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PHARMACOTHERAPEUTICS in Obstetrics & Gynecology



Ashok Kumar
Neha Pruthi Tandon

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Chapter

7

Mechanical and Prosthetic Heart Valves: Anticoagulant Therapy

Jaya Chawla, Kiran Dhawan

MAGNITUDE OF THE PROBLEM

Heart disease complicates pregnancy in about 1.46% of cases, as per most recently published data on Southeast Asia.[1] The European Society of Cardiology (ESC) Registry of Pregnancy and Cardiac disease (ROPAC) estimates 29% cases of heart disease in pregnancy to be accounted for by valvular heart disease and the likelihood of facing a pregnancy complication with mechanical valve prosthesis is astronomically high at 42%.[2]

Since, being on anticoagulation is an independent risk factor for heart failure and maternal mortality, this chapter has been dedicated to a focused discussion on the options of anticoagulant therapy in pregnant women with mechanical valve prosthesis.[2]

Mechanical valve prosthesis merits lifelong anticoagulation to mitigate the risks of thromboembolism which are potentially lethal to both the mother and the fetus. This risk is amplified during pregnancy and puerperium owing to the hypercoagulable state and owing to physiological changes of pregnancy that alter the pharmacokinetics of the drugs used. The risk is further modified based on the site of the prosthesis with right-sided lesions faring worse than the left-sided ones and mitral valve prosthesis having a graver prognosis compared to aortic in terms of thromboembolic sequelae. The ROPAC data suggests that the risk of valve thrombosis during pregnancy overall is nearly 4.7% with mortality rates as high as 20%.[2]

This risk varies with the anticoagulant medication. The two most appropriate drugs to keep the maternal risks of thromboembolism in check are the vitamin K antagonists and heparin.

Vitamin K antagonists: They are one of the two most important categories of drugs used in anticoagulation. The prototype drug in this category is warfarin, others being acenocoumarol and phenprocoumon.

Vitamin K taken from diet is reduced by the enzyme vitamin K reductase to vitamin KH2 (reduced vitamin K). This reduced vitamin K is the substrate for the carboxylation of glutamate to carboxyglutamate in tissues. This conversion is necessary for the biological activity of coagulation factors II, VII, XI, and X. This carboxylation is coupled to another reaction that oxidizes reduced vitamin K to vitamin K epoxide. The enzyme vitamin KO reductase is needed to reduce vitamin K epoxide to K1. Warfarin blocks this step thereby reducing the bioavailability of these clotting factors.[3]

In addition, as is understood, supplementing vitamin K_1 in any form oral or parenteral can circumvent this block. Also,

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the step of carboxylation of glutamate also takes place in bones. Placental transfer of warfarin in the first trimester affects this step leading to features of warfarin embryopathy, discussed later in this chapter.

PHARMACOKINETICS

Warfarin, administered orally, is completely absorbed through the gastrointestinal tract. It is 99% protein bound in circulation. Its half-life on an average is 40 hours (20–60 hours range). It is a racemic mixture of two optically active isomers S-warfarin and R-warfarin. The former being 5 times more potent than the latter and the half-life of the former being slightly shorter than the latter (37–89 hours vs. 21–43 hours).[4] It is metabolized in the liver via the cytochrome P450 enzyme pathway. Therefore, enzyme-inducing agents are likely to have a drug–drug interaction (DDI) with warfarin **(Table 1)**.

TABLE 1: Warfarin: Drug interactions.[5]

S. no.	*Bioavailability*		
	Increased by	***Decreased by***	***Mechanism***
1.		Cholestyramine	Decreases absorption
2.		Barbiturates	Decrease clearance
3.		Rifampicin	Induces cytochrome P450
4.		Carbamazepine	Decrease clearance
5.		Phenytoin prolonged use	Induces cytochrome P450
6.	Phenytoin initially		Displaces warfarin from protein binding sites
7.	Trimethoprim-sulfamethoxazole		Decreased clearance
8.	Sulfonamides		Decrease absorption of vitamin K by altering gut flora
9.	Metronidazole		Decreased clearance
10.	2nd/3rd-generation cephalosporins		Interrupt the vitamin K cycle **(Fig. 1)**
11.	Phenylbutazone		Decreased clearance
12.	Sulfinpyrazone		Decreased clearance
13.	Salicylates in doses >1.5 g/d		Anticoagulant properties
14.	Aspirin, NSAIDs, penicillins, moxalactam		Decrease platelet function
15.	Cimetidine and omeprazole		Decrease clearance*
16.	Thyroxine		Accelerates metabolism of clotting factors
17.	Amiodarone		Decrease clearance

*Warfarin is made up of a racemic mixture of two optically active isomers warfarin-S and warfarin-R. These drugs decrease clearance of the less potent R isomer. Therefore, effect is not very significant clinically.
(NSAID: nonsteroidal anti-inflammatory drug)

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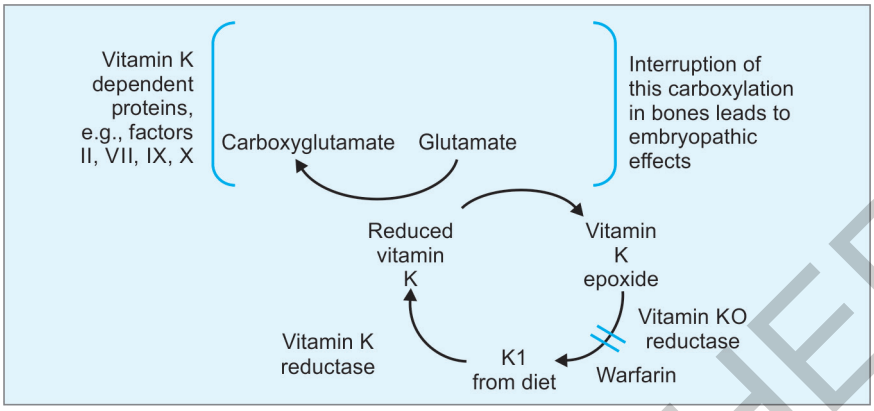


Fig. 1: Mechanism of action of warfarin.

MONITORING OF ANTICOAGULANT EFFECT: WARFARIN

The anticoagulant effect of warfarin is measured using prothrombin time (PT) international normalized ratio (INR). It reflects changes in three out of the four clotting factors that are dependent on vitamin K for their biological activity. The rate of curtailment of their activity by warfarin is proportionate to their corresponding half-lives. Hence, for the initial few days of therapy alteration in PT is a result of reduction in factor VII activity, whose half-life is 6 hours. Thereafter, further increase in PT is related to ameliorated activity of factors II and X.

Optimum anticoagulant effect is expected within 2–7 days after initiation of therapy, depending upon the dose. It usually takes 3 days to stabilize.[5] Since anticoagulation achieved with warfarin would take time, it is prudent to initiate simultaneous therapy with low molecular weight heparin (which has a shorter peak) when rapid therapeutic action is desired. The initial dose of warfarin is usually 2–3 mg once a day which is later titrated to achieve an INR between 2 and 3 **(Table 2)**.[3]

ADVANTAGES

The risk of valve thrombosis in a regime using VKA throughout pregnancy is between 0.4 and 4%,[7] which is the minimum risk when compared with all other choices as discussed later. Acknowledging the lack of robust evidence, in the form of randomized controlled trials, the ESC recommends that VKA throughout regimes are the safest regime to prevent valvular thrombosis during pregnancy, when administered under stringent INR monitoring.[8]

DISADVANTAGES

Vitamin K antagonists cross the placenta and are therefore associated with embryopathy in the first trimester between weeks 6 and 12. The risk is dose dependent. With low dose VKAs (implying warfarin <5 mg per day, acenocoumarol <2 mg per day, and phenprocoumon <3 mg per day), the risk is between 0.45 and 0.9%.[7,9,10]

Warfarin embryopathy is characterized by skeletal defects such as epiphysial stippling of long bones, nasal bridge hypoplasia, central nervous system anomalies such as ventriculomegaly and agenesis of corpus callosum and congenital cardiac defects.[6]

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TABLE 2: *Anticoagulant drugs in pregnancy with mitral valve replacement:* Clinical considerations.

S. no.	Name	Dosage	Maximum dose	Route/ frequency of administration	Pharmacokinetics	Adverse effects	Contraindications	Cost*
1.	*Vitamin K antagonist*							
a.	Warfarin	1/2/5 mg tablets	10 mg/d	Per oral once a day	• *T½:* 40 hours • Metabolism in liver by CYP450	• Warfarin embryopathy, fetopathy, miscarriage, intrauterine demise • Hemorrhage	Malignant hypertension	Varies from 11 to 20 INR for a pack of 10 tablets
b.	Acenocoumarol	1/2/3/4 mg tablets	5 mg/d	Per oral once a day	• *T½:* 8–11 hours • Metabolism in liver by CYP450	Hemorrhage		Varies from 31 to 64 INR for a pack of 10 tablets depending on strength
c.	Phenprocoumon	50/100/200/300/400 mg tablets	5 mg/d	Per oral once a day	• *T½:* 6 days • Metabolism in liver by CYP2C9, CYP3A4	Hemorrhage	Hypersensitivity, hypotension, left ventricular outflow tract obstruction, cardiogenic shock	
2.	*Heparin*							
							• Active hemorrhage (antepartum or postpartum) DIC, thrombocytopenia (platelet count <75,000/cc), uncontrolled hypertension defined as diastolic BP >120 mm Hg or systolic BP >200 mm Hg, medical renal disease with GFR <30 mL/min/1.73 m^2, severe hepatic dysfunction with increased prothrombin time, history of stroke within last 4 weeks • Bleeding disorders like von Willebrand's disease or hemophilia	

Contd...

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S. no.	Name	Dosage	Maximum dose	Route/ frequency of administration	Pharmacokinetics	Adverse effects	Contraindications	Cost*
a.	UFH	25,000 IU in 5 mL vial	5,000 units for every single dose		• *T½:* 1–2 hours • Hepatic metabolism	Hemorrhage, heparin-induced thrombocytopenia, heparin-induced osteopenia	• The platelet count is 100,000/mm or lower • The patient cannot have routine monitoring tests performed to monitor therapeutic heparin • The patient has an active, uncontrollable bleed except for DIC • Patients with a history of heparin-induced thrombocytopenia should also avoid heparin use • Patients with known case of bleeding disorders	204–305 INR
b.	LMWH	• 40 mg/ 0.4 mL • 60 mg/ 0.6 mL	120 mg BD or 180 mg OD of enoxaparin		• *T½:* 2–7 hours • Renal metabolism	Hemorrhage	• The platelet count is 100,000/mm or lower • The patient cannot have routine monitoring tests performed to monitor therapeutic heparin • The patient has an active, uncontrollable bleed except for DIC • Patients with known case of bleeding disorders	• 385–427 INR • 355–577 INR

*From Med India

(DIC: disseminated intravascular coagulation; LMWH: low molecular weight heparin; UFH: unfractionated heparin)

Source: Royal College of Obstetricians and Gynaecologists. Reducing the risk of venous thromboembolism during pregnancy and the puerperium. Green Top Guideline No. 37a. London (UK): RCOG; 2015.[6]

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In addition, with use in the second and third trimesters, there is a risk of fetopathy involving the fetal central nervous system (CNS) and eyes. The estimated risk is 0.7–2%. Warfarin is also associated with a dose-dependent risk of miscarriage and fetal demise. Owing to the risk of fetal intracranial hemorrhage, vaginal birth is contraindicated when the mother is on warfarin.[8]

The rate of postpartum hemorrhage increases with all anticoagulant drugs. Keeping this in mind, it is prudent to delay the overlap of warfarin with low molecular weight heparin (LMWH) by 5–7 days post-delivery irrespective of the route of birth.[6]

Warfarin toxicity: The most clinically relevant side effect is bleeding which could manifest as postpartum hemorrhage besides bleeding from other sites, such as hematemesis, melena, epistaxis, and hematuria.

How to treat bleeding due to warfarin: Four-factor prothrombin complex concentrate (4f-PCC) should ideally be administered for reversal. In case 4f-PCC is not available, fresh frozen plasma can be used.[11] If there is no bleeding but the INR is close to 10, warfarin should be stopped and oral vitamin K started 1–5 mg a day. The oral route will take at least 24 hours to reverse warfarin-induced coagulopathy, so in case of bleeding or when a more rapid response is desired, intravenous vitamin K, 1–10 mg as guided by the severity should be administered. This route is expected to reverse the pathology in 4–6 hours.

In case a more rapid response is warranted, 4f-PCC can reverse coagulopathy in 15–30 minutes and with much less volume transfused than FFP.[12,13]

HEPARIN STRUCTURE AND BIOSYNTHESIS

Heparin is a biomolecule belonging to the class of glycosaminoglycans (GAGs) that are large linear polysaccharide structures, composed of repeated structural motifs. Heparin synthesis occurs through a complex process that involves many enzymatic steps.[14] The discovery that heparins' anticoagulant effects toward coagulation factor Xa (FXa) and thrombin could be separated, led to the production of shorter heparin subtypes with optimized anticoagulant activity and reduced risk of bleeding as compared with UFH. These heparins are obtained by fragmentation of UFH and are commonly known as LMWHs. The size of UFH molecules ranges from 6 to 60 kDa; while LMWHs vary between 1 and 10 kDa.[15,16]

Pharmacokinetics

Heparin is a large, highly ionized molecule which is not absorbed orally. When injected intravenously (IV) it acts immediately, but after subcutaneous (SC) injection anticoagulant action takes approximately 60 minutes. Heparin does not cross the blood–brain barrier or placenta thus, making it a safe option for the fetus during pregnancy. It is metabolized in liver by the enzyme heparinase and excreted in urine. Heparin is released endogenously from mast cells and is degraded by tissue macrophages. After administering IV injection of doses <100 U/kg, the half life averages 1 hour. Beyond this period, dose-dependent inactivation is seen and t½ is prolonged to 1–4 hours. Half life is longer in patients with cirrhosis and renal failure, and is shorter in patients suffering from pulmonary embolism.[17]

Mechanism of Action

Heparin is an immediately acting anti-coagulant which is effective both in vivo and in vitro. It acts by indirectly activating plasma antithrombin III (AT III, a serine proteinase inhibitor) **(Fig. 2)**. This heparin-AT III complex then binds to clotting factors of the

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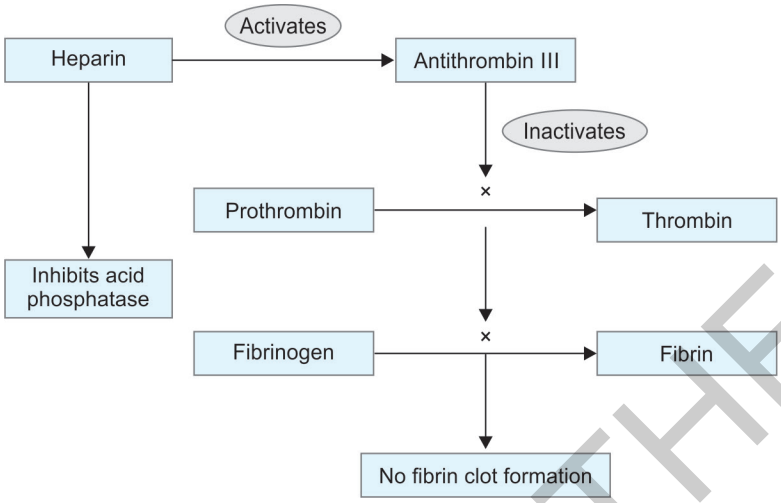


Fig. 2: Mechanism of action of heparin.

intrinsic and common pathways (Xa, IIa, IXa, XIa, XIIa, and XIIIa) which then inactivate them. At low concentrations of heparin, factor Xa-mediated conversion of prothrombin to thrombin is selectively affected. The anticoagulant mechanism of heparin is exerted mainly by inhibition of factor Xa as well as thrombin (IIa) mediated conversion of fibrinogen to fibrin.[17]

The LMWH has several advantages over UFH as it has a higher bioavailability, has a better predictable dosing, and is associated with less adverse reactions. Thus, LMWH has become the heparin of choice for many clinical conditions such as venous thromboembolism (VTE), major surgery, and acute coronary syndrome.[18,19] UFH, however, is usually preferred in patients with renal failure due to less dependence on the kidneys for clearance and also improved reversibility with protamine.[20]

Unfractionated Heparin

Unfractionated heparin (UFH) is administered parenterally, used subcutaneously when given for prophylaxis and as a continuous intravenous infusion when administered therapeutically as it assures fast and potent anticoagulation when given intravenously. UFH has a faster onset of action when compared to warfarin. Therapeutic efficacy of UFH is achieved within 20–60 minutes when administered subcutaneously. The half-life of UFH is shorter than LMWH, being 1.5 hours when administered subcutaneously and 30 minutes via intravenous route **(Table 3)**.[8]

Side Effects and Reversal Agents

- Hemorrhage is the main adverse reaction in patients receiving UFH. The incidence of major bleeding depends on the indication of its use, dosage, and route of administration. Usually, UFH when used for therapeutic purposes is associated with a 2.0% incidence of major bleeding event.[9]
- Effect of UFH can be reversed with protamine sulfate. The dose depends on the amount of UFH administered. One milligram of protamine sulfate neutralizes 100 units of UFH.
- Another important adverse reaction associated with UFH use is heparin-induced thrombocytopenia (HIT).

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TABLE 3: Heparin and its derivatives.

	UFH	*LMWH*
Mechanism	Enhances AT effect on factor Xa and thrombin	Enhances AT effect more specifically on factor Xa than thrombin
Plasma protein binding	Nonspecific	Less binding
Dose response curve	Unpredictable	More predictable
Half life	1–2 hours	2–7 hours
Dosing frequency	Continuous IV drip, subcutaneous twice or thrice daily	Subcutaneous BD or once daily
Clearance	Hepatic and reticuloendothelial system. No renal clearance	Renal clearance. Dose adjustment required in renal impairment
Ability to cause HIT	Yes	Yes
Routine monitoring	aPTT	Factor Xa

(aPTT: activated partial thromboplastin time; AT: antithrombin; LMWH: low molecular weight heparin; UFH: unfractionated heparin)

It occurs in 0.1–5% of patients who receive therapeutic doses of heparin.[10] There are two types of HIT, with the first type, which is rare in clinical practice, is associated with the exposure of patients to UFH or high heparin doses for the first time. This is due to a nonimmune thrombocytopenic response caused by binding of heparin to platelet factor 4, which results in ultra-large complexes (ULCs) that trigger platelet activation or via a fibrinogen receptor modulated lowering of platelet counts. HIT type 2 is an immune-mediated response where antibodies are generated against ULCs. It causes life-threatening thrombosis and thrombocytopenia and is seen usually 5–10 days after the initiation of heparin therapy. Immediate stopping of heparin is important to allow increase of platelet counts. American Society of Hematology recommends the use of nonheparin anticoagulants (such as danaparoid, fondaparinux) for treatment of acute HIT.[7] However, data supporting their use in pregnancy is very limited.

Low Molecular Weight Heparin

These are parenterally administered drugs, and include dalteparin, enoxaparin, and tinzaparin. Compared with UFH, the LMWHs have the advantage of having a more predictable dose-response curve.[11] Thus, the LMWHs are administered at a fixed dose, which is based on total body weight, and do not require tight regulation and monitoring as is with the use of warfarin and UFH.[11] These drugs have nearly 100% bioavailability and reach peak levels within 2–4 hours after subcutaneous administration.[8,11] Their half-life is of 3–4 hours and these drugs are eliminated majorly (80%) via renal clearance, thus requiring dose reduction in patients with renal insufficiency.[8] Additionally, since dose is based on total body weight, dosing complications arise in obese patients.[11] Although therapeutic monitoring is not routinely indicated, in cases of patients with renal insufficiency, obesity, or in an iatrogenic overdose, anti-factor Xa levels can be used to monitor LMWH.[8,11] Ideally, the anti-factor

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Xa level should be obtained 4 hours after the administration of LMWH. Certain studies though recommend routine monitoring with a combination of trough and peak anti-Xa levels in high-risk patients (i.e., women with MHV), and only peak anti-Xa levels in patients with low-risk pregnancies (i.e., women with acute VTE during pregnancy). Generally, LMWH is administered every 12 hours, and the dose is adjusted to maintain anti-Xa levels based on the specific indication for anticoagulation (i.e., for patients with MHV: target trough anti-Xa level is 0.6 U/mL, and peak anti-Xa level 1.0–1.2 U/mL; and for patients with acute VTE: target peak anti-Xa level is 0.5–1.0 U/mL).[12-14]

Side Effects and Reversal Agents

- Acute bleeding is the major risk associated with LMWH. When used in prophylactic doses the incidence of major bleeding is 1.5–1.7%.[15]
- When given in therapeutic dosage, risk of acute bleeding is slightly raised at 2%, with even higher incidences observed when it is used to treat acute coronary syndrome (ACS).[15] In the event of major bleeding, protamine sulfate can be used as a partial reversal agent and can neutralize up to 60% of the anticoagulation effect of LMWH.[15] Initial doses of 1 mg per 100 units of antifactor Xa should be administered within 8 hours of LMWH administration.[16] A second dose of 0.5 mg per 100 units anti-factor Xa can also be repeated. In case of major bleeding associated with LMWH, cryoprecipitate and FFP are also recommended.[15,17]

Data on other adverse or side effects of heparin use is scarce. These include the association of heparin with osteoporosis[18] and skin lesions.[19] It is usually seen that long-term use of UFH is associated with a 2.2–5% incidence of heparin-induced osteoporotic fracture, which is far less associated with LMWH. The molecular mechanism of heparin-induced osteoporosis usually involves the resorption of bone by osteoclasts. In addition, there is also suppression of osteoblast function.[19] Very little data is available on the incidence of heparin-induced skin lesions, but a study from 2009 found that 7.5% of patients receiving subcutaneous heparin developed skin lesions. In all these patients, a delayed-type hypersensitivity reaction was the reason for the lesion which occurred after prolonged heparin use.

ANTICOAGULATION IN PREGNANCY: TRIMESTER-WISE RECOMMENDED PROTOCOLS

As per the ESC guidelines,[8] women on VKAs should be counseled regarding the dose-related risk of embryopathy and offered the choice of:

- Continuing with VKAs throughout pregnancy
- Switching over to heparin from 6 to 12 weeks to mitigate this risk and switch back to VKAs from 12 weeks onward

In both circumstances, at 36 weeks of gestation, they should be admitted for switch over to heparin, to prevent going in labor on a VKA as this has the potential risk of intracranial hemorrhage for the fetus.

After 6 hours of birth, women should be started on unfractionated heparin for anticoagulation and their aPTT monitored **(Fig. 3)**.

In case of cesarean birth, therapeutic dose of LMWH should be stopped 24 hours of elective surgery and women shifted to unfractionated heparin which is monitored using aPTT. Unfractionated heparin is stopped 6 hours prior to surgery and spinal

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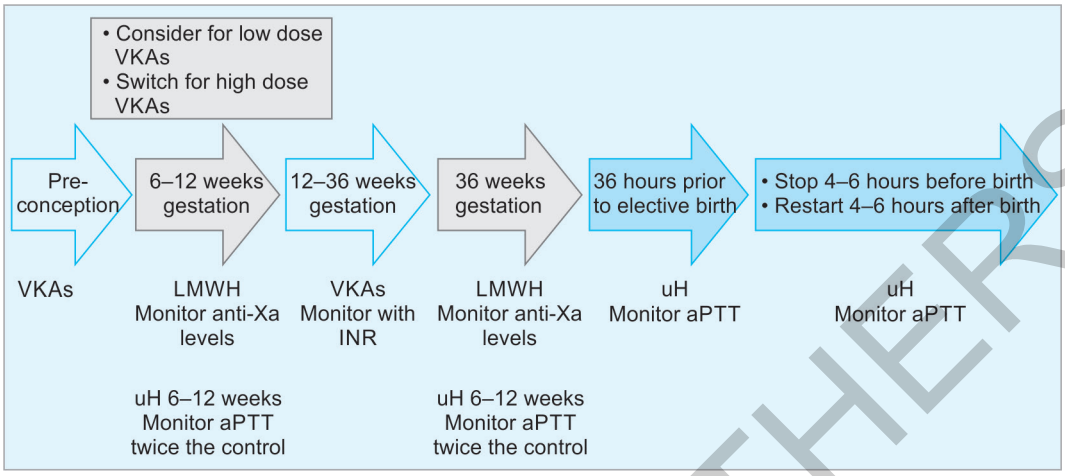


Fig. 3: Recommended timeline for anticoagulants in pregnancy. (VKA: vitamin K antagonists; LMWH: low molecular weight heparin; uH: unfractionated heparin; aPTT: activated partial thromboplastin time; INR: international normalized ratio)
Source: ESC guidelines[8]

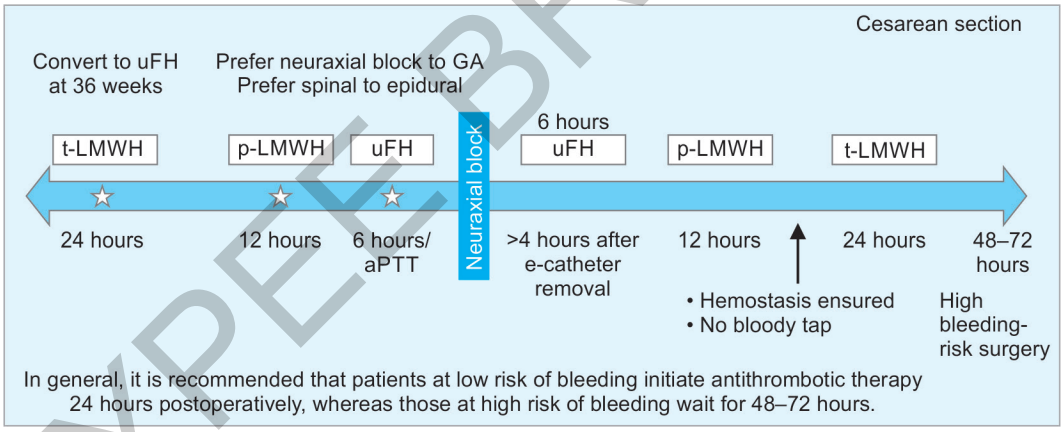


Fig. 4: Timeline of anticoagulant therapy immediately prior to and following a cesarean section. (t-LMWH: therapeutic dose low molecular weight heparin; p-LMWH: prophylactic dose low molecular weight heparin; GA: general anesthesia; e-catheter: epidural catheter)

anesthesia is preferred. If there is no risk of hemorrhage, UFH may be restarted 6 hours later (taking care that epidural catheter, if inserted, has been removed at least 4 hours prior). Therapeutic dose of LMWH can be started after 24 hours provided there is no risk of hemorrhage. In case of high risk of bleeding, this should be delayed for until 48 hours **(Fig. 4)**.[8]

All anticoagulants carry an increased risk of miscarriage. VKAs during the first trimester are associated with an increased

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risk of miscarriage compared with LMWH or UFH (28.6% vs. 9.2%), and the live birth rate is lower.[20] The risk of fetal loss is dose-related (13.4–19.2% with low dose VKA; overall risk with VKA is 32.5%). Incidence of fetal loss with a combined heparin/VKA regimen is approximately 22.7% and with LMWH throughout pregnancy is 12.2%.[7,21] VKA use in the first trimester is associated with embryopathy (limb defects, nasal hypoplasia) in 0.6–10% of cases; in second and third trimester, risk of fetopathy (ocular and central nervous system abnormalities, intracranial hemorrhage) is around 0.7–2%.[7,22-26] Hemorrhagic complications (including retroplacental bleeding leading to premature birth and fetal demise) and postpartum hemorrhage in the mother occur with all anticoagulants, but the incidence is lower with VKA throughout pregnancy than with LMWH/UFH.[7]

KEY POINTS

- Unfractionated heparin (UFH) and LMWH do not cross the placenta, thus substitution of VKA with UFH or LMWH in weeks 6–12 almost eliminates the risk of embryopathy.
- The risk of embryopathy is also dose-dependent (0.45–0.9% with low-dose warfarin).[7,21]
- During the second and third trimesters and until the 36th week, VKAs are recommended in women who require low-dose anticoagulation.
- It is ideal to discontinue VKA and start adjusted-dose intravenous UFH (maintaining aPTT ≥2 control) or adjusted-dose LMWH at the 36th week of gestation because of their lower half lives.
- If the woman delivers while on VKA or in less than 2 weeks after discontinuation of a VKA, cesarean section is indicated to prevent intracranial hemorrhage in the fetus.
- It is recommended to anticipate the timing of delivery to ensure safe and effective peripartum anticoagulation.
- Immediate echocardiography is recommended in women with mechanical valves presenting with dyspnea and/or an embolic event.
- Addition of low-dose aspirin to VKA or heparin has no proven advantage in preventing valve thrombosis but is associated with significantly more maternal bleeding complications, including fatal events.[8]

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