THROMBOEMBOLISM IN OBSTETRIC AND GYNECOLOGY PRACTICE

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Thromboembolism in Obstetric Practice

- Pregnant women have a four fold to five fold increased risk of thromboembolism compared with non-pregnant women.
- Prevalence – 0.5 to 2 per 1000 pregnant women
- Venous thromboembolism including pulmonary embolism accounts for 1. 1 deaths 100000 maternal deaths
- One of the main cause of maternal mortality

Venous Thrombo-embolism (VTE)

- 75% -80% of pregnancy associated venous thrombo-embolism are caused by DVT.
- 20% -25% - Pulmonary embolism
- 50% during pregnancy, 50% during puerperium
- Risk is higher in third trimester compared to second and first trimester
- Risk of VTE is higher during puerperium than it is during pregnancy especially during the first week.

Physiological and Anatomical changes of pregnancy

- Hypercoagulability
- Increased venous stasis
- Decreased venous outflow
- Compression of IVC and pelvic veins by pregnant uterus

Changes in the coagulation system during pregnancy

Procoagulants

- Increased fibrinogen
- Increased factor VII
- Increased factor VIII
- Increased factor X
- Increased Von Willebrand factor
- Increased plasminogen activator inhibitor -1
- Increased plasminogen activator inhibitor-2

ANTICOAGULANTS

- Free protein S - decreased

RISK FACTORS FOR VTE IN PREGNANCY AND PUERPERIUM

Preexisting Thrombophilia

- **Heritable Thrombophilia**
  - Anti thrombin deficiency
  - Protein C deficiency
  - Protein S deficiency
  - Factor V Leiden mutation
  - Prothrombin gene mutation

PRE-EXISTING

- **Acquired Thrombophilia**
  - Antiphospholipid antibodies
  - Persistent lupus anticoagulant and /or
  - Persistent moderate/high titre anticardiolipin antibodies and/or beta 2 glycoprotein 1 antibodies

Medical comorbidities

- Cancer, heart failure, active SLE
- Inflammatory polyarthropathy
- nephrotic syndrome,
- type 1 diabetes mellitus with nephropathy
- sickle cell disease
- current IV drug user

Pre-existing

- Age > 35 years
- Obesity (BMI≥30 kg/m2) either pre pregnancy or in early pregnancy
- Parity ≥3
- Smoking
- Gross varicose veins (symptomatic or above knee or with associated phlebitis, oedema, skin changes)
- Paraplegia

Obstetric risk factors

- Multiple pregnancy
- Current pre-eclampsia
- Caesarean section
- Prolonged labour (>24 hours)
- Mid-cavity or rotational operative delivery
- Stillbirth
- Preterm birth
- Postpartum haemorrhage (>1 L requiring transfusion)

New onset/transient

- Any surgical procedure
- Hyperemesis, dehydration
- Ovarian hyperstimulation syndrome
- Immobility (≥3 days bed rest)
- Current systemic infections
- Long-standing travel (>4 hours)

ANTICOAGULATION THERAPY DURING PREGNANCY

INDICATIONS

- Acute VTE during pregnancy
- Women with history of thrombosis
- Women who are increased risk of VTE during pregnancy or puerperium

Routine anticoagulation therapy for all pregnant mother is not warranted.

Prevention

Risk assessment

- Prepregnancy and antenatal risk assessment for all women in early pregnancy or pregnancy
- This should be repeated if she is admitted or develops other intercurrent problems.
- Repeated again intrapartum or immediate postpartum
- All women with **four or more current risk factors** (other than previous VTE or thrombophilia) should be considered for prophylactic low-molecular-weight heparin(LMWH) through antenatal period and will usually require prophylactic LMWH for 6 weeks postnatally with postnatal risk assessment.

Risk assessment (Cont:)

- All women with **three current risk factors** (other than previous VTE or thrombophilia) should be considered for prophylactic LMWH from 28 weeks and will usually require prophylactic LMWH for 6 weeks postnatally with postnatal risk assessment.

- All women with **two current risk factors** (other than previous VTE or thrombophilia) should be considered for prophylactic LMWH for at least 10 days postpartum.

- Pregnant women admitted to hospital without specific contraindications (labour or active bleeding) should usually be offered thromboprophylaxis with LMWH.

Previous VTE

Single previous VTE

- Should be offered prepregnancy counselling and prospective management plan in pregnancy.
- Should be referred at the earliest opportunity in prepregnancy to an expert clinician.
- Should be offered thromboprophylaxis with LMWH throughout antenatal period.
- Should have a careful history documented.

Thrombophilia-associated VTE

Heritable Thrombophilia

- Should be offered prophylactic high dose LMWH antenatally and for 6 weeks postpartum or until returned to oral anticoagulant therapy.
- Should take collaboration with expert haematologist for antenatal anti-Xa monitoring and potential antithrombin replacement at initiation of labour or prior to caesarean section.
- If anti-Xa levels are measured, 4-hour peak levels of 0.05-1.0 iu/ml aimed for.
- Other heritable thrombophilic defects with lower risk should be managed with standard doses of thromboprophylaxis.

Acquired thrombophilia

- VTE with antiphospholipid syndrome should be managed with thromboprophylatic higher dose LMWH antenatally and 6 weeks postpartum or until returned to oral anticoagulant therapy.

- Should take collaboration with expert haematologist and/or rheumatologist.

Previous recurrent VTE

- Advice from an expert clinician for doses of LMWH in pregnancy.
- Require higher dosed of LMWH.
- Those on long-term anticoagulants should be offered about risks to the fetus and advice to stop and change to LMWH as soon as pregnancy is confirmed.
- Those without long-term anticoagulants should be advised to start LMWH as soon as having a positive pregnancy test.

Thromboprophylaxis during labour and delivery, the use of regional analgesia

- Women receiving antenatal LMWH with active vaginal bleeding or established labour should not inject any further LMWH throughout reassessment on admission.
- Regional analgesia should be avoided until at least **12 hours** after previous prophylactic dose of LMWH.
- Regional analgesia should be avoided until at least **24 hours** after previous therapeutic dose of LMWH
- LMWH should not be given for **4 hours** after spinal anaesthesia or removal of epidural catheter.
- Women receiving antenatal LMWH with elective caesarean section should receive a prophylactic dose of LMWH on the day prior to delivery and omitting of morning dose on the day of the operation.

- Without postpartum haemorrhage and use of regional anaesthesia, the first prophylactic dose of LMWH should be given as soon as possible after delivery.
- Those with high risk of haemorrhage with risk factors (major antepartum haemorrhage, coagulopathy, progressive wound haematoma, suspected intra-abdominal bleeding, postpartum haemorrhage) may be offered anti-embolism stocking (AES), foot impulse devices or intermittent pneumatic compression devices. Unfractionated heparin may also be considered.
- If women on LMWH therapy develop haemorrhagic problems, the treatment should be stopped and get expert haematologist advice.
- Thromboprophylaxis should be started as soon as the immediate risk of haemorrhage is reduced.

Thromboprophylaxis after delivery

- Women with class 3 obesity (BMI ≥40) or two or more persisting risk factors should be considered for prophylactic LMWH for their weight for 10 days after delivery.

Previous VTE

- Those with previous confirmed VTE should be offered prophylactic LMWH or warfarin for at least 6 weeks postpartum regardless of mode of delivery.

Asymptomatic thrombophilia

- Those with a family history of VTE and identified thrombophilia should be considered for 6 weeks postnatal thromboprophylaxis.

Caesarean section

- All women having additional risk factors and caesarean section should be considered for prophylactic LMWH for 10 days after delivery.
- Women should be offered risk assessment at least once after delivery, before discharge and arrangements for LMWH prescription and administration in the community where necessary.
- Thromboprophylaxis should be continued for 6 weeks in high-risk women and for 10 days in intermediate-risk women.
- Women with additional persistent risk factors (prolonged admission, wound infection or surgery in puerperium) should be offered thromboprophylaxis up to 6 weeks or until additional risk factors are no longer present.

Thromboprophylatic agents

- Low-molecular-weight-heparin
- The agents of choice for antenatal and postnatal thromboprophylaxis.
- Doses are based on weight.
- If only history of exposure to unfractionated heparin, platelet count is necessary to be monitored.
- If LMWH is used, monitoring of anti-Xa levels is not required.
- Doses of LMWH should be reduced in those with renal impairment.
- LMWH is safe in breastfeeding.

Unfractionated heparin

- In women with very high risk of thrombosis and risk of hemorrhage or use of regional analgesia, unfractionated heparin may be used peripartum in preference to LMWH.

- If used in caesarean section, platelet count should be monitored every 2-3 days from day 4-14 or until heparin is stopped.

Danaparoid

- Potential use in conjunction with consultant haematologist with expert in haemostasis and pregnancy.

Fondaparinux

- Should be reserved for women intolerant of heparin compounds.
- Use in pregnancy should be in conjunction with consultant haematologist with expert in haemostasis and pregnancy.

Low-dose aspirin

- Is not recommended for thromboprophylaxis in obstetric patients.

Warfarin

- Warfarin use in pregnancy is restricted to the few situations when heparin is considered unsuitable.
- Women receiving long-term anticoagulant with warfarin can be converted from LMWH to heparin postpartum when the risk of haemorrhage is reduced, usually 5-7 days after delivery.
- Warfarin is safe in breastfeeding.

Dextran

- Should be avoided antenatally and intrapartum due to risk of anaphylactic reaction.

Oral thrombin and Xa inhibitors

- Non-vitamin K antagonist oral anticoagulant (NOACs) should be avoided in pregnant women.
- Its use is not currently recommended in women who are breastfeeding.

Anti-embolic stockings

- Appropriate size and graduated compression with a calf pressure of 14-15 mmHg is recommended in pregnancy and the puerperium for women who are hospitalized and have a contraindication to LMWH.

Contraindications to LMWH

- Higher risk of bleeding
- Previous or current allergic reactions

Suggested thromboprophylactic doses for antenatal and postnatal LMWH

weight	Enoxaprin	Dalteprin
<50 kg	20 mg daily	2500 units daily
50- 90 kg	40 mg daily	5000 units daily
91-130 kg	60mg daily	7500 units daily
131-170 kg	80 mg daily	10000 units daily
>170 kg	0.6 mg/kg/day	75u/kg/day

Diagnosis of DVT during pregnancy

CLINICAL FEATURES

- Pain and swelling of extremity
- A difference in calf circumference of 2 cm or more is suggestive of DVT in lower extremity

INVESTIGATIONS

- compression duplex ultrasonography of the proximal veins
- MRI- when results are equivocal and iliac vein thrombosis is suspected.
- D-dimer level- high D-dimer level does not predict VTE in pregnancy. D-dimer testing should not be performed in the investigation of acute VTE during pregnancy

Before start of anticoagulation therapy

- FBC
- Coagulation screen
- Urea and electrolytes
- LFT

Thrombophilia screen prior to therapy is not recommended.

TREATMENT OF VTE IN PREGNANCY

Initial treatment

In clinically suspected VTE, low molecular weight heparin should be commenced immediately until the diagnosis is excluded by objective testing unless treatment is strongly contraindicated.

Dose

Dose is titrated against women's booking or early pregnancy weight

Monitoring

Routine platelet count monitoring is not recommended. Routine measurement of anti-Xa activities is not recommended except in women of extreme body weight (less than 50 kg and 90 kg or more, recurrent VTE, renal impairment)

- Obstetric patients who are postoperative and receiving unfractionated heparin should have

  Platelet count monitoring performed every 2 to 3 days from day 4 to 14 until heparin is stopped.

INITIAL DOSE OF ENOXAPRIN

Booking or early pregnancy weight	Initial dose of enoxaprin
<50 kg	40 mg twice daily or 60 mg once daily
50-69 kg	60 mg twice daily or 90 mg once daily
70-89kg	80 mg twice daily or 120 mg once daily
90-109 kg	100 mg twice daily or 150 mg once daily
110-125 kg	120 mg twice daily or 180 mg once daily
>125 kg	Discuss with hematologist

INITIAL DOSE OF DALTEPRIN

Booking or early pregnancy weight	Initial dose of enoxaprin
<50 kg	5000 iu twice daily or 10000 iu once daily
50-69 kg	6000 iu twice daily or 12000 iu once daily
70-89kg	8000 iu twice daily or 16000 iu once daily
90-109 kg	10000 iu twice daily or 20000 iu once daily
110-125 kg	12000 iu twice daily or 24000 iu once daily
>125 kg	Discuss with hematologist

ADDITIONAL THERAPY

- In the initial management of DVT, the leg should be elevated and a graduated elastic compression elastic stocking applied to reduce odema.

- IVC filters can be considered in patients with iliac vein VTE to reduce risk of PE or in patients with proven DVT and who have recurrent PE despite adequate anticoagulation

MAINTENANCE TREATMENT OF VTE DVT /PE

- Treatment with therapeutic doses of subcutaneous LMWH should be employed during the remainder of pregnancy and at least 6 weeks postpartum and at least 3 months of treatment has been given in total.
- Self injection
- Outpatient follow up should include clinical assessment and advice with monitoring of blood platelets and peak anti-Xa levels if appropriate.
- Pregnant women who develop heparin induced thrombocytopenia or have heparin allergy should be managed with an alternative anticoagulant under specialist advice

Newer anticoagulants

- fondaparinux
- argatroban
- r-hirudin

Vitamin K antagonist (such as warfarin) should not be used antenatally because of adverse effects on fetus

ANTICOAGULANT THERAPY DURING DELIVERY

- When VTE occurs at term, consider use of IV unfractionted heparin which is more easily manipulated.
- Women on LMWH for maintenance therapy should be advised that once she is in established labor or thinks she is in labour,not to inject further heparin.
- Where delivery is planned either by elective caesarean section or IOL, LMWH maintenance therapy should be stopped 24 hours prior to delivery
- Regional anaesthetic or analgesic techniques should not be undertaken until at least 24 hours after the last dose of therapeutic LMWH.

- LMWH should not be given for 4 hours after the use of spinal anaesthetics or after the epidural catheter has been removed
- Epidural catheter should not be removed within 12 hours of the most recent injection.

SPECIFIC SURGICAL MEASURES

- In patients receiving therapeutic doses of LMWH, wound drains (abdominal and rectus sheath) should be considered at caesarean section and skin incision should be closed with interrupted sutures to allow drainage of haemtoma.

- Any women who is considered to be at high risk of haemorrhage and in whom continued heparin treatment is considered essential, shouid be managed with IV unfractionated heparin until the risk factor for hemorrhage have resolved.

POSTNATAL ANTICOAGULATION

- Therapeutic anticoagulant therapy should be continued for the duration of pregnancy and at least 6 weeks postpartum and at least 3 months of treatment has been given in total.
- Before discontinuing the treatment assess the continuing risk of thrombosis
- Women should be offered a choice of LMWH or oral anticoagulants after discussion about the need for regular blood tests for monitoring warfarin particularly during the first 10 days of treatment.
- Postpartum warfarin should be avoided until at least the fifth day and for longer in women at increased risk of PPH
- Heparin or warfarin is not contraindicated in breastfeeding

PREVENTION OF POST THROMBOTIC SYNDROME

- Wearing of graduated elastic compression stockings on the affected leg to reduce pain and swelling

POSTNATAL FOLLOW-UP

- At the obstetric medicine clinic
- Joint care
- Thrombophilia testing should be performed once anticoagulant therapy has been discontinued.

Clinical Features of PE

Classical Presentation

- Abrupt onset of pleuritic chest pain
- Shortness of breath
- Hypoxia (Decreased oxygen saturation)
- Haemoptysis (less frequest)

- **Non-specific symptoms**
  - Back pain, shoulder pain, high fever, productive cough, hiccoughs and wheezing.

- May present with shock,refractory hypoxaemia

PULMONARY EMBOLISM

- Echocardiogram
- ECG
- CXR
- Ventilation-perfusion scanning
- CT angiography
- Both are asssociated with relatively low radiation exposure for fetus
- CT angiography- associated with maternal breast radiation exposure
- V/Q Scan is associated with slightly increased risk of childhood cancer.

Management of massive life threatening PE in pregnancy and puerperium

- Managed by team of experienced clinicians, multidisciplinary team including physician, surgeon, obstetrician, radiologist
- Managed on an individual basis regarding: IV unfractionated heparin, thrombolytic therapy or thoracotomy and surgical embolectomy.
- IV unfractionated heparin is treatment is preferred initial treatment in massive PE with cardiovascular compromise.
- Urgent Echogram or CTPA within 2 hour of presentation
- Immediate thrombolysis in some extreme cases

Management of massive life threatening PE in pregnancy and puerperium

- Loading dose of 80 units /kg of unfractionated heparin followed by a continuous IV infusion of 18 units/kg/hour
- If patient has received thrombolysis the loading dose should be omitted and infusion started at 18 units/kg/hour
- To measure APTT level 4-6 hours after the loading dose

  6 hours after any dose change,at least daily when in the therapeutic range

Therapeutic target APTT ratio is 1.5 -2.5 times the average laboratory control value

Management of massive life threatening PE in pregnancy and puerperium

APTT ratio	Dose change (units/kg/hr)	Additional action	Next APTT(hour)
< 1.2	+ 4	Re bolus 80 units /kg	6
1.2-1.5	+2	Re bolus 40 units /kg	6
1.5-2.5	No change		24
2.5-3	-2		6
>3	-3	Stop infusion 1 hour	6

VTE IN GYNECOLOGICAL PRACTICE

- The incidence of DVT in Gynecological surgery with no prophylasix is 16% and incidence of pulmonary embolism is 1%.
- VTE usually occurs 1-2 weeks following surgery.
- DVT may be asymptomatic and may lead to PE and sudden death or long term morbidity secondary to venous insufficiency or post-thrombotic syndrome

PREVENTION OF VTE

- In order to minimize the risk of VTE in patients undergoing surgery each patient should be assessed carefully for individual risk factors.
- In the absence of thromboprophylasix, patients undergoing major(>30 min) general and gynaecological surgery have a significant risk of both asymptomatic (approximately 30%) and symptomatic (approximately 8%) venous thromboembolism.

GYNECOLOGY

Patient related risk factors for VTE

- Age > 60 years
- Obesity (BMI >30 kg/m2)
- Personal or family history of VTE
- Oral contraceptive pills or HRT
- Varicose veins with associated phlebitis
- Thrombophilia including factor V leiden, prothrombin mutation, deficiencies of protein C and protein S and antithrombin
- Antiphospholipid syndrome
- Severe infection
- Acute medical illness

- Active cancer or cancer treatment
- Active heart or respiratory failure
- Continuous travel more than 3 h approximately 4 weeks before or after surgery
- Immobility
- Inflammatory bowel disease
- Nephrotic syndrome
- Recent myocardial infarction or stroke

PREVENTION OF DVT

- Patients on COC who are undergoing surgery with subsequent immobilization should stop COC 4 weeks prior to operation
- Ample hydration
- Early ambulation
- Leg exercise by physiotherapy
- Mechanical prophylaxis in all patients with no risk factors for VTE
- Pharmacological prophylaxis –for those with risk factor for VTE

MECHANICAL PROPHYLAXIS

- Compression stockings
- Intermittent pneumatic compression
- Electrical stimulation
- Foot impulse devices
- Thigh-length graduated compression stocking, knee –length graduated compression stocking

PHARMACOLOGICAL PROPHYLAXIS

Low-Molecular-Weight-Heparin (LMWH)

- The main advantage is its reduced binding to plasma proteins and cells resulting in a more predictable dose-response relationship , a longer plasma half life and a lower risk of throbombocytopenia and osteopenia compared with unfractionated heparin.
- Both decrease the risk of VTE and increase the risk of bleeding

Fondaprinux (alternative)

- Synthetic pentasaccharide .It is administered subcutaneously once daily. It is more effective than LMWH at reducing the risk of DVT, but has not been shown to reduce the risk of PE but associated with larger bleeds.

Diagnosis of DVT

- High suspicious of DVT following major surgery especially high risk patients.
- Calf is the most common site and manifests with swelling, erythema and pain.
- Examination shows low grade pyrexia with a swollen. Tender and warm calf.
- Patients with these manifestations should be treated as having DVT until proved otherwise.
- Can be diagnosed by Doppler ultrasound on leg veins.
- Intravenous venography may be necessary, but risk of embolism.

Diagnosis of Pulmonary Embolism

Classical Presentation

- Abrupt onset of pleuritic chest pain
- Shortness of breath
- Hypoxia
- Haemoptysis (less frequest)

Non-specific symptoms

- Back pain, shoulder pain, high fever, productive cough, hiccoughs and wheezing.

Screening for Pulmonary Embolism

D-dimer

- If the test is positive/or if there is a high probability of PE, diagnostic imaging should be carried out.

ECG

- Tachycardia, non-specific ST-T wave changes, S1Q3T3 changes, peaked P waves, right axis deviation, atrial fibrillation
- (only present in 20% of cases of PE)

Chest X-ray

- To exclude other causes

Definitive diagnosis of PE

Contast Pulmonary Angiography

- Invasive,

Spiral CT scan

- Preferred primary diagnostic test

Ventilation/Perfusion Scan

Treatment of Venous Thromboembolism

- Immediate treatment with Low-molecular-weight heparin(LMWH) or Unfractionated heparin(UFH) in therapeutic doses.

LMWHs

- Preferred initial treatment of choice.
- More effective than UFH
- Lower mortality
- Fewer haemorrhagic complications
- As effective as UFH
- Fixed-dose regimen reducing need for monitoring
- Lower risk of heparin-induced thrombocytopenia, osteoporosis and bone fractures than UFH.

Unfractionated Heparin

- Intravenous UFH remains the preferred treatment in massive PF due to its rapid effect and extensive experience.

LMWH should be converted to oral anticoagulants once patient is in the stable postoperative period and the risk of bleeding has reduced.

- Life-threatening massive PE requires an immediate multidiscipline approach involving a senior anaesthetist, haematologist, physician, gynaecologist and need intensive care.

- Cardiopulmonary resuscitation, thrombolytic therapy, percutaneous catheter thrombus fragmentation or surgical embolectomy may be needed in some cases.

THANK YOU