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Chapter 1

Anticoagulants in Pregnancy and Postpartum

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Introduction

Anticoagulants use in modern obstetrics and gynecology is not very uncommon. In this chapter, we will discuss the various anticoagulants and their use in pre-conceptional period, pregnancy and puerperium.

As a treating clinician, it is very important that we should know the four basic concepts—which is the right anticoagulant, what is the right timing and dose, how to prevent the potential teratogenic effect of the drug and the fine-tuning during labour and delivery to prevent antepartum hemorrhage/postpartum hemotrrhage (APH/PPH) and its complications. Use of anticoagulants in pregnancy requires an expert balancing act, as both the mother and the baby should be protected.

The common indications of anticoagulant use in pregnancy are:

1. Antiphospholipid syndrome (APS)
2. To prevent deep venous thrombosis (DVT)
3. To prevent venous thromboembolism (VTE)
4. Treatment of DVT and VTE
5. Prosthetic heart valve
6. Inherited thrombophilia
7. Atrial fibrillation.

CHOICE OF ANTICOAGULANT

- Low molecular weight heparin (LMWH) and unfractionated heparin (UFH) are the preferred anticoagulants in pregnancy as they do not cross the placenta.[1] Both these molecules are equally effective and extensively studied. LMWH is commonly recommended as it is easy to administer, do not require routine monitoring and the incidence developing heparin-induced thrombocytopenia (HIT) is also less.[2] The advantage of UFH is however its cost and that its effects can be rapidly reversed. Moreover, in patients with renal dysfunction, UFH is advised as it is excreted by both kidney and liver against LMWH which is primarily excreted by kidney.
- We will discuss more about these two drugs further in the chapter.
- Warfarin crosses the placenta leading to fetal embryopathy if given in first trimester and intracranial hemorrhage (ICH) later in pregnancy. Women receiving warfarin should be converted to LMWH/UFH prior to conceiving.
- Synthetic anticoagulants which act as indirect inhibitor of factor Xa like fondaparinux,[4] heparinoids like danaparoid and synthetic thrombin inhibitors like

argatroban are less studied in pregnancy and their effects on fetus are not known.[3–5] This limits their use in pregnancy but can be used rarely as alternative drug in women where LMWH and UFH are not tolerated.

- Direct anticoagulants such as rivaroxaban, dabigatran, edoxaban, and apixaban are not used in pregnancy as fetal safety is not yet proven.

This leaves us with two most common drugs—LMWH and UFH with occasional exceptional use of warfarin.

LOW MOLECULAR WEIGHT HEPARIN (LMWH)

Initiation of treatment: Can be started soon as patient conceive. However, the initiation depends on the indication and risk factors. **Table 1.3** explains the details on initiation of treatment. When started in first trimester it is advisable to confirm the pregnancy via urine pregnancy test or serum β-hCG. There is no role of starting LMWH prior to conception. In women, who are already on chronic coagulation a change from oral anticoagulants to LMWH is advisable.

Administration: Subcutaneous injection is usually very well-tolerated. Local ice application prior to injection may reduce bruising, however this is not necessary.

Baseline laboratory testing: The incidence of heparin-induced thrombocytopenia (HIT) is very less during pregnancy. However, it is prudent to do a baseline CBC followed by a CBC test after 4 weeks of commencing treatment with LMWH. If no decline in platelet count there is no need for further monitoring. Monitoring of Xa levels is not indicated.[6] If monitoring needs to be done, peak anti-factor Xa activity levels should be measured 4 to 6 hours after the last dose. The dosage should be titrated to maintain a target peak anti-factor Xa activity of approximately 0.6–1.2 units/ml.[7] There is not much data supporting the need for laboratory monitoring of therapeutic dose of LMWH.

Pharmacology: LMWH is metabolised in liver and excretion happens via kidney. Individuals with chronic renal disease may have higher plasma levels and therefore need monitoring with subsequent use of lower dosage. Peak drug levels are reached 3–5 hours after subcutaneous and 2 hours after intravenous administration. Half-life varies from 5 to 7 hours. It is only after 2–3 days of treatment that drug levels reach on steady state.

The preferred interval between prophylactic dose of LMWH and any form of regional anaesthesia is 12 hours.[8]

Advantages

- Monitoring not required
- Incidence of HIT is lower
- Dose to response relationship is predictable.

Limitation

- Dose may have to be reduced in patients with renal impairment.
- Antidote not available
- Rapid reversal not possible in case of early delivery or APH.

Dosing

Dosing of LMWH **(Table 1.1)** depends on mainly two factors:

1. Risk of thromboembolism
2. Anticoagulation desired.

Contraindications

- Patients who have active bleeding or are at high risk of having bleeding (APH, PPH)
- Patients with known bleeding disorders (hemophilia)
- Patient with past history of LMWH-induced HIT or skin allergy
- Thrombocytopenia (platelet $<75 \times 10^9$/L)
- Severe liver and renal disorders
- Uncontrolled hypertension (blood pressure >200 mmHg systolic or >120 mmHg diastolic).

UNFRACTIONATED HEPARIN (UFH)

Initiation of treatment: As soon as intrauterine pregnancy confirmed. Details of the initiation of treatment are mentioned in **Table 1.2**.

Table 1.1: LMWH dosing	
Prophylactic dosing Minimal dose required to prevent thromboembolism without risk of bleeding	40 mg, enoxaparin, subcutaneous, OD 5000 units dalteparin, subcutaneous, OD
Intermediate dosing	40 mg enoxaparin, subcutaneous, OD, to be increased as pregnancy progresses up to 1 mg/kg, OD*
This refers to the need of increase in dose with increasing weight in pregnancy, and certain special situations (Table 1.3)	5000 units dalteparin, subcutaneous, OD, to be increased as pregnancy progresses up to 100 units/kg, OD*
Therapeutic dosing To be used in women with high risk of thromboembolism or to treat VTE	1 mg/kg enoxaparin, subcutaneous, BD 100 units/kg dalteparin, subcutaneous, BD

*There is no evidence to suggest that the dosage may be altered as per the weight of pregnant women. However, few studies have reported risk of VTE when pregnant women were given low prophylactic doses. LMWH: Low molecular weight heparin; VTE: Venous thromboembolism

Table 1.2: UF dosing	
Prophylactic	5000 units, subcutaneous, BD
Intermediate	1st trimester: 5000 to 7500 units, subcutaneous, BD 2nd trimester: 7500 to 10,000 units, subcutaneous, BD 3rd trimester: 10,000 units, subcutaneous, BD
Therapeutic	Can be given as a continuous IV infusion or subcutaneous, BD. Should be titrated to maintain the aPTT in the therapeutic range.

Administration: Subcutaneous injection. UFH can also be given intravenous, especially during labour and delivery or situations where strict monitoring and rapid anticoagulation are desired.

Baseline laboratory testing: Baseline CBC may be suggested as mentioned above. Baseline prothrombin time (PT) and aPTT to rule out underlying coagulopathies. Monitoring of prophylactic dose of UFH is not recommended. When given in therapeutic dose aPTT to be monitored 6 hours after injection and dose adjusted to maintain aPTT at 1.5–2.5 times the baseline aPTT of the patient. Daily aPTT is recommended till the desired effect achieved and then to be repeated every 1 to 2 weeks.

Pharmacology: UFH is metabolized mainly in the liver and the reticuloendothelial system, and it is excreted in the urine. Elimination is not dependent on kidney function, however in individuals with high-dose requirement, dose may need adjustment. Action of UFH when given intravenous is instantaneous, peak action happens 2–4 hours after subcutaneous administration. Half-life of the UFH is 45 minutes to 1 hour.

The advisable interval between prophylactic dose of UFH and any form of regional anaesthesia is 4 hours.[8]

Advantages

- Rapid onset, so can be used when immediate anticoagulation needed.
- Shorter half-life. This is especially important in obstetrics to prevent APH.
- Ability to monitor with aPTT, a test which is easily available.
- Action can be reversed as antidote present in the form of protamine sulphate.

Table 1.3: Obstetric thromboprophylaxis risk assessment and management[15]

Risk	*Antenatal risk factors*	*Postnatal risk factors*
High risk • Antenatal prophylaxis with LMWH • Minimum 6 weeks postpartum LMWH	Any previous history of VTE	• Previous history of VTE • Women who are on LMWH antenatally and with high-risk thrombophilia
Intermediate risk • Consider antenatal prophylaxis with LMWH • At least 10 days postnatal LMWH	• Pregnant women who need hospital admission • Previous VTE after a major surgery • High-risk thrombophilia • Medical diseases, *e.g.* heart failure, IBD, active SLE, sickle cell disease, nephrotic syndrome, type-1 diabetes with nephropathy • Any surgical procedure during pregnancy • OHSS (first trimester only)	• Caesarean section • BMI ≥40 kg/m^2 • Readmission or prolonged admission (≥3 days) required in postpartum period • Any surgical procedure in the puerperium except postpartum perineal repair • Medical diseases, *e.g.* heart failure, IBD, active SLE, sickle cell disease, nephrotic syndrome, type-I diabetes with nephropathy
Low risk *Initiation of treatment antenatally:* • Four or more risk factors—prophylaxis from first trimester • Three or more risk factors—prophylaxis to be started from 28 weeks • Fewer than three risk factors • Early mobilization • Avoid dehydration • No anticoagulation *Initiation of treatment postnatally:* • Two or more risk factors—anticoagulation same as in intermediate risk • Less than two risk factors—early mobilization • Avoid dehydration • No anticoagulation	• Age >35 • Parity ≥3 • Obesity (BMI >30 kg/m^2) • Pre-eclampsia • Multiple pregnancy • IVF pregnancy • Smoker • Gross varicose veins • Family history of VTE in first-degree relative • Low-risk thrombophilia *Transient risk:* • Dehydration/hyperemesis • Infection • Long-distance travel	• Age >35 years • Parity ≥3 • Smoker • Obesity (BMI ≥30 kg/m^2) • Elective caesarean section • Current pre-eclampsia • Multiple pregnancy • Preterm delivery • Stillbirth in this pregnancy • Mid-cavity rotational or operative delivery • Prolonged labour (>24 hours) • PPH with >1 litre or blood transfusion • Family history of VTE • Low-risk thrombophilia • Gross varicose veins • Current systemic infection • Long-distance travel

SLE: Systemic lupus erythematosus; IBD: Inflammatory bowel disease; OHSS: Ovarian hyperstimulation syndrome; IVF/ART: *In vitro* fertilization/assisted reproductive techniques

Limitations

- Shorter half-life may be an advantage as well as limitation. More dosages may be needed
- Dose to response is unpredictable
- Long-term use is associated with HIT, skin reactions and osteoporosis.

Dosing: Table 1.2

Contraindications: Same as mentioned with LMWH.

WARFARIN

It is best to convert women on warfarin to UFH/LMWH, preconceptionally. Warfarin

use in pregnancy is best avoided, in view of its teratogenicity, exception being women with high risk of thrombosis like presence of mechanical heart valve. In such situations, the benefits and risks of continuing warfarin are weighed in each trimester, and conversion to alternative agent is done towards the end of third trimester to avoid bleeding complications.

For preterm labour in an women taking warfarin, it is important to remember risk to the fetus in view of the anticoagulation. Cardiologist, neurologist and obstetrician should be involved in the decision-making. Caesarean delivery should be considered to prevent risk of fetal intracranial hemorrhage. Antidotes of warfarin are vitamin K and fresh frozen plasma (FFP), to be given to the neonate post-delivery, as per the situation.

Warfarin can be restarted postpartum once the risk of haemorrhage is reduced, approximately 5–7 days after delivery. Warfarin is generally safe in breastfeeding.

Warfarin Teratogenicity

The teratogenic effect of warfarin is dose-dependent. Doses <5 mg/day are associated with high-safety margins. Overall incidence of warfarin embryopathy/fetal warfarin syndrome/Di Sala syndrome is estimated to be <10%. The common developmental abnormalities affect bones and cartilage, characterized by short limbs and digits (brachydactyly), nasal hypoplasia, skeletal abnormalities and stippled epiphyses. The risk is maximum when fetus is exposed to warfarin in the first trimester between 6th and 12th week of gestation.[14] There are a few reports of central nervous system abnormalities (ventriculomegaly, microcephaly, microphthalmia, intellectual disability, hypotonia, etc.) associated with warfarin use at any stage during pregnancy. Besides the risk of neonatal cerebral haemorrhage remains due to the anticoagulation effect.

COMPLICATIONS OF ANTICOAGULANTS

Bleeding

Spotting or minor bleeding which stops spontaneously does not warranty the stoppage of anticoagulants. In women with subchorionic hematoma (SCH) but with no active bleeding, anticoagulants continuation will depend on benefit versus risks.

Women with active bleeding or imminent bleeding, *e.g.* vaginal/caesarean delivery, placenta previa, placental abruption or expanding SCH, protamine sulphate can be used to reverse the effect of UFH. It may not be an effective antidote when LMWH is used, nevertheless its administration does reduce bleeding by neutralising the high molecular weight fractions of heparin.[9]

Administration of protamine sulphate

- Slow IV infusion started at 5 mg/min
- Total dose should not exceed 50 mg which has to be given over 10 min.

UFH	• Dose 1 mg protamine sulphate/100 units heparin • It may be difficult to estimate amount of heparin in plasma at that given moment • Single dose 25–50 mg as described above and aPTT monitored
LMWH	• LMWH administered within 8 hours: 1 mg protamine/1 mg of enoxaparin. • LMWH administered >8 hours ago: 0.5 mg protamine/1 mg of enoxaparin.

Potential adverse effects of protamine sulphate include hypotension and anaphylactoid-like reactions.[10]

Heparin-induced Thrombocytopenia

The incidence of heparin-induced thrombocytopenia (HIT) is up to 5% in patients who are on UF or LMWH. It is a life-threatening complication, that occurs, regardless of the dose, schedule, or route of administration. It is more common with UFH compared to LMWH. HIT during pregnancy is extremely rare.[11]

A small decrease in platelet count in pregnancy is not an indication to investigate the HIT. On the other hand, if there is a significant fall, it is prudent to investigate other causes of thrombocytopenia in pregnancy before coming to the diagnosis of HIT. If the situation of HIT arises in pregnancy, a multidisciplinary management in tertiary care centre is warranted. Anticoagulation agents such as warfarin or synthetic anticoagulants (danaparoid, argatroban or fondaparinux) may be used to achieve desired results. The 2012 American College of Chest Physicians (ACCP) guidelines recommend danaparoid as an alternative drug for pregnant patients with HIT. The choice of non-heparin anticoagulant depends on urgency, cost, availability, hepatic and renal function and the potential need of reversal.

Local Allergic Reaction and Skin Necrosis

Allergic reactions are more common with UFH compared to LMWH. Local allergic skin reaction at the site of subcutaneous injections may manifest as itching and rash 2 weeks after starting the dose. Delayed reactions are rare. Risk factors include obesity and prolong use. The treatment is to shift to another heparin product.

Hyperkalemia

It is a rare but not unknown complication with use of heparins. As such does not need any treatment. However, in patients who have chronic renal disease it could be more serious.

Osteoporosis

Long-term use of UF (>6 months) is associated with irreversible risk of bone demineralization. Osteoporosis risk with LMWH is rare. In situations, where there is need to take heparin over prolong period, supplementation with calcium, vitamin D_3 and regular weight-bearing exercise is encouraged.

LABOUR AND DELIVERY

- Women with low risk of peripartum bleeding and preterm labour: LMWH till 38–39 weeks of gestation or until 24 hours prior to anticipated lower segment cesarian section (LSCS/induction or normal delivery.[12]
- Women at high risk of preterm labour or antepartum hemorrhage (APH): Shift from LMWH to UFH at 35–36 weeks of gestation or earlier. This minimises the risk that labour or delivery will happen within 24 hours of LMWH. Beside protamine sulphate is a better antidote for UFH as against LMWH.

If spontaneous labour starts when women are still taking UFH/LMWH, anticoagulation should immediately stop. The risk of bleeding when women undergo normal delivery within 24 hours of LMWH dose is very rare. Caesarean delivery may have increased incidence of blood loss and wound hematomas. It is important to electively plan the delivery of women who are at increased risk of thrombosis such as with mechanical heart valve and who are on warfarin. Multidisciplinary team of cardiologist, intensivist, anaesthesiologist and obstetrician should be available at the time of delivery and management should be individualised. Vaginal delivery is preferred. LSCS is indicated for obstetric reasons only.

NEURAXIAL ANAESTHESIA

Neuraxial anesthesia techniques (spinal, epidural, etc.) are contraindicated if a patient is anticoagulated due to the risk of spinal or epidural hematoma.

The duration for which anticoagulation has to stop prior to neuraxial anaesthesia is as follows:

- Prophylactic dose LMWH—after at least 12 hours since the last dose.
- Intermediate and therapeutic dose LMWH—after at least 24 hours since the last dose.

- Prophylactic and therapeutic dose of UFH—once the aPTT has normalized following discontinuation. In patients on therapeutic doses of unfractionated heparin, the aPTT is usually normal 6 hours after stopping intravenous administration but can take 24 hours to normalize after stopping subcutaneous administration.

It is possible that in the future, thromboelastography (TEG) may be used to determine when neuraxial anaesthesia can be initiated following discontinuation of LMW heparin, but more data are needed before this approach can be used.[13]

Routine use of protamine sulphate is not indicated unless there is excessive or unexpected bleeding due to the anticoagulant drug.

SPECIAL SITUATIONS

If an elective procedure such as cervical os tightening or any other minor surgical procedure needs to be done when patient is on anticoagulants, heparin discontinuation is enough to prevent bleeding complications. Stopping UFH 4–6 hours prior and LMWH 24 hours prior to procedure is enough. If the procedure needs to be done urgently, monitoring of aPTT or anti-factor Xa activity level can be monitored to confirm the resolution of the effect UFH or LMWH.

POSTPARTUM AND BREASTFEEDING

With the exception of patients who are receiving anticoagulation for recurrent pregnancy loss, all women on anticoagulants during pregnancy should be restarted on the treatment post delivery.

- *Therapeutic dosing:* For acute VTE within 3 months of active treatment or women with high risk of thromboembolism, the recommended drug is UFH/LMWH in therapeutic dose to be started immediately postpartum. Alternatively overlap of UFH/LMWH with warfarin for 5 days or till the desired anticoagulation is achieved, followed by continuation of only warfarin. UFH or LMWH can be started after 4–6 hours of vaginal delivery or 6–12 hours after caesarean delivery. The decision of when to start depends on the clinical scenario, risk of VTE and the clinician judgement.
- *Prophylactic dose:* In women who were taking prophylactic dose during antenatal period or in women who were not on anticoagulants before but need anticoagulation postpartum, the urgency of starting anticoagulation is less. UFH/LMWH can be started 6–12 hours and 12–24 hours post-vaginal delivery and caesarean delivery, respectively.

Duration of anticoagulation depends upon the indication of why the anticoagulant was started at the first place and the risk of VTE in future. When given for obstetric indication, the anticoagulants can stop 6 weeks postpartum. As a general rule, women who were on anticoagulants prior to pregnancy will have to continue the same for a prolong period in consultation with the hematologist, refer to **Table 1.3**.

As per the 2018 American Society of Hematologist Guidelines, in addition to UFH and LMWH, warfarin or vitamin K antagonist, danaparoid and fondaparinux are also safe in breastfeeding.

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