparoid, r-hirudin-are options for women who cannot tolerate heparins, for example following heparin-induced thrombocytopenia.

MECHANICAL AND INTERVENTIONAL MEASURES

Graduated compression stockings and intermittent pneumatic compression are recommended by several bodies for all women undergoing caesarean section, beginning before surgery and continuing until fully ambulant.[43] Their attraction is the absence of bleeding risk; their limitation is modest and inconsistent evidence of efficacy and imperfect adherence.

Inferior vena cava filters capture emboli before they reach the pulmonary circulation. Experience in pregnancy is limited and complications-filter fracture, migration, failure of retrieval, and caval perforation-are documented.[44] RCOG guidance suggests considering a temporary filter in the peripartum period for women with iliac vein thrombosis, or

with proven DVT and recurrent PE despite adequate anticoagulation.[28] ACOG offers no pregnancy-specific recommendation. A systematic review of publications from 1981 to 2014 identified 124 pregnant women, all from case reports or small series, in whom filters were placed predominantly for absolute indications: failure of anticoagulation, or complications of or contraindications to anticoagulation.[45]

Thrombolysis and catheter-directed therapy are reserved for limb- or life-threatening thromboembolism. Concerns centre on maternal haemorrhage and placental complications including abruption, preterm labour and fetal demise, although transplacental passage of tissue plasminogen activator and streptokinase is minimal. Pharmacomechanical catheter-directed thrombolysis offers a less morbid approach to acute iliofemoral DVT than systemic lysis. Surgical embolectomy is generally reserved for haemodynamically unstable PE where thrombolysis has failed or is contraindicated.

THE GUIDELINES AND THEIR DISCORDANCE

WHERE THEY AGREE

All major guidelines agree that LMWH is the agent of choice; that vitamin K antagonists and DOACs should be avoided antenatally; that women with previous VTE or high-risk thrombophilia warrant prophylaxis; that risk should be formally assessed at booking, on any antenatal admission and after delivery; and that the puerperium carries higher instantaneous risk than the antenatal period.

WHERE THEY DIVERGE

Divergence concerns the large middle population: women with common, individually modest risk factors-caesarean delivery, obesity, age, parity, pre-eclampsia, prematurity-who constitute the great majority of any obstetric cohort.

Table No. 3: Broad orientation of major guidelines to postpartum pharmacological prophylaxis

	RCOG (GTG 37a)	ACOG	ASH
Framework	Cumulative risk score; high/intermediate/low strata	Narrower, history-driven indications; mechanical prophylaxis emphasised for caesarean	Evidence-graded recommendations; explicit acknowledgement of low certainty
Population captured for postpartum LMWH	Large-a majority of post-caesarean women in most cohorts	Small-a minority	Intermediate
Duration	≥10 days (intermediate risk); 6 weeks (high risk)	Variable by indication	Variable by indication
Practical consequence	Higher drug volume, cost and injection burden	Fewer women treated; greater reliance on mechanical measures	-

This table summarises orientation rather than reproducing recommendation text. Readers should consult the current version of each guideline, since all are periodically revised.

The quantitative consequences of these differences have been measured. Palmerola and colleagues compared three major guidelines applied to post-caesarean patients and found that under ACOG recommendations a minority would receive pharmacological prophylaxis whereas under RCOG recommendations a large majority would, concluding that research comparing the risks and benefits of the competing recommendations was urgently needed.[43] Federspiel and colleagues applied different guideline criteria to a US national readmissions cohort and found that the estimated VTE incidence among patients recommended for prophylaxis ranged from 35.2 per 1,000 deliveries under 2018 ASH criteria to 2.5 per 1,000 under 2015 RCOG criteria-a fourteen-fold spread generated entirely by definitional choices rather than by any difference in underlying biology.[46] Kayikci and colleagues evaluated ACOG and RCOG recommendations against real-world practice and found significant discrepancies in dose and duration, agreement with clinical approach of approximately 53%, a tendency towards undertreatment under RCOG and overtreatment

under ACOG relative to actual practice, and a markedly greater requirement for prefilled LMWH syringes under RCOG.[47]

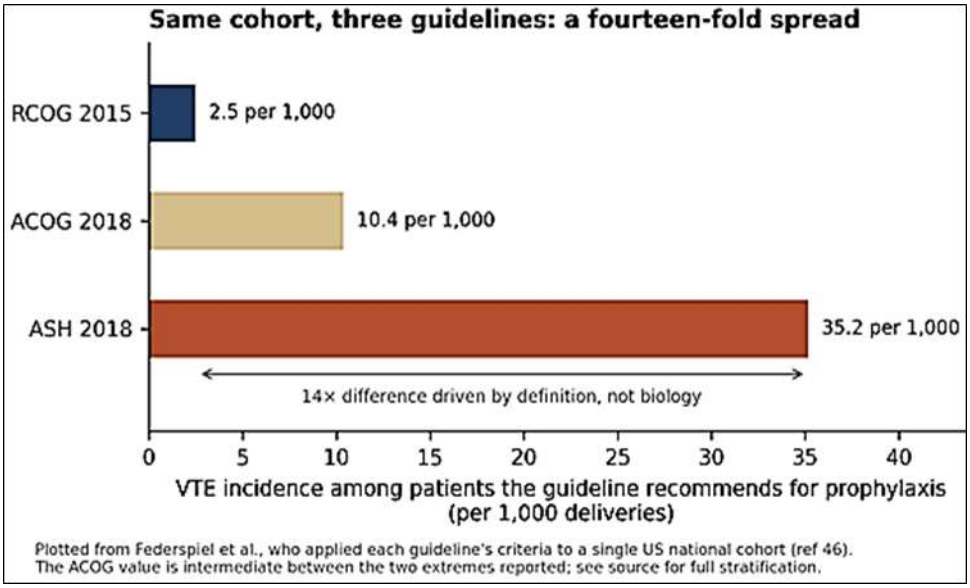

Figure No. 4: Applying three guidelines to a single cohort produces a fourteen-fold difference in the VTE incidence observed among the women each guideline selects for prophylaxis. Because the underlying population is identical, the spread reflects the breadth of each guideline's inclusion criteria rather than any difference in biology: broader criteria dilute the treated population with lower-risk women. Original figure plotted from Federspiel *et al.* (ref 46).

The interpretation is uncomfortable but straightforward. When expert panels reviewing overlapping evidence produce recommendations that differ several-fold in the population treated, the disagreement is not primarily about values or context. It is a signal that the evidence does not determine the answer.

THE UNDERLYING EVIDENCE BASE

The 2021 Cochrane review of VTE prophylaxis in pregnancy and the early postnatal period included 29 trials and 3,839 women, judged overall to be at moderate to high risk of bias, with poorly defined VTE risk factors among participants. For the specific comparison of postnatal LMWH versus no treatment or placebo, there were no events for maternal death, symptomatic thromboembolic events, symptomatic PE or symptomatic DVT-across a maximum of two trials and 58 women. Adverse effects severe enough to stop treatment were not reported. The review concluded that the evidence is very uncertain regarding both benefits and harms.[48] The earlier 2014 Cochrane review reached the same conclusion, finding no differences between five- and ten-day post-caesarean regimens and no difference in bleeding between LMWH and placebo.[39]

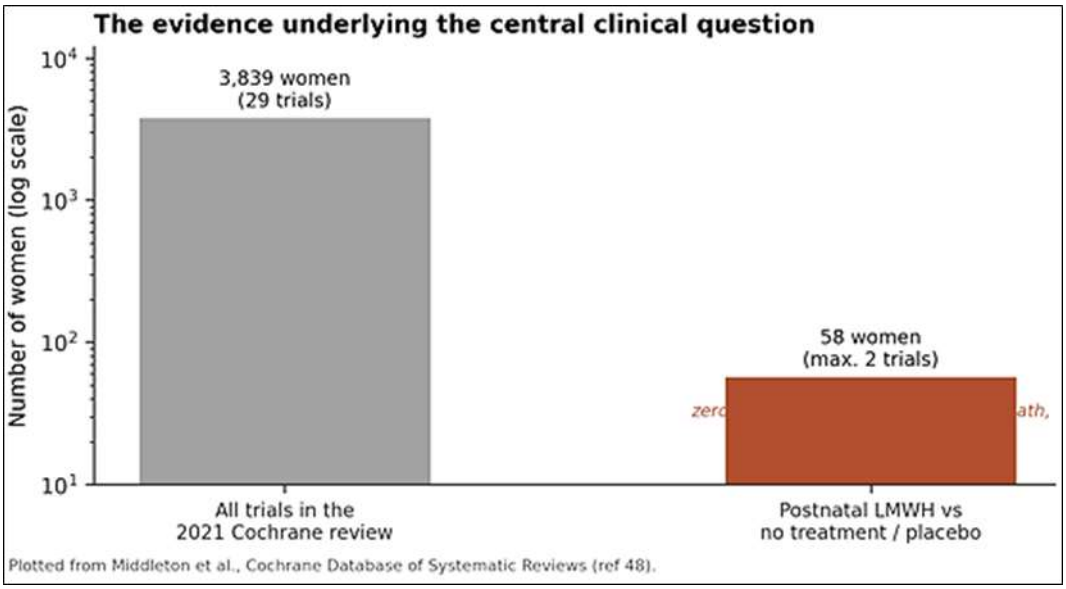

Figure No. 5: The evidence gap at the centre of the field. The 2021 Cochrane review pooled 29 trials and 3,839 women, but the specific comparison that determines postpartum policy-LMWH versus no treatment or placebo-rested on a maximum of two trials and 58 women, in which no events of any kind were recorded. Note the logarithmic vertical scale. Original figure plotted from Middleton *et al.* (ref 48)

A feasibility study for a randomised open-label trial of postpartum LMWH concluded that conventional trial designs may be unworkable at the required scale, and that cluster randomisation, before-and-after observational designs or opt-out consent may be necessary.[49] The 2024 health technology assessment concluded that a randomised trial of thromboprophylaxis in obese postpartum women would carry substantial value and be more acceptable and feasible than one recruiting women with previous VTE.[24] Kotaska's appraisal concluded that for most postpartum women LMWH may do more harm than good, and that women with common risk factors should be offered prophylaxis only as part of a randomised trial.[25]

Table No. 4: Summary of principal evidence syntheses

Study	Design	Principal finding
Middleton *et al.* 2021[48]	Cochrane review; 29 trials, 3,839 women	Very uncertain evidence; no events in postnatal LMWH vs no treatment (max. 2 trials, 58 women)
Bain *et al.* 2014[39]	Cochrane review	No difference 5- vs 10-day post-caesarean LMWH; no bleeding difference vs placebo
Davis *et al.* 2024[24]	HTA; systematic review + economic model	Risk models perform poorly in unselected/post-caesarean women; RCT in obese postpartum women high-value
Kotaska 2018[25]	Critical appraisal	Benefits overstated, harms under-appreciated; NNT and NNH absent from guidelines
Greer & Nelson-Piercy 2005[35]	Systematic review; 2,603 pregnancies	LMWH safe and effective; bleeding 1.98%, skin reaction 1.80%, HIT 0%
Blondon *et al.* 2016[18]	Meta-analysis	Caesarean vs vaginal OR 3.7 (3.0-4.6); ≈3 per 1,000 absolute risk
Bistervels *et al.* 2022[38]	RCT; 1,110 women with prior VTE	Intermediate-dose 2% vs low-dose 3%; not significant
Federspiel *et al.* 2021[46]	Retrospective cohort	VTE incidence among those recommended for prophylaxis: 2.5–35.2 per 1,000, depending on guideline

GAPS AND A RESEARCH AGENDA

Five gaps stand out.

1. NO ADEQUATELY POWERED RANDOMISED TRIAL IN THE COMMON-RISK-FACTOR POPULATION

This is the central gap and everything else follows from it. The arithmetic is discouraging but not prohibitive: detecting a reduction in symptomatic VTE from 1% to 0.3% with 80% power at α = 0.05 requires roughly 2,065 women per arm; from 2% to 0.6%, roughly 1,024 per arm. These are large but not unprecedented obstetric trials, and multicentre or cluster designs bring them within reach. The alternative-continuing to treat or withhold treatment from very large numbers of women on the basis of expert opinion-is not obviously more acceptable.

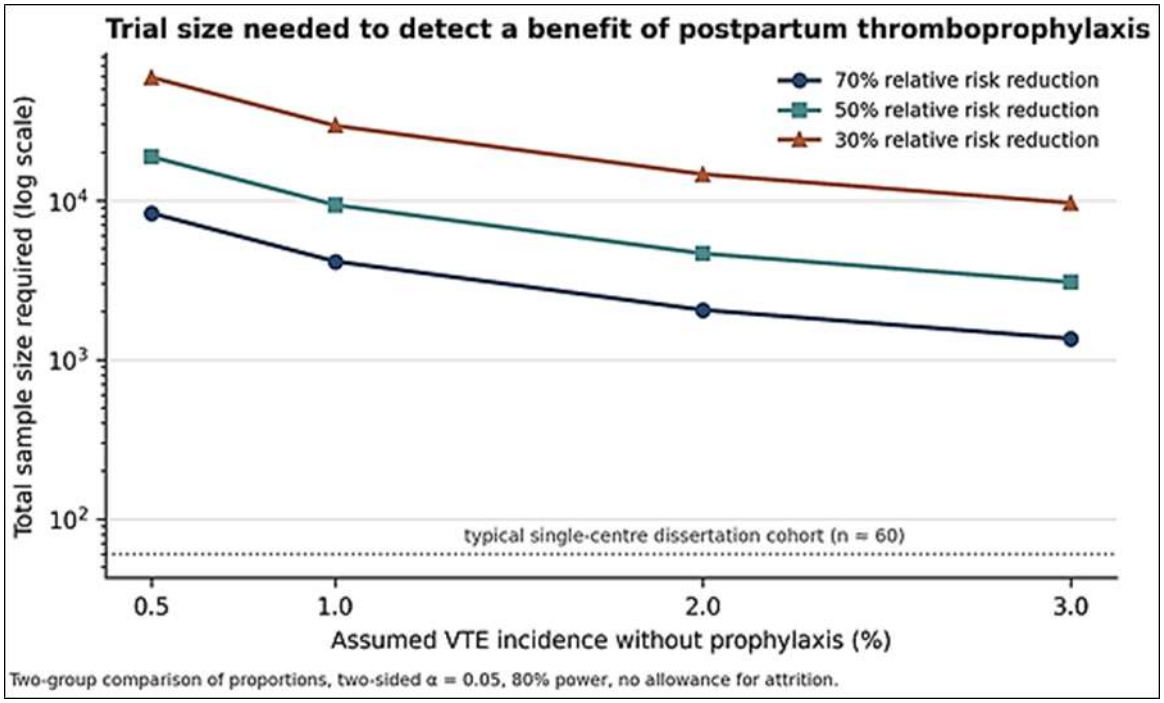

Figure No. 6: Total sample size required to detect a benefit of postpartum thromboprophylaxis, by assumed baseline incidence and effect size. Because the outcome is rare, required trial size is dominated by the baseline event rate: at a plausible 1% incidence, demonstrating even a 70% relative risk reduction requires over 4,000 women. The dotted line marks a typical single-centre dissertation cohort, illustrating why individual small studies cannot resolve this question and why multicentre or cluster designs are necessary. Two-sided α = 0.05, 80% power, no allowance for attrition

2. OUTCOME DEFINITIONS ARE INCONSISTENT

Studies reporting screening-detected asymptomatic DVT are not measuring the same thing as studies reporting symptomatic events, and pooling them inflates apparent benefit. Future work should pre-specify symptomatic, objectively confirmed VTE as the primary outcome, with asymptomatic events reported separately.

3. HARMS ARE UNDER-MEASURED

Bleeding, wound complications, haematoma, injection-site reactions, HIT and treatment discontinuation should be captured with the same rigour as the efficacy outcome, and numbers needed to treat and to harm should be reported. Their consistent absence from guideline documents is a serious gap.

4. RISK-ASSESSMENT MODELS NEED EXTERNAL VALIDATION

Existing models perform poorly, and none has been validated in South Asian populations. Model development should incorporate locally relevant exposures-including duration and degree of postpartum immobility, which is culturally patterned and currently unmeasured.

5. INDIAN INCIDENCE DATA ARE ABSENT

Before any position can be taken on whether RCOG guidance should be adopted, adapted or set aside in India, the denominator is needed. A multicentre prospective registry recording RCOG risk stratification, prophylaxis received, and objectively confirmed symptomatic VTE through six postpartum weeks would be feasible within existing tertiary networks and would be of immediate value. The observation that only 0.8% of eligible women at one South Indian centre actually received prophylaxis[22] means that India currently constitutes a large natural experiment whose results are simply not being recorded.

Two further practical points deserve emphasis. Duration of follow-up in most studies is too short: risk peaks in the first three postpartum weeks and persists for six, yet many studies, including much of the interventional literature, observe for ten days or fewer. Cost and burden are legitimate outcomes: the substantially greater syringe requirement under RCOG criteria[47] is a material consideration in resource-constrained public health systems, and should be reported in any economic evaluation applicable to India.

CONCLUSION

The physiology of pregnancy-associated hypercoagulability is well characterised, and the case that the puerperium carries elevated thrombotic risk is not in dispute. What remains unresolved is the clinical question that matters: whether pharmacological prophylaxis benefits the large population of postpartum women with common, individually modest risk factors. Major guidelines answer that question differently enough that applying one rather than another changes the treated population several-fold and changes the estimated event rate among those treated by more than an order of magnitude. Successive systematic reviews have found the underlying evidence very uncertain, and the specific comparison of postnatal LMWH against no treatment rests on a handful of women.

LMWH is safe in pregnancy and the puerperium on all available evidence, and the practical barrier to prophylaxis is not maternal toxicity. But safety is not efficacy, and the absence of demonstrated harm is not a reason to treat. Until an adequately powered randomised trial with symptomatic, objectively confirmed outcomes and full harm ascertainment is completed, clinicians will continue to make this decision without evidence. In India specifically, where incidence is poorly characterised, ascertainment is likely incomplete, and cultural postpartum immobility adds an unmeasured exposure, the immediate priority is a prospective incidence registry. Without a reliable local denominator, neither the adoption nor the rejection of imported guidance can be defended.

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