# ANTICOAGULATION IN PREGNANCY

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## I DEFINITION AND PHYSIOLOGICAL RATIONALE (ESC PREGNANCY GUIDELINES)

- **Physiological Hypercoagulability of Pregnancy:** Normal pregnancy induces a prothrombotic physiological state characterized by marked increases in **coagulation factors VII, VIII, X, von Willebrand factor, and fibrinogen**, decreased free **Protein S** activity, acquired resistance to activated Protein C, and venous stasis from gravid uterine compression of the inferior vena cava.
- **The Clinical Balancing Act:** Anticoagulation in pregnancy (indicated primarily for **Mechanical Prosthetic Heart Valves**, **Venous Thromboembolism [VTE]**, or high-risk **Atrial Fibrillation / Intracardiac Shunts**) must balance the prevention of **fatal maternal valve thrombosis or pulmonary embolism** against the risks of **fetal teratogenicity (Warfarin embryopathy), fetal intracranial hemorrhage, and maternal peripartum hemorrhage**.

## II PLACENTAL TRANSFER AND SAFETY PROFILES OF ANTICOAGULANTS

- **Low Molecular Weight Heparin (LMWH — Enoxaparin, Dalteparin):**
  - **Placental Transfer:** Does **NOT** cross the placental barrier; completely free of fetal teratogenicity or fetal bleeding risk.
  - **Altered Pregnancy Pharmacokinetics:** Maternal plasma volume expansion (by 40 to 50 percent) and a **50 percent increase in Glomerular Filtration Rate (GFR)** accelerate renal clearance of LMWH, rendering fixed weight-based dosing inadequate for mechanical valves.
  - **Mandatory Anti-Xa Monitoring (Class I):** For mechanical prosthetic valves, LMWH must be administered **twice daily** with **weekly or bi-weekly Peak Anti-Xa monitoring** drawn **4 hours post-injection** (targeting **0.8 to 1.2 U/mL** for aortic valves and **1.0 to 1.2 U/mL** for mitral/right-sided valves), plus **trough Anti-Xa levels** prior to the next dose maintained at **0.6 U/mL or greater**.
  - **Unfractionated Heparin (UFH):**
  - **Placental Transfer:** Does **NOT** cross the placenta.
  - **Clinical Role:** Used primarily during the **peripartum window (from 36 weeks of gestation to delivery)** as a continuous intravenous infusion (target **aPTT >=2.0 times control**) because of its short half-life (1 to 2 hours) and complete, rapid reversibility with **Protamine Sulfate**. Prolonged use throughout pregnancy is avoided due to maternal **osteoporosis**, **heparin-induced thrombocytopenia (HIT)**, and erratic subcutaneous absorption.
  - **Vitamin K Antagonists (VKAs — Warfarin, Acenocoumarol):**
  - **Placental Transfer:** Freely **CROSSES the placenta**.
  - **First-Trimester Teratogenicity (Weeks 6 to 12):** Disrupts vitamin K-dependent osteocalcin/matrix Gla protein synthesis during fetal organogenesis, causing **Warfarin Embryopathy** (**nasal bone hypoplasia, depressed nasal bridge, and stippled epiphyses [chondrodysplasia punctata]**).
  - **Second/Third-Trimester and Delivery Risks:** Causes a low (1 to 2 percent) risk of fetal CNS/ocular anomalies and a high risk of **fatal fetal intracranial hemorrhage during traumatic vaginal delivery** if Warfarin is not discontinued at week 36 (as the immature fetal liver has low clotting factor levels and clears Warfarin slowly).
  - **Crucial Dose-Dependency Threshold:** The risk of Warfarin embryopathy and fetal loss is strictly **dose-dependent**: when the maternal Warfarin dose is **5 mg/day or less** (or Acenocoumarol <=2 mg/day), the risk of embryopathy is low (**less than 1 to 3 percent**), whereas at doses **greater than 5 mg/day**, embryopathy and fetal loss rates rise sharply (**exceeding 8 to 10 percent**).
  - **Direct Oral Anticoagulants (DOACs — Apixaban, Rivaroxaban, Dabigatran, Edoxaban) and Fondaparinux:**
  - **DOACs (Class III — Strictly Contraindicated):** DOACs cross the placenta, are associated with reproductive toxicity/miscarriage, and are **strictly contraindicated in both pregnancy and mechanical prosthetic valves** (per the **RE-ALIGN** and **PROACT Xa** trials). (Fondaparinux crosses the placenta in small amounts and is reserved only for severe HIT when danaparoid is unavailable.)

| Anticoagulant Class | Crosses Placenta? | Maternal Valve Protection | Fetal Risk Profile | Mandatory Monitoring & Target |
|---|---|---|---|---|
| **Warfarin (VKA) <=5 mg/day** | **Yes** | **Highest** (~1–3% valve thrombosis) | Low embryopathy (<1–3% in Wk 6–12); high fetal ICH risk if used in vaginal delivery | Weekly/bi-weekly **INR** (Mitral: **2.5–3.5**; Aortic: **2.0–3.0**) |
| **Warfarin (VKA) >5 mg/day** | **Yes** | **Highest** | **High embryopathy (>8–10%)** & fetal loss in Weeks 6–12 | Switch to LMWH/UFH during **Weeks 6–12**, then resume VKA in **Weeks 13–35** |
| **LMWH (Twice Daily)** | **No** (Fetal safe) | Intermediate (~5–9% valve thrombosis; fatal if unmonitored) | Zero teratogenicity or fetal bleeding | Weekly/bi-weekly **4-h Peak Anti-Xa** (**0.8–1.2 U/mL** AVR; **1.0–1.2 U/mL** MVR) + **Trough >=0.6 U/mL** |
| **Intravenous UFH** | **No** (Fetal safe) | Intermediate; ideal for **Week 36 to Delivery** | Zero fetal risk; maternal HIT & osteoporosis if prolonged | **aPTT >= 2.0x control** (checked every 6–12 h during IV infusion) |
| **DOACs** | **Yes** | **Ineffective / Harmful** in mechanical valves | Embryotoxic / Contraindicated | **Class III (Harm): Strictly Contraindicated** |

## III TRIMESTER-BY-TRIMESTER PROTOCOL FOR MECHANICAL PROSTHETIC VALVES (ESC / ACC-AHA)

- **Strategy A — Low Baseline Warfarin Dose Requirement (Warfarin <=5 mg/day):**
  - **First Trimester (Weeks 6 to 12): Continue Warfarin** throughout the first trimester (**Class IIa preferred option**), as it provides the lowest maternal valve thrombosis and mortality rate with a very low (<3%) embryopathy risk.
  - **Second and Third Trimesters (Weeks 13 to 35): Continue Warfarin** (Class I).
  - **Peripartum Window (Week 36 to Delivery): Discontinue Warfarin at Week 36** and hospitalize to switch to continuous **IV UFH (aPTT >=2.0x)** or therapeutic **dose-adjusted LMWH (Anti-Xa 0.8 to 1.2 U/mL)**.
  - **Strategy B — High Baseline Warfarin Dose Requirement (Warfarin >5 mg/day):**
  - **First Trimester (Weeks 6 to 12): Discontinue Warfarin between Weeks 6 and 12** and switch to **in-hospital dose-adjusted twice-daily LMWH** (with strict weekly Peak and Trough Anti-Xa monitoring) or continuous **IV UFH** (**Class IIa**) to avoid high-dose Warfarin embryopathy.
  - **Second and Third Trimesters (Weeks 13 to 35): Switch BACK to Warfarin at Week 13** (once fetal organogenesis is complete) and continue until Week 35 (**Class I**).
  - **Peripartum Window (Week 36 to Delivery): Discontinue Warfarin at Week 36** and transition to **IV UFH** or monitored **LMWH**.

## IV DELIVERY, EMERGENCY CESAREAN AND POSTPARTUM PROTOCOL

- **Planned Delivery Timing:** Planned **vaginal delivery** (with assisted second stage) is preferred in stable patients to minimize maternal blood loss and thrombosis risk:
- Switch from LMWH to **continuous IV UFH at least 36 hours prior to planned delivery** (or hold the last therapeutic LMWH dose **at least 24 hours** before neuraxial epidural anesthesia or induction).
- **Stop IV UFH infusion 4 to 6 hours prior to delivery** and confirm normal aPTT.
- **Restart IV UFH 4 to 6 hours postpartum** (provided there is no active obstetric bleeding or spinal hematoma) and re-initiate oral **Warfarin** 24 to 48 hours postpartum, overlapping heparin until the INR is therapeutic for 2 consecutive days (**Warfarin is completely safe during breastfeeding**, as it is not excreted in active form into breast milk).
- **Emergency Delivery While Fully Anticoagulated on Warfarin (Class I):** If a woman goes into preterm labor while still taking Warfarin, **Vaginal Delivery is Contraindicated** due to the high risk of fatal fetal cranial compression hemorrhage; an **urgent Cesarean Section** must be performed after reversing maternal/fetal anticoagulation with **Fresh Frozen Plasma (FFP) or 4-factor Prothrombin Complex Concentrate (PCC) + low-dose IV Vitamin K (plus Fresh Frozen Plasma + Vitamin K administered directly to the neonate at birth)**.

## V LANDMARK REGISTRY EVIDENCE (ROPAC REGISTRY)

- **ROPAC Registry (van Hagen et al., *Circulation* 2015):** In the European Society of Cardiology **Registry of Pregnancy and Cardiac Disease (ROPAC)** evaluating 212 pregnant women with mechanical heart valves, **maternal mortality was 1.4 percent**, **mechanical valve thrombosis occurred in 4.7 percent** (half of which occurred during the first-trimester switch to heparin), **hemorrhagic complications occurred in 23.1 percent**, and **only 58 percent of women had an uncomplicated pregnancy resulting in a live birth**—confirming that VKA throughout pregnancy yields the lowest maternal thrombosis rate, while unmonitored or sub-therapeutic LMWH carries catastrophic maternal risk.

### KEY REFERENCES


- **Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al.:** 2018 ESC Guidelines for the management of cardiovascular diseases during pregnancy, *European Heart Journal*, 2018.
- **Otto CM, Nishimura RA, Bonow RO, et al.:** 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease, *Circulation*, 2021.
- **van Hagen IM, Roos-Hesselink JW, Ruys TPE, et al. (ROPAC Investigators):** Pregnancy in Women With a Mechanical Heart Valve: Data of the European Society of Cardiology Registry of Pregnancy and Cardiac Disease (ROPAC), *Circulation*, 2015.