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THROMBOPROPHYLAXIS IN PREGNANCY: CLINICAL PROTOCOLS, PATHOPHYSIOLOGY, RISK ASSESSMENT MODELS, AND MANAGEMENT STRATEGIES IN LOW- AND MIDDLE-INCOME COUNTRIES

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ABSTRACT Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), remains a leading cause of maternal morbidity and mortality worldwide [1,2]. Pregnancy induces a physiological hypercoagulable state driven by hormonal shifts, altered clotting factor concentrations, reduced natural anticoagulants, and mechanical venous stasis [3]. In low- and middle-income countries (LMICs) such as India, the clinical burden is further amplified by unique epidemiological factors, including a higher incidence of postpartum cerebral venous sinus thrombosis (CVST), high multiparity, infection, anemia, and delayed healthcare presentation [4,5]. While international guidelines—such as those from the Royal College of Obstetricians and Gynaecologists (RCOG), American College of Obstetricians and Gynecologists (ACOG), American Society of Hematology (ASH), and Federation of Obstetric and Gynaecological Societies of India (FOGSI)—provide risk-stratified thromboprophylaxis algorithms, implementation in resource-constrained settings faces significant hurdles [5,6]. This review synthesizes current evidence on the physiological mechanisms of pregnancyassociated hypercoagulability, evaluates major risk assessment models (RAMs), outlines pharmacological (LMWH, UFH) and non-pharmacological management strategies, and addresses specific diagnostic and therapeutic challenges encountered in Indian clinical practice.

KEYWORDS :

1. INTRODUCTION

Venous thromboembolism (VTE) is one of the most critical and preventable causes of direct maternal death worldwide [1,2]. The physiological adaptations of pregnancy, designed evolutionarily to protect against catastrophic hemorrhage during parturition, inherently increase the risk of thromboembolic events by 4- to 5-fold compared to non-pregnant women of similar age [3]. The incidence of pregnancyassociated VTE is estimated at 1 to 2 per 1,000 pregnancies in high-income countries [2]. However, in resource-constrained settings like India, true incidence figures are often obscured by underreporting, non-uniform diagnostic facilities, and regional disparities [4,5]. Furthermore, maternal mortality in LMICs remains heavily influenced by postpartum complications, among which unrecognised PE and cerebral venous sinus thrombosis (CVST) play major roles [5,8].

Effective thromboprophylaxis requires early risk identification, accurate risk stratification, and timely intervention with pharmacological or mechanical modalities [6]. However, applying Western risk assessment models (RAMs) directly to LMIC settings often presents challenges regarding cost, compliance, and clinical feasibility [5,9]. This review provides a narrative synthesis of the hypercoagulable state of pregnancy, clinical risk factors, risk stratification frameworks, and practical management strategies, with a particular focus on Indian healthcare scenarios.

2. Physiology of Coagulation in Pregnancy

Pregnancy represents a classic manifestation of Virchow's Triad: hypercoagulability, venous stasis, and vascular endothelial injury [3].

2.1 Hypercoagulability

From the first trimester, circulating levels of procoagulant factors rise significantly. Factors VII, VIII, X, von Willebrand factor (vWF), and fibrinogen increase by 200–300%, creating a prothrombotic environment [3,7]. Concurrently, natural anticoagulant pathways are suppressed: free Protein S levels fall markedly due to increased binding to C4b-binding protein, and acquired activated protein C (APC) resistance develops [3]. Fibrinolysis is simultaneously inhibited by placental expression of plasminogen activator inhibitor-1 (PAI-1) and PAI-2 [7].

2.2 Venous Stasis

Progesterone-mediated smooth muscle relaxation causes progressive venodilation and a ~50% reduction in lower-limb venous blood velocity by the third trimester [2]. Furthermore, mechanical compression of the inferior vena cava and left common iliac vein by the enlarging gravid uterus leads to marked stasis [3]. This anatomical dynamic explains why over 80% of deep vein thrombosis (DVT) during pregnancy occurs in the left lower extremity [2,3].

2.3 Endothelial Injury

During labor and delivery—whether vaginal or via Cesarean section—pelvic vascular trauma and microvascular disruption occur, completing Virchow's Triad and triggering localized coagulation activation [7].

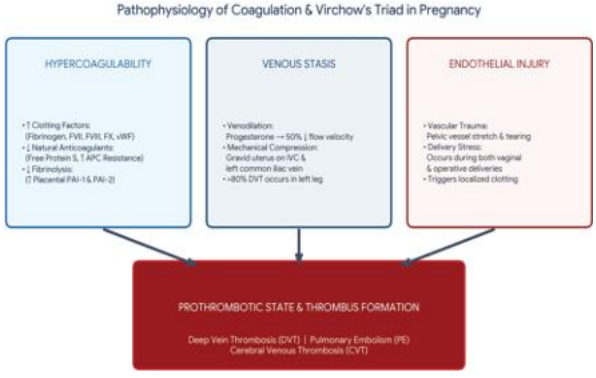

Figure 1: Pathophysiology of Pregnancy-Associated Hypercoagulability and Virchow's Triad.

3. Epidemiology of Pregnancy-Associated VTE

3.1 Global Perspective

Globally, the risk of VTE is elevated throughout all three trimesters, peaking during the immediate postpartum period (particularly the first 6 weeks after delivery), where the daily risk is up to 20 to 80 times higher than in non-pregnant women [6,7]. Approximately 75–80% of pregnancy-associated VTE cases present as DVT, while 20–25% manifest as PE, which carries a mortality rate of up to 15% if untreated [2,6].

3.2 The Indian Epidemiological Landscape

In India, while classic lower-limb DVT and PE are well-documented, the epidemiological profile exhibits notable differences [4,5]:

1. **High Burden of Postpartum CVST:** Cerebral venous sinus thrombosis accounts for a significantly higher proportion of maternal VTE in India compared to Western populations [5,8]. Factors contributing to this include unhygienic post-partum isolation practices, severe dehydration, anemia, and home

deliveries [5,8].

2. **Impact of Anemia and Infection:** Severe nutritional anemia and peripartum systemic infections are highly prevalent in rural India, both of which accelerate endothelial dysfunction and promote thrombosis [4,5].
3. **Multiparity and Advanced Maternal Age:** High parity and rising maternal age in urban centers further compound thrombotic risks [4,10].

4. Risk Factors for Pregnancy-Associated VTE

Risk factors can be broadly classified into pre-existing, transient/gestational, and intrapartum/postpartum factors [6]:

4.1 Pre-existing Risk Factors

- Prior history of unprovoked or estrogen-related VTE (strongest individual predictor) [6].
- Inherited thrombophilia (e.g., Factor V Leiden mutation, Prothrombin G20210A mutation, Antithrombin III deficiency, Protein C/S deficiency) [6,7].
- Acquired thrombophilia (Antiphospholipid Syndrome - APS) [6].
- Obesity (BMI ≥30 kg/m², particularly BMI ≥40 kg/m²) [6,10].
- Pre-existing medical comorbidities (systemic lupus erythematosus, inflammatory bowel disease, sickle cell disease, chronic kidney disease) [6].

4.2 Obstetric / Gestational Risk Factors

- Multiple gestation (twins/triplets) [6,10].
- Preeclampsia and fetal growth restriction (FGR) [6,7].
- Placental Abruption (Abruptio Placentae): Premature placental separation serves as an acute transient obstetric risk factor for VTE due to endothelial injury, retroplacental clot formation, and systemic procoagulant activation [2,6].
- Hyperemesis gravidarum leading to severe dehydration and hemoconcentration [6,10].
- Assisted reproductive technology (ART), particularly complicated by Ovarian Hyperstimulation Syndrome (OHSS) [6].
- Immobility or prolonged bed rest (>3 days) [6].

4.3 Intrapartum and Postpartum Risk Factors

- Emergency Cesarean delivery (hazard ratio ~2–4 higher than elective vaginal delivery) [6,7].
- Postpartum hemorrhage (PPH >1000 mL) requiring blood transfusion [5,6].
- Peripartum infection / endometritis / sepsis [5,6].
- Stillbirth or prolonged labor [6].

5. Risk Assessment Models (RAMs)

To standardize care, professional societies have developed validated Risk Assessment Models (RAMs) [6,7].

5.1 RCOG Green-top Guideline No. 37a Framework

The RCOG model utilizes a point-based scoring tool where patients are evaluated pre-conceptually/early pregnancy, during hospitalization, and postpartum [7,9]. A cumulative score dictates whether thromboprophylaxis is indicated for 10 days, 6 weeks, or the entire antenatal/postpartum period [7].

5.2 ACOG and ASH Risk Stratification

ACOG and ASH focus heavily on categorical risk assessments, categorizing patients into Low, Moderate, and High Risk based primarily on prior VTE history, thrombophilia status, and delivery mode [6].

5.3 Application and Limitations in LMICs (India)

While the RCOG RAM is widely referenced in Indian tertiary care centers, universal adoption across rural and secondary healthcare centers remains limited due to [5,9,10]:

- High cost and limited availability of specialized thrombophilia screening panels [5,10].
- Over-allocation of risk scores for common variables (e.g., high parity, mild anemia, routine Cesarean sections), leading to potential over-prescribing of costly LMWH [5,9].
- Lack of centralized registries to validate Western RAM scores against native Indian patient cohorts [5,10].

6. Pharmacological Thromboprophylaxis

Low-Molecular-Weight Heparin (LMWH) is the gold-standard anticoagulant for both prophylaxis and treatment during pregnancy [6,7].

6.1 Why LMWH is Preferred

- **Fetal Safety:** LMWH does not cross the placenta and does not cause fetal anticoagulation or teratogenicity [6,7].
- **Predictable Pharmacokinetics:** Lower risk of Heparin-Induced Thrombocytopenia (HIT) and lower risk of heparin-induced osteoporosis compared to Unfractionated Heparin (UFH) [6,7].
- **No Routine Monitoring:** Does not require routine anti-Factor Xa monitoring except in extreme body weights (BMI <18 or >40 kg/m²) or renal impairment [6,7].

6.2 Unfractionated Heparin (UFH)

UFH is reserved for specific clinical situations [6]:

- Severe renal impairment (CrCl<30 mL/min) [6].
- Near delivery (due to short half-life of 1–2 hours and rapid reversibility with Protamine Sulfate) [6].

6.3 Direct Oral Anticoagulants (DOACs) and Warfarin

- **Warfarin:** Crosses the placenta; teratogenic in 1st trimester (warfarin embryopathy) and increases risk of fetal hemorrhage [6]. Strictly contraindicated except in pregnant women with mechanical heart valves [6].
- **DOACs (Rivaroxaban, Apixaban, Dabigatran):** Cross the placenta and lack safety data in pregnancy.

Contraindicated during pregnancy and lactation [6].

6.4 Implementation Nuances in LMICs (India)

In low-resource settings, LMWH availability and affordability present significant barriers [5]. Standard UFH or low-dose aspirin may be considered when LMWH is financially unviable, though aspirin alone is not recommended as primary VTE thromboprophylaxis by guidelines [5,6]. Detailed patient education regarding proper subcutaneous injection technique and storage is vital [1].

7. Mechanical Thromboprophylaxis

Mechanical methods are essential adjuncts to pharmacological prophylaxis, particularly when pharmacotherapy is contraindicated due to active bleeding or high bleeding risk [5,6].

- **Graduated Compression Stockings (GCS):** Standard 16–20 mmHg compression stockings reduce venous stasis [6]. Proper sizing and patient compliance are critical [5].
- **Intermittent Pneumatic Compression (IPC):** Highly recommended peri-operatively during Cesarean section and in immobilized postpartum patients [5,6].
- **Early Mobilization & Hydration:** Basic, non-costly strategies that must be universally promoted across all delivery units in LMICs [5].

8. Management Around Delivery and Postpartum

Managing anticoagulation around labor and delivery requires a delicate balance between thrombotic prevention and peripartum hemorrhage control [6,7].

8.1 Timing of LMWH Discontinuation Before Neuraxial Anesthesia

- **Prophylactic Dose LMWH:** Discontinue at least 12 hours prior to planned induction of labor or Cesarean delivery [6,7].
- **Therapeutic Dose LMWH:** Discontinue at least 24 hours prior to delivery [6,7].
- **Neuraxial Anesthesia (Epidural/Spinal):** Must not be administered within 12–24 hours of LMWH administration to prevent spinal/epidural hematoma [6,7].

8.2 Postpartum Resumption

Prophylactic LMWH can be safely restarted 4–6 hours after vaginal delivery or 6–12 hours after Cesarean delivery, provided spinal catheters are removed and hemodynamic stability is achieved without active bleeding [6,7].

8.3 Postoperative Outcomes with Institutional LMWH Prophylaxis

Institutional utilization of prophylactic Low-Molecular-Weight Heparin (LMWH) in high-risk obstetric cohorts—specifically patients presenting with risk factors such as prior history of DVT, obesity, elevated BMI, diabetes mellitus, gestational hypertension, or those undergoing prolonged second-stage Lower Segment Cesarean Section (LSCS) resulting in delayed postoperative mobilization—has demonstrated complete prevention of major thrombotic events in the postoperative period.

9. Special Situations in LMICs (INDIA)

9.1 Postpartum Cerebral Venous Sinus Thrombosis (CVST)

CVST presents typically in the first 2–3 weeks postpartum with severe headache, seizures, focal neurological deficits, or altered sensorium [5,8]. Emergency neuroimaging (MR Venography or CT Venography) is mandatory [8]. Immediate therapeutic dose LMWH/UFH is indicated, even in the presence of hemorrhagic venous infarction [5,8].

9.2 Rheumatic Heart Disease (RHD) and Mechanical Valves

In LMICs, RHD with mechanical prosthetic valves remains a leading cause of maternal cardiac complications [2,5]. Therapeutic anticoagulation requires meticulous management (e.g., Warfarin vs. LMWH regimens) under joint multidisciplinary supervision [5].

10. Comparative Analysis of International & Indian Guidelines

Table 1 summarizes the recommendations from major international and national professional organizations. Full expanded organization names and definitions are detailed below.

FOGSI Adapted RCOG model Universal mechanical LMWH (Enoxaparin); UFH (Federation of Obstetric tailored for Indian settings prophylaxis (IPC/GCS) + if LMWH unaffordable and Gynaecological Selective LMWH for highSocieties of India) risk CS

Table 1: Comparison of International and Indian Clinical Practice Guidelines on Pregnancy-Associated VTE Thromboprophylaxis.

Organization (Abbreviation & Full Form)	Universal Antenatal Risk Assessment	Post-Cesarean Prophylaxis Strategy	Primary Pharmaco-logical Agent
RCOG (Royal College of Obstetricians and Gynaecologists)	Mandatory for all pregnant women at 1st visit, admission, & peripartum	Risk-score based (Score ≥2 receives 10 days LMWH; Score ≥3 receives 6 weeks)	LMWH (Dalteparin / Enoxaparin)
ACOG (American College of Obstetricians and Gynecologists)	Targeted assessment based on prior VTE and severe thrombophilia	Selective: Prophylaxis for high-risk cases or emergency CS with additional risk factors	LMWH or UFH
ASH (American Society of Hematology)	Standardized categorical assessment (Low, Moderate, High)	Selective: Pharmacological prophylaxis for patients with prior VTE or thrombophilia	LMWH preferred

Full Forms of Abbreviations in Table 1:

1. *RCOG: Royal College of Obstetricians and Gynaecologists (United Kingdom)*
2. *ACOG: American College of Obstetricians and Gynecologists (United States)*
3. *ASH: American Society of Hematology (United States)*
4. *FOGSI: Federation of Obstetric and Gynaecological Societies of India (India)*

Other Key Abbreviations: LMWH = Low-Molecular-Weight Heparin; UFH = Unfractionated Heparin; CS = Cesarean Section; IPC = Intermittent Pneumatic Compression; GCS = Graduated Compression Stockings; VTE = Venous Thromboembolism.

11. Future Directions & Research Needed in LMICs

1. **Validation of LMIC-Specific RAMs:** Development and prospective validation of a simplified, lowcost risk scoring tool tailored for South Asian / LMIC populations [5,10].
2. **National VTE Registries:** Establishing systematic national databases in India to capture exact incidence rates of DVT, PE, and CVST [5,9].
3. **Cost-Effectiveness & Generic LMWH Studies:** Evaluating the efficacy, safety, and bioequivalence of generic biosimilar LMWHs to reduce treatment costs [5].

12. CONCLUSION

Pregnancy-associated VTE is a preventable yet life-threatening condition. While international guidelines offer strong frameworks, implementation in resource-limited settings demands pragmatic adaptation. Emphasizing early risk identification, routine adoption of adapted RAMs, promoting affordable LMWH/UFH access, and reinforcing mechanical prophylaxis and early mobilization can significantly reduce maternal morbidity and mortality in India and other LMICs.

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