Anticoagulants in pregnancy

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Heparin

Anticoagulation is sometimes needed during pregnancy and/or the postpartum period, including individuals at high risk of **deep vein thrombosis, a history of venous thromboembolism, with prosthetic heart valves, atrial fibrillation, left ventricular dysfunction, or a history of fetal loss**.

Low molecular weight (LMW) heparins : most experts recommend LMW heparin rather than unfractionated heparin for all but the final weeks of the pregnancy, **because LMW heparins are effective and easier to administer than unfractionated heparin.**

LMW heparins produce a more predictable anticoagulant response than unfractionated heparin **and do not require routine monitoring** .

The incidence of developing **heparin-induced thrombocytopenia (HIT)** is also less with LMW heparin than unfractionated heparin.

Unfractionated heparin :
Unfractionated heparin is a reasonable alternative to a LMW heparin when **cost** or need for rapid reversal is important **(for delivery or perioperatively).**

Unfractionated heparin is preferred over LMW heparin in individuals with **severely reduced kidney function (creatinine clearance <30 mL/min)** because LMW heparin clearance is almost exclusively by the kidney, while elimination of unfractionated heparin is by the kidney and liver.

Fondaparinux, argatroban, danaparoid : There is less information on the fetal effects of these agents, but available evidence **suggests they are reasonable options**.

Another anticoagulant

Fondaparinux(Anti-factor Xa inhibitors) is preferred for individuals with a history of HIT (**or active HIT**).

Argatroban is most likely to cross the placenta.

Use of heparins during pregnancy

Heparin	Dose level	Dose
LMW heparin	Prophylactic*	Enoxaparin 40 mg SC once daily
		Dalteparin 5000 units SC once daily
	Intermediate¶	Enoxaparin 40 mg SC once daily, increase as pregnancy progresses to 1 mg/kg once daily
		Dalteparin 5000 units SC once daily, increase as pregnancy progresses to 100 units/kg once daily
	Therapeutic	Enoxaparin 1 mg/kg SC every 12 hours
		Dalteparin 100 units/kg SC every 12 hours
Unfractionated heparin	Prophylactic	5000 units SC every 12 hours
	Intermediate¶	First trimester: 5000 to 7500 units SC every 12 hours
		Second trimester: 7500 to 10,000 units SC every 12 hours
		Third trimester: 10,000 units SC every 12 hours
	Therapeutic	Can be given as a continuous IV infusion or an SC dose every 12 hours. Titrated to keep the aPTT in the therapeutic range.

Table 3. Suggested thromboprophylactic doses for antenatal and postnatal LMWH

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Weight	Enoxaparin	Dalteparin	Tinzaparin (75 u/kg/day)
< 50 kg	20 mg daily	2500 units daily	3500 units daily
50–90 kg	40 mg daily	5000 units daily	4500 units daily
91–130 kg	60 mg daily*	7500 units daily	7000 units daily*
131–170 kg	80 mg daily*	10 000 units daily	9000 units daily*
> 170 kg	0.6 mg/kg/day*	75 u/kg/day	75 u/kg/day*
High prophylactic dose for women weighing 50–90 kg	40 mg 12 hourly	5000 units 12 hourly	4500 units 12 hourly

*may be given in 2 divided doses

Risk factors for VTE

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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)	1[a]
Age (> 35 years)	1
Obesity	1 or 2[b]
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 labour	2
Elective caesarean section	1
Mid-cavity or rotational operative delivery	1
Prolonged labour (> 24 hours)	1
PPH (> 1 litre 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 sterilisation	3
Hyperemesis, dehydration	3
OHSS	4
Current systemic infection (requiring intravenous antibiotics or admission to hospital)	1
Immobility	1

Appendix III: Risk assessment for venous thromboembolism (VTE)

- If total score ≥ 4 risk factors antenatally, consider thromboprophylaxis from the first trimester.
- If total score 3 risk factors antenatally, consider thromboprophylaxis from 28 weeks.
- If total score ≥ 2 risk factors postnatally, consider thromboprophylaxis for at least 10 days.
- If admitted to hospital antenatally consider thromboprophylaxis.
- If readmitted 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.

- For prophylactic-dose LMWH, a fixed low-dose LMWH regimen can be used in most cases.
- In women with **acute VTE requiring therapeutic LMWH dose**, **routine anti-factor Xa monitoring has not been shown to affect clinical outcomes despite fluctuations** of anti-factor Xa levels during pregnancy and should only be considered in women **with renal insufficiency or obesity,** where adjustment for body weight may result in overdosing.
- **Monitoring of anti-factor Xa levels** is essential in women with **MHVs on therapeutic-dose LMWH**: at **least weekly until target level is achieved** or when there is a below target level at any stage, and regular monitoring thereafter (every 2–4 weeks depending on stability).
- Recommended peak anti-factor Xa levels should be individualized based on type and location of the valve (**between 1.0 and 1.2 U/mL)** and additional trough level measurement may be indicated in selected cases with increased thrombosis risk.

HIT

However, if a pregnant patient with a history of HIT requires anticoagulation for another reason, or if a patient develops HIT immediately prior to or during pregnancy, an anticoagulant other than heparin should be used.

All sources of heparin (including heparin flushes) should be avoided.

The 2012 American College of Chest Physicians (ACCP) guidelines **recommend danaparoid** as **the preferred alternative** to heparin for pregnant patients; this agent is not available in the United States.

For patients who cannot receive danaparoid, **argatroban or fondaparinux** can be used.

- Converting from **therapeutic dose LMW to unfractionated heparin** (acute pulmonary embolism in the third trimester) –: A rough calculation for converting **from enoxaparin 1 mg/kg every 12 hours would be to use 250 units of unfractionated heparin per kg of body weight,** given subcutaneously **every 12 hours** (sample calculation for a 100 kg patient: **250 units/kg x 100 kg = 25,000 units subcutaneously every 12 hours**)

Delivery and labor

- Subcutaneous LMW or unfractionated heparin is discontinued for most patients when spontaneous labor begins, **or 12 to 24 hours before planned induction of labor or cesarean delivery** (**12 hours for prophylactic dose; 24 hours for higher doses**)

- Convert from subcutaneous LMW heparin to unfractionated heparin prior to delivery, and from subcutaneous unfractionated heparin to intravenous unfractionated heparin prior to anticipated delivery **in those who require more continuous anticoagulation**.
- If preterm labor develops in a patient receiving heparin, **protamine sulfate** has been used to reverse maternal heparinization.

oral anticoagulants

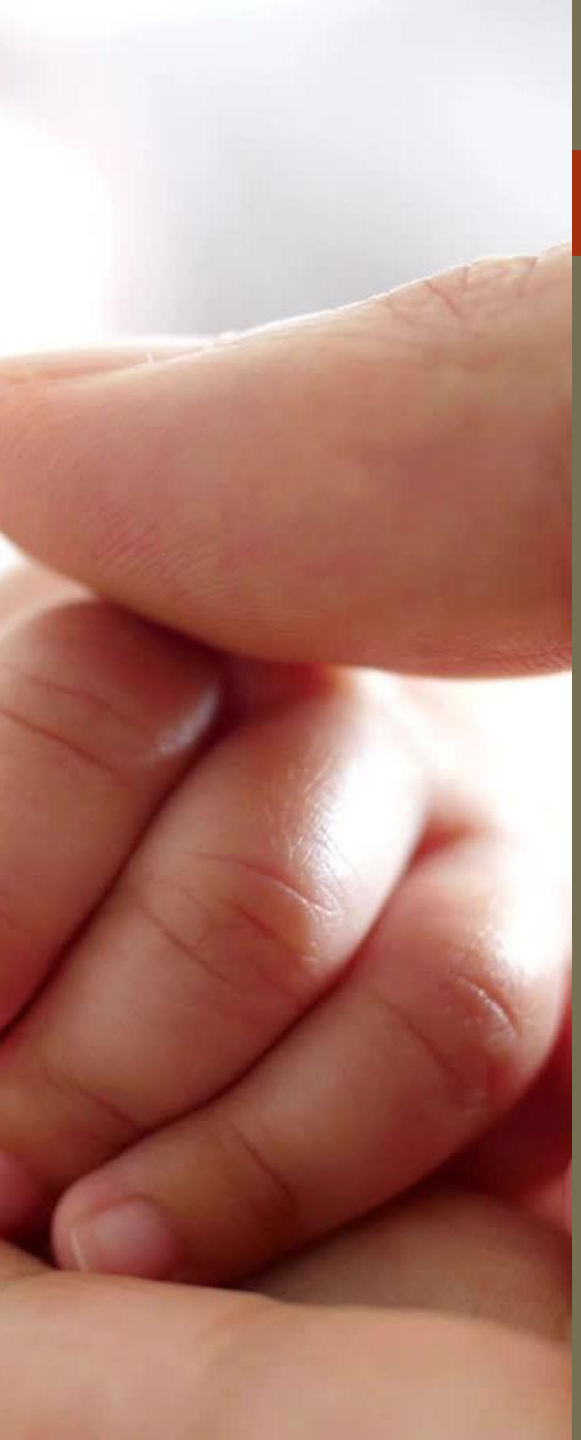
Vitamin K antagonists (warfarin) are oral but are teratogenic (especially weeks 6–12) and increase fetal bleeding risk near delivery.

Despite this, warfarin may be used in pregnancy for very high maternal-risk conditions (most commonly some **women with mechanical prosthetic heart valves**) after careful counselling because it better prevents valve thrombosis in some situations.

Direct oral anticoagulants (DOACs: **dabigatran, rivaroxaban, apixaban,** edoxaban) are currently contraindicated in pregnancy and breastfeeding because they cross the placenta, safety data are limited, and there are reports of fetal and maternal bleeding and treatment failure.

What oral agents and how they are used?

- **Warfarin (vitamin K antagonist)**
- Mechanism: inhibits vitamin K–dependent clotting factors.
- Use in pregnancy: **generally avoided in the first trimester** because of embryopathy; sometimes used in the 2nd and 3rd trimesters (and sometimes throughout pregnancy) for women at very high maternal thrombotic risk — most commonly some mechanical heart valve patients. Use requires thorough counselling about fetal risks.
- Typical monitoring and targets:
- Dose is individualized; start/titrate to target INR.
- Usual INR target: 2.0–3.0 for most indications; 2.5–3.5 (or higher) for mechanical mitral valves (institution-specific).
- Frequent INR checks (weekly after dose change, then every 1–2 weeks when stable).



Warfarin

- Benefit: **very effective anticoagulation**; in some high-risk maternal conditions (particularly certain mechanical heart valves) it has a lower maternal thrombotic risk compared with heparin strategies in some studies.
- The use of anticoagulants during pregnancy represents a **complex balance of risks and benefits, influenced by specific indications**, and hampered by low-quality evidence.

Adverse fetal and neonatal outcomes

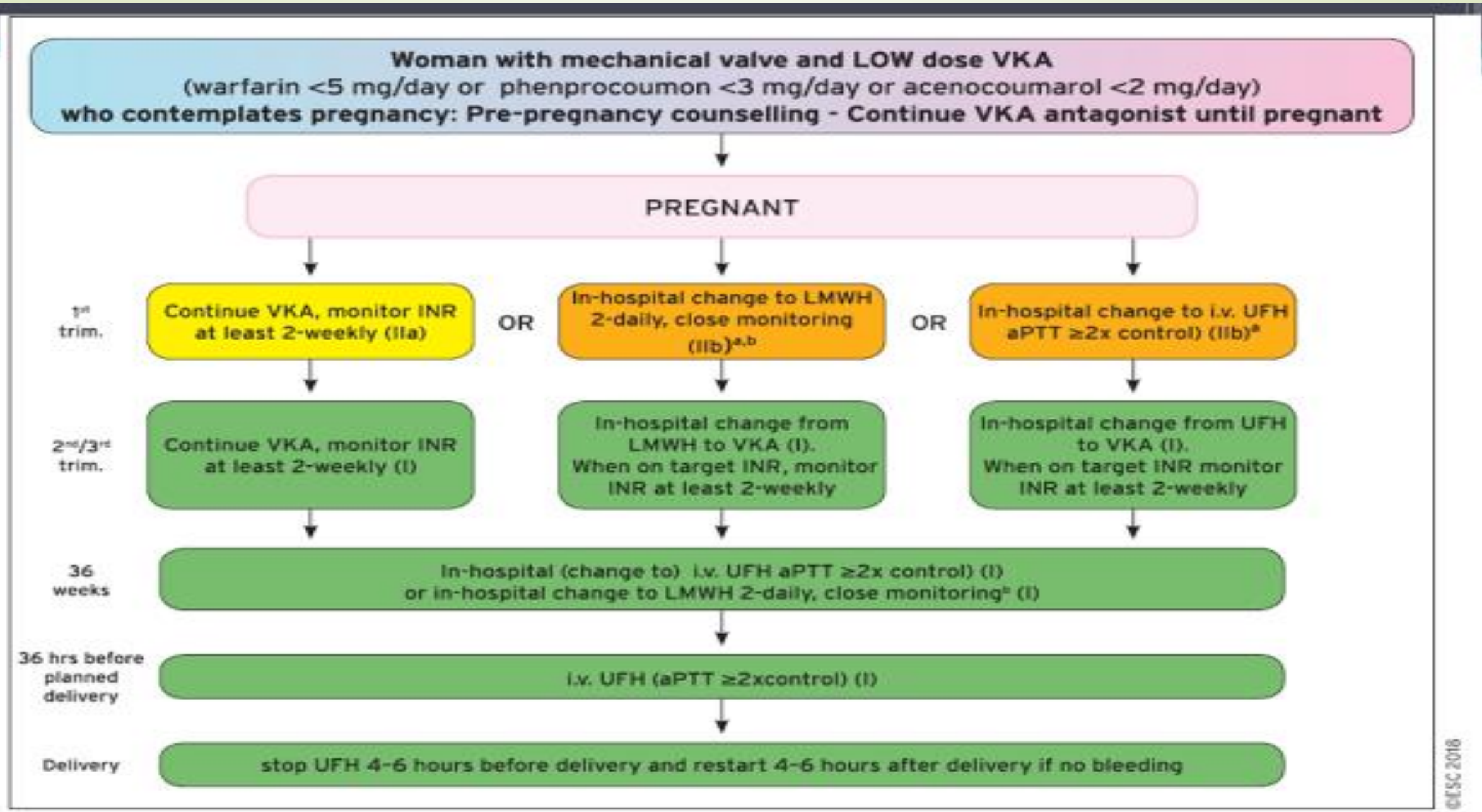
- **Warfarin embryopathy** (classic features if exposure primarily in weeks ~6–12):
- Nasal bone hypoplasia, stippled epiphyses (chondrodysplasia punctata), growth restriction, skeletal abnormalities, limb hypoplasia, and variable developmental problems.
- **Fetal/neonatal bleeding**
- Warfarin crosses placenta → risk of fetal intracranial hemorrhage, especially near delivery if maternal INR is therapeutic.
- **Miscarriage and stillbirth**
- Increased risk with inadequate anticoagulation of maternal disease and with some anticoagulants or disease states.
- Adverse impact is highest in the first trimester **(0.6%–12% of embryopathy)** and much lower but persisting in later stages of pregnancy (**0.7%–2% risk of fetopathy, e.g. central nervous anomalies, intracranial hemorrhage).**
- The risk of embryopathy in the first trimester depends on the VKA dose.
- The risk was **0.45%–0.9%** in pregnancies with low-dose warfarin according to two systematic reviews.

Counselling and monitoring

Discuss maternal vs fetal risks and alternatives in detail; obtain **informed consent if warfarin is considered**.

Frequent anticoagulation monitoring: **INR for warfarin;** anti-Xa levels if therapeutic LMWH is used in special circumstances (e.g., obesity, mechanical valves, renal impairment).

Serial fetal ultrasound and growth surveillance as clinically indicated when warfarin exposure has occurred.


Woman with mechanical valve and LOW dose VKA
(warfarin <5 mg/day or phenprocoumon <3 mg/day or acenocoumarol <2 mg/day)
who contemplates pregnancy: Pre-pregnancy counselling - Continue VKA antagonist until pregnant
PREGNANT
1st trim.
Continue VKA, monitor INR at least 2-weekly (IIa)
OR
In-hospital change to LMWH 2-daily, close monitoring (IIb)a,b
OR
In-hospital change to i.v. UFH aPTT ≥2x control) (IIb)a
2nd/3rd trim.
Continue VKA, monitor INR at least 2-weekly (I)
In-hospital change from LMWH to VKA (I). When on target INR, monitor INR at least 2-weekly
In-hospital change from UFH to VKA (I). When on target INR monitor INR at least 2-weekly
36 weeks
In-hospital (change to) i.v. UFH aPTT ≥2x control) (I)
or in-hospital change to LMWH 2-daily, close monitoringa (I)
36 hrs before planned delivery
i.v. UFH (aPTT ≥2xcontrol) (I)
Delivery
stop UFH 4-6 hours before delivery and restart 4-6 hours after delivery if no bleeding
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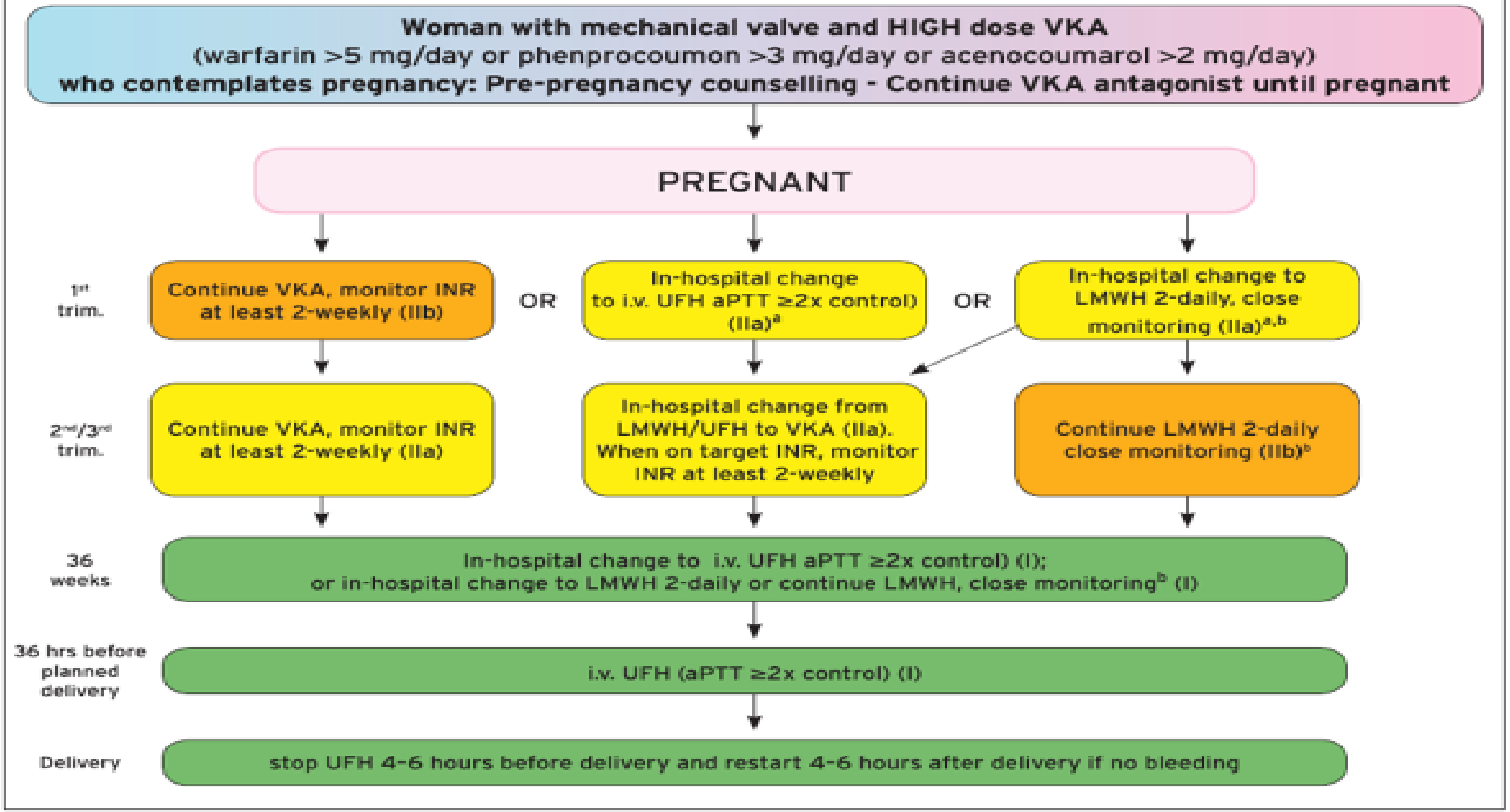
Woman with mechanical valve and HIGH dose VKA
(warfarin >5 mg/day or phenprocoumon >3 mg/day or acenocoumarol >2 mg/day)
who contemplates pregnancy: Pre-pregnancy counselling - Continue VKA antagonist until pregnant
PREGNANT
1st trim.
Continue VKA, monitor INR at least 2-weekly (IIb)
OR
In-hospital change to i.v. UFH aPTT ≥2x control) (IIa)a
OR
In-hospital change to LMWH 2-daily, close monitoring (IIa)a,b
2nd/3rd trim.
Continue VKA, monitor INR at least 2-weekly (IIa)
In-hospital change from LMWH/UFH to VKA (IIa). When on target INR, monitor INR at least 2-weekly
Continue LMWH 2-daily close monitoring (IIb)b
36 weeks
In-hospital change to i.v. UFH aPTT ≥2x control) (I);
or in-hospital change to LMWH 2-daily or continue LMWH, close monitoring b (I)
36 hrs before planned delivery
i.v. UFH (aPTT ≥2x control) (I)
Delivery
stop UFH 4-6 hours before delivery and restart 4-6 hours after delivery if no bleeding
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European Heart Journal (2025) **46**, 4462–4568
https://doi.org/10.1093/eurheartj/ehaf193

Table 10 List of anticoagulation regimens and disease entities in which they are indicated

Indication	Type of anticoagulant	Dosing	Timing
Low thrombosis risk			
VTE prevention/no indication for oral anticoagulation[a]	LMWH	Prophylactic dose	o.d.
Uncomplicated Fontan circulation[b]	LMWH	Prophylactic dose	o.d.
Intermediate thrombosis risk			
VTE (DVT/PE) during pregnancy[a]	LMWH	Therapeutic dose	o.d. or b.i.d.
Persistent/permanent AF at elevated thromboembolic risk[c]	LMWH	Therapeutic dose	o.d. or b.i.d.
Decreased ventricular function (EF <35%) and/ or intracardiac thrombus[d]	LMWH	Therapeutic dose	o.d. or b.i.d.
High thrombosis risk			
Mechanical heart valves[e]			
1. First trimester			
Low VKA dose to achieve required INR[f]	First trimester: VKA or LMWH	INR: weekly to every 2 weeks	
		LMWH: dose adjusted to peak anti-factor Xa level	b.i.d.
High VKA dose to achieve required INR	Switch to LMWH	Dose adjusted to peak anti-factor Xa level (weekly until threshold, every 2–4 weeks thereafter)	b.i.d.
2. From week 13: shared decision			
(a) Continue/switch to VKA with weekly to every 2 weeks INR			
(b) Continue LMWH with dose adjustment as above			
Delivery: refer to *Section 4.5.6.2.* (for urgent delivery) and *Section 4.5.6.1* (for planned delivery)			

Delivery in women on anticoagulants

Planned delivery In women with mechanical heart valves (MHVs) taking VKAs, suspension of VKAs and bridging with heparin [either therapeutic-dose low-molecular-weight heparin (LMWH) or i.v. unfractionated heparin (UFH)] **is recommended at least 2 weeks before planned delivery** .

This is because of the slow metabolism of VKA in the fetus.

If therapeutic-dose LMWH is used, one strategy is to switch to i.v. therapeutic UFH at least 36 h before planned delivery.

In these settings the target activated partial thromboplastin time (aPTT) is ≥2 times control values. **UFH can then be stopped 4–6 h before surgery** (in case of caesarean section) or before insertion of regional anesthesia or **anticipated vaginal delivery.**

For women who are on therapeutic-dose LMWH for non-MHV indications, dosing can be **omitted for 24 h prior** to caesarean section or anticipated vaginal delivery with no need for bridging. In women with MHVs who are on LMWH and aspirin in combination, consideration should be given to **stopping aspirin 4 days before delivery**.

Delivery on vitamin K antagonists

If women require urgent delivery and have been taking **VKAs within the last 2 weeks**, then delivery **by caesarean section is recommended to reduce the risk of fetal intracranial bleeding**.

When urgent delivery is required, preventing bleeding complications with administration of **I.V. four-factor prothrombin complex concentrate (4F-PCC),**

depending on the international normalized ratio (INR) **(25 U/kg** for a therapeutic INR range of 2–4) is the preferred method for rapid INR normalization.

If necessary, **vitamin K should be given.**

The fetus may remain anticoagulated **for 8– 10 days** after discontinuation of maternal VKAs, and may need to be **given FFP and higher doses of vitamin K.**

If 4F-PCC is not available, **fresh frozen plasma (FFP) is an alternative**, but it takes longer to reverse an elevated INR and requires a larger fluid challenge.

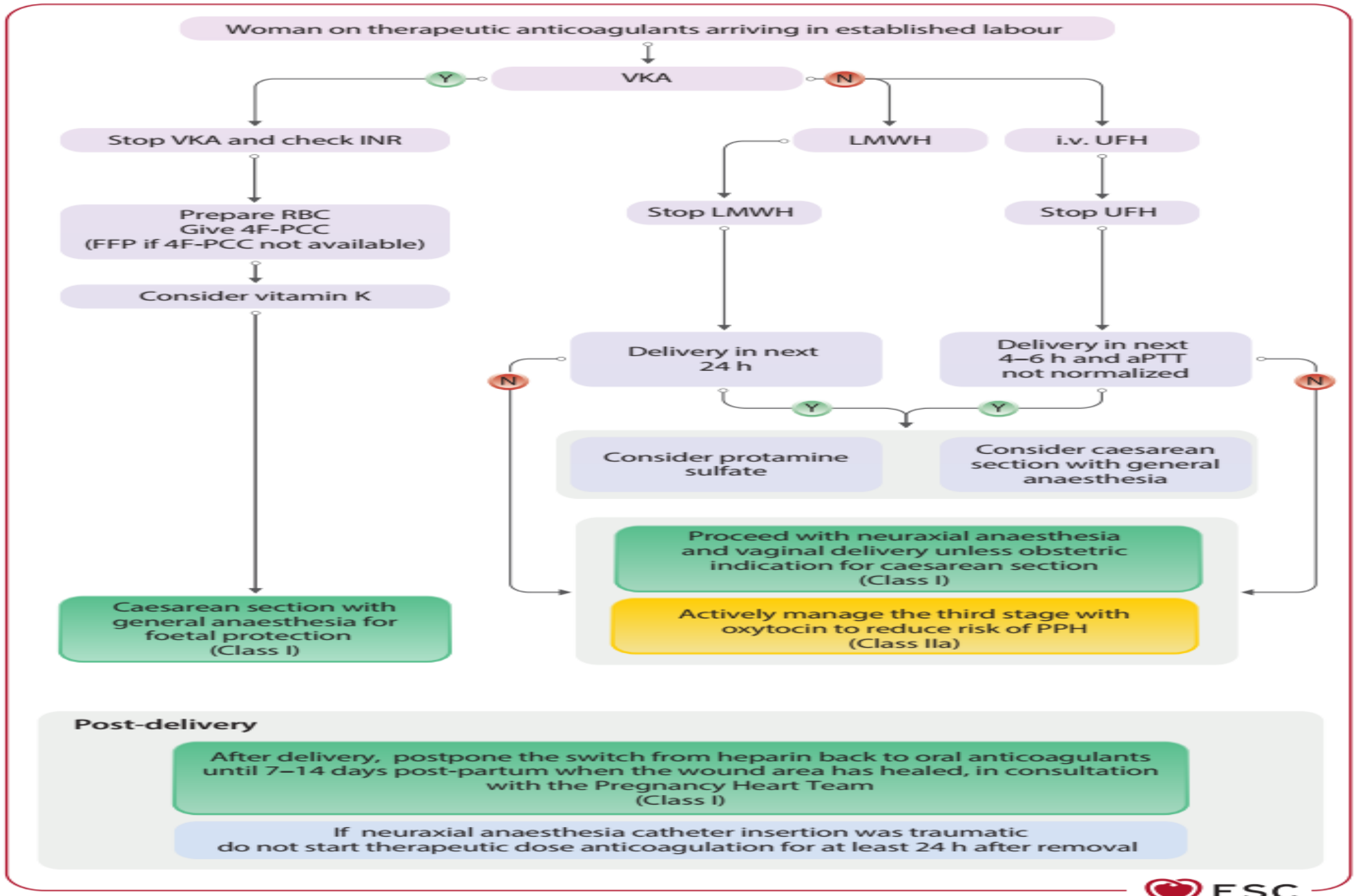
anticoagulation after delivery

Restarting **UFH** (aPTT levels ≥2 times the control) **or low/ intermediate doses of LMWH** are all valid options.

Techniques to reduce bleeding risk include active management of the third stage of labor with oxytocin.

Recently, the effect of adding 2 IU oxytocin over 10 min to a standard treatment of **low-dose infusion for 4 h [10 IU of oxytocin in 500 mL of normal saline given i.v. at 36 mL/h for 4 h** (12 mU/min)] was analysed.

VKA should only be started 7–14 days or later post-partum to reduce the risk of late bleeding


Woman on therapeutic anticoagulants arriving in established labour
VKA
Y
N
Stop VKA and check INR
Prepare RBC
Give 4F-PCC
(FFP if 4F-PCC not available)
Consider vitamin K
Caesarean section with general anaesthesia for foetal protection
(Class I)
LMWH
i.v. UFH
Stop LMWH
Stop UFH
Delivery in next 24 h
Delivery in next 4–6 h and aPTT not normalized
N
Y
Y
N
Consider protamine sulfate
Consider caesarean section with general anaesthesia
Proceed with neuraxial anaesthesia and vaginal delivery unless obstetric indication for caesarean section
(Class I)
Actively manage the third stage with oxytocin to reduce risk of PPH
(Class IIa)
Post-delivery
After delivery, postpone the switch from heparin back to oral anticoagulants until 7–14 days post-partum when the wound area has healed, in consultation with the Pregnancy Heart Team
(Class I)
If neuraxial anaesthesia catheter insertion was traumatic
do not start therapeutic dose anticoagulation for at least 24 h after removal
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Direct oral anticoagulants(*Direct oral factor Xa inhibitors)*

- Direct oral anticoagulants have shown better bleeding profiles than a LMWH or VKA regimen across diverse indications in **non-pregnant populations.**
- Outcome data on their use in pregnancy are scarce and inconsistently captured in pharmacovigilance databases, indicating a need for a more robust system of reporting.
- **The fetal effects of DOACs are controversial.**
- Animal and *in vitro* studies showed that **dabigatran, rivaroxaban, and apixaban crossed the placenta.**
- Prescription information based on these data reported variable adverse effects in pregnant rodents and rabbits**: post-implantation loss, maternal bleeding, or malformation at >4 times the recommended maternal doses**.
- Counselling women on DOACs who are planning a pregnancy is advised, considering the complexity of pre- and post-conceptional switches to alternative

Reproductive Considerations and Pregnancy Considerations (direct acting oral anticoagulants)

- Clinically **significant uterine bleeding requiring surgical intervention** may occur during therapy in patients of reproductive potential.
- **Information related to the use of direct acting oral anticoagulants in pregnancy is limited**; until safety data are available, **adequate contraception is recommended** during therapy for patients who may become pregnant.
- **Patients planning to become pregnant should be switched to alternative anticoagulants prior to conception.**
- When used in pregnancy, there is also the **potential for fetal bleeding or subclinical placental bleeding** which may increase the **risk of miscarriage, preterm delivery, fetal compromise, or stillbirth** .
- Data are insufficient to evaluate the safety of direct acting oral anticoagulants **during pregnancy and use in pregnant patients is not recommended (ACOG 2018)**
- Agents other than rivaroxaban are preferred for the treatment of AF or VTE in pregnant patients .

Breastfeeding Considerations

- **Rivaroxaban is present in breast milk.**
- The relative infant dose (RID) of rivaroxaban is 3.6% when calculated using the highest breast milk concentration located and compared to the weight-adjusted maternal dose of 30 mg/day.
- In general, breastfeeding is considered acceptable when the RID is <10% (Anderson 2016; Ito 2000).
- The RID of rivaroxaban was calculated using a milk concentration of 86.4 mcg/L, providing an estimated daily infant dose via breast milk of 12.96 mcg/kg/day. This was the highest milk concentration obtained following maternal administration of oral rivaroxaban 15 mg twice daily for 3 days to one woman on postpartum days 7 to 10 (calculation based on actual maternal weight)
- **According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.** Until safety data are available, **direct acting oral anticoagulants are not recommended for use in patients who are breastfeeding; use of an alternative anticoagulant is preferred (ACOG 2018;**).
- In lactating women treated **with 15–20 mg/day rivaroxaban**, the breastfed infant would receive a low dose, corresponding to 1.3%–5% of the maternal weight-adjusted dosage.(**ESC GUIDELINES.2025**)
- Therefore, **dabigatran and rivaroxaban may be taken cautiously during lactation.**
- **Signs of bleeding should be monitored in neonates of lactating mothers taking dabigatran.**

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European Heart Journal (2025) **46**, 4462–4568
https://doi.org/10.1093/eurheartj/ehaf193

Delivery in women on anticoagulants		
It is recommended that the timing of delivery is planned to ensure safe and effective peripartum anticoagulation.	I	C
It is recommended to discontinue VKAs and start therapeutic-dose LMWH or adjusted-dose i.v. UFH at the 36th week of gestation or 2 weeks before the planned delivery.[179]	I	C
In women at low risk[d] on therapeutic-dose LMWH, neuraxial anaesthesia and vaginal delivery (or caesarean section for obstetric indications) is recommended 24 h after the last dose of LMWH.[180]	I	C
In women at high risk[d], it is recommended to convert LMWH to i.v. UFH at least 36 h prior to delivery and stop the UFH infusion 4–6 h prior to anticipated delivery. The aPTT should be normal before regional anaesthesia.[180]	I	C
If delivery starts while the mother is on VKAs or <2 weeks after discontinuation of VKAs, caesarean section is recommended for foetal protection.	I	C
Post-delivery, it is recommended that the decision to restart LMWH or UFH is made after discussion with the Pregnancy Heart Team and the woman who gave birth.[170]	I	C
It is recommended to postpone the switch from heparin back to oral anticoagulants until 7–14 days post-partum when the wound area has healed, in consultation with the Pregnancy Heart Team.[177]	I	C
In women on therapeutic-dose LMWH, planned delivery should be considered at around 39 weeks to avoid the risk of spontaneous labour while fully anticoagulated.	IIa	C
In women who are on antenatal anticoagulation, active management of the third stage of labour with oxytocin should be considered.[158]	IIa	C

Contraindications/cautions to LMWH use

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Known bleeding disorder (e.g. haemophilia, von Willebrand's disease or acquired coagulopathy)	
Active antenatal or postpartum bleeding	
Women considered at increased risk of major haemorrhage (e.g. placenta praevia)	
Thrombocytopenia (platelet count < 75×10^9/l)	
Acute stroke in previous 4 weeks (haemorrhagic or ischaemic)	
Severe renal disease (glomerular filtration rate [GFR] < 30 ml/minute/1.73m^2)	
Severe liver disease (prothrombin time above normal range or known varices)	
Uncontrolled hypertension (blood pressure > 200 mmHg systolic or > 120 mmHg diastolic)	

Appendix IV: Summary of guideline for thromboprophylaxis in women with previous VTE and/or thrombophilia (also see Appendix I)

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Very high risk	Previous VTE on long-term oral anticoagulant therapy	Recommend antenatal high-dose LMWH and at least 6 weeks' postnatal LMWH or until switched back to oral anticoagulant therapy
	Antithrombin deficiency Antiphospholipid syndrome with previous VTE	*These women require specialist management by experts in haemostasis and pregnancy*
High risk	Any previous VTE (except a single VTE related to major surgery)	Recommend antenatal and 6 weeks' postnatal prophylactic LMWH
Intermediate risk	Asymptomatic high-risk thrombophilia homozygous factor V Leiden/compound heterozygote Protein C or S deficiency	Refer to local expert Consider antenatal LMWH Recommend postnatal prophylactic LMWH for 6 weeks
	Single previous VTE associated with major surgery without thrombophilia, family history or other risk factors	Consider antenatal LMWH (but not routinely recommended) Recommend LMWH from 28 weeks of gestation and 6 weeks' postnatal prophylactic LMWH
Low risk	Asymptomatic low-risk thrombophilia (prothrombin gene mutation or factor V Leiden)	Consider as a risk factor and score appropriately (see Appendix III) Recommend 10 days' if other risk factor postpartum (or 6 weeks' if significant family history) postnatal prophylactic LMWH

Thank you for your attention