SHARED CARE GUIDELINE

ENOXAPARIN
Treatment and prophylaxis of venous thromboembolism in obstetric patients

INTRODUCTION – Indication and Licensing

Venous thromboembolism (VTE) remains the major cause of direct maternal deaths (0.85 per 100,000 maternities) [1].VTE can occur at any stage of pregnancy, during delivery and in the postnatal period. NICE estimates that low-molecular weight heparin (LMWH) reduces VTE risk in medical and surgical patients by 60% and 70% respectively, therefore it is reasonable to presume LMWH may reduce the risk of VTE in pregnancy and the puerperium.
Enoxaparin (agent of choice at the Homerton), a LMWH, is licensed in the treatment and prevention of deep vein thrombosis (DVT) as it is effective and is less likely to induce heparin induced thrombocytopenia. LMWH is not known to be harmful and does not cross to the placenta. It is not licensed for use in the pregnant population however it is routinely used globally to prevent and treat VTE. Until recently, Clexane® was the only enoxaparin product on the market. Inhixa®, an enoxaparin biosimilar was launched in September 2017, so there are now two enoxaparin products. Prescribing must therefore be **brand specific**.

This Shared Care Guideline (SCG) is written for all health care professionals looking after obstetric patients that are involved in the prescribing, dispensing or administration of LMWH. This SCG aims to provide sufficient information to ensure the LMWH is used in the obstetric population safely and appropriately in primary care under shared care arrangements.

Although a formal VTE risk assessment is completed by the midwife at the booking appointment, where appropriate, the GP may initiate enoxaparin and refer the patient to a consultant lead antenatal clinic.

Below are the **high risk indications** where it may be appropriate for the **GP to initiate enoxaparin** (at their discretion) prior to midwife booking appointment. Liaison with Haematology Registrar (bleep 254), Obstetric Registrar (bleep 004/005) or Obstetric Consultant (bleep 181) is recommended in these circumstances. **If the GP does not feel that they are able to initiate the enoxaparin in primary care, then the GP should refer the patient urgently to the obstetrician-led antenatal clinic if patient is less than 20 weeks pregnant. This can be arranged by emailing the obstetric query email huh-tr.obstetricquery@nhs.net**

- Previous VTE
- Use of oral anticoagulation
- Antithrombin deficiency
- Enoxaparin in a previous pregnancy
- Protein C deficiency
- Protein S deficiency

A risk assessment should be done based on the RCOG guideline [2]. All antenatal women at high risk of VTE (risk score ≥ 3) will be reviewed in antenatal clinic by an obstetrician and considered for prophylaxis. This can commence either in the first trimester (if the patients risk score ≥ 4) or from 28 weeks gestation (risk score 3).

All pregnant women will be risk assessed in the antenatal period according to the approved risk assessment tool below. The risk scoring sheet is in Appendix 1:

Antenatal assessment and management (to be assessed at booking and repeated if admitted)

Any previous VTE except a single event related to major surgery

→ **HIGH RISK**

Requires antenatal prophylaxis with LMWH

Refer to trust-nominated thrombosis in pregnancy expert/team

Obstetric Consultant bleep 141
Obstetric Registrar bleep 004/005
Haematology Registrar bleep 254

Hospital admission

Single previous VTE related to major surgery

High-risk thrombophilia + no VTE

Medical comorbidities e.g. cancer, heart failure, active SLE, IBD or inflammatory polyarthropathy, nephrotic syndrome, type I DM with nephropathy, sickle cell disease, current IVDU

Any surgical procedure e.g. appendicectomy

OHSS (first trimester only)

→ **INTERMEDIATE RISK**

Consider antenatal prophylaxis with LMWH

Obesity (BMI > 30 kg/m^2)

Age > 35

Parity ≥ 3

Smoker

Gross varicose veins

Current pre-eclampsia

Immobility, e.g. paraplegia, PGP

Family history of unprovoked or estrogen-provoked VTE in first-degree relative

Low-risk thrombophilia

Multiple pregnancy

IVF/ART

→ **Four or more risk factors: prophylaxis from first trimester**

Three risk factors: prophylaxis from 28 weeks

Fewer than three risk factors

Transient risk factors:
Dehydration/hyperemesis; current systemic infection; long-distance travel

→ **LOWER RISK**

Mobilisation and avoidance of dehydration

APL – antiphospholipid antibodies (lupus anticoagulant, anticardiolipin antibodies, β_2-glycoprotein 1 antibodies); ART – assisted reproductive technology; BMI based on booking weight; DM – diabetes mellitus; FHx – family history; gross varicose veins – symptomatic, above knee or associated with phlebitis/oedema/skin changes; high-risk thrombophilia – antithrombin deficiency, protein C or S deficiency, compound or homozygous for low-risk thrombophilias; IBD – inflammatory bowel disease; immobility – ≥ 3 days; IVDU – intravenous drug user; IVF – in vitro fertilisation; LMWH – low-molecular-weight heparin; long-distance travel – > 4 hours; low-risk thrombophilia – heterozygous for factor V Leiden or prothrombin G20210A mutations; OHSS – ovarian hyperstimulation syndrome; PGP – pelvic girdle pain with reduced mobility; PPH – postpartum haemorrhage; thrombophilia – inherited or acquired; VTE – venous thromboembolism.

RESPONSIBILITY FOR PRESCRIBING

Duration of treatment	Initial supply to be made by	Subsequent supply to be made by
Antenatal – up to 20 days	Hospital to supply the full course	Not applicable
Antenatal – more than 20 days	Hospital to supply initial 20 days	GP to continue prescribing
Postpartum - up to 6 weeks	Hospital to supply the full course	Not applicable
Postpartum - more than 6 weeks	Hospital to supply initial 20 days	GP to continue prescribing

A letter will be sent to the individual GP detailing the indication for LMWH, the dose, schedule and duration.

TRAINING AND ADMINISTRATION

The hospital team will provide training on the administration of injections. If the patient is unable to self-administer then the patient would be referred to the community district nurse team to administer the injections. Where GP initiates enoxaparin, training **must** be provided by the surgery.

PROPHYLAXIS PRESCRIBING GUIDELINE

If a woman is deemed high risk prior to booking her pregnancy with the midwife and needs LMWH from the first trimester, this should be initiated in primary care at the GP's discretion where possible. If the GP does not feel that they are able to initiate the enoxaparin in primary care, then the GP should refer the patient **urgently** to the obstetrician-led antenatal clinic if patient is less than 20 weeks pregnant. This can be arranged by emailing the **obstetric query** email huh-tr.obstetricquery@nhs.net

According the RCOG Green Top Guideline No. 37a, the recommended dosage for prophylaxis on most recent weight is:

Body weight in Kg at time pregnancy confirmed	Dose of Enoxaparin	Prescription Initiated by	Prescription Continued by	*Monitored by	Duration
< 50	20mg daily	Haematologist/ Obstetricians/GP in exceptional cases	GP	Haematologist/ Obstetricians	Until onset of labour
50 - 90	40mg daily				
91 – 130	60mg daily*				
131 – 170	80mg daily*				
> 170	0.6mg/kg daily*				
High risk (intermediate) dose 50- 90 kg	40mg BD	Haematologist/ Obstetricians/GP in exceptional cases	GP	Haematologist/ Obstetricians	Until onset of labour

*May be given in 2 divided doses (2)

The doses in the table above are only suggestions and doses for obese women are not evidence-based. Occasionally women at **very high risk** (especially those usually on long-term oral anticoagulant due to previous recurrent VTE) or those with a very high BMI may warrant a higher prophylactic (intermediate) dose of LMWH. Liaison with Haematology Registrar (bleep 254), Obstetric Registrar (bleep 004/005) or Obstetric Consultant (bleep 181) is recommended in these circumstances. There is no guidance on the maximum dosage for an individual. Warfarin has significant teratogenic potential, crosses the placenta and is therefore reserved for very limited circumstances in the antenatal period – principally for women with mechanical prosthetic heart valves.

TREATMENT PRESCRIBING GUIDELINE: DVT/PE diagnosed in pregnancy or postpartum

Women with confirmed diagnosis of DVT or PE will be referred immediately by the obstetrician to the medical registrar and on-call haematologist. LMWH is indicated for either 6 weeks postpartum or 6 months- whatever time period gives the longest thromboprophylaxis. For postpartum patients, LMWH will commence in hospital with a 6 weeks supply from hospital and continued by the GP if the duration exceeds 6 weeks. The RCOG Green Top Guideline 37b recommends the following dose:

Dose (using actual body weight)	**Prescription Initiated by**	**Prescription Continued by**	***Monitored by**	**Duration**
Enoxaparin 1mg/kg twice daily subcutaneously	Obstetrician Discharge letter sent to GP including dose, schedule and treatment duration	GP	Haematologist	Until 6 weeks post-partum or 6 months whichever is longer

* Blood test monitoring if necessary as decided by haematologist

CONTRAINDICATIONS WITH LMWH

- Bleeding during the antenatal period
- Coagulopathy (e.g. von Willebrand's disease, haemophilia)
- Severe liver/renal disease
- Thrombocytopenia (platelet count <75 x 10^9)
- Recent CVA
- Allergy to LMWH
- Previous heparin induced thrombocytopenia

Please consult the haematology and/or obstetric team prior to initiating/continuing to prescribe LMWH in any of these circumstances

KEY ADVERSE EFFECTS & ACTIONS

Adverse effects	**Symptoms/signs** *(specify what would prompt action)*	**Actions (***what action should the GP take if identified in primary care)*
Local irritation	Occasionally skin irritation at site on injection occurs	If severe seek advice from haematologist
Haemorrhage	Bleeding	Following clinical assessment, refer to A&E if appropriate and/or stop treatment. Seek advice from haematologist
Heparin induced thrombocytopenia (HIT)	Low platelet count on FBC Bruising Bleeding gums	Refer to Emergency Obstetric Unit (EOU) if antenatal or A+E if postnatal

This only lists the key important ADRs-For comprehensive information on cautions, contra-indications and interactions please refer to the current British National Formulary and Summary of Product Characteristics.

THROMBOPROPHYLAXIS IN THE POSTPARTUM PERIOD

All women who are discharged from hospital with LMWH will have the indication, dose, schedule and duration stated on their discharge summary.

The hospital will initiate treatment and GP's will only need to continue the prescription if more than 6 weeks of LMWH is required. Details of the remaining duration of LMWH will be stated in the discharge summary. In the vast majority of cases, the LMWH course will be for 6 weeks postnatally.

Examples are:

- All women with previous VTE
- All women who received LMWH in the antenatal period
- High risk thrombophilia (antithrombin III, Protein S, Protein C Deficiency)
- Low risk thrombophilia (Factor V Leiden, Prothrombin gene mutation) and a family history of VTE
- Additional risk factors (e.g. wound infection, prolonged admission, further surgery) thromboprophylaxis should be extended to 6 weeks

PREGNANCY AND BREASFEEDING

Enoxaparin is considered safe to be used during pregnancy and breast feeding. Enoxaparin does **not** cross the placenta and has been used during all trimesters of pregnancy when clinically needed.

COST (BNF Online July 2018 edition)

Drug Product	**Cost in primary care for 30 days**	
Enoxaparin/daily dose	**Clexane® brand**	**Inhixa® brand**
20mg	£62.58	£50.07
40mg	£90.81	£72.66
60mg	£117.78	£94.23
80mg	£165.39	£132.3
100mg	£216.90	£173.52
120mg	£263.79	Strength not available

SHARED CARE RESPONSIBILTIES

Obstetricians/Haematologists

1. Ensure that patients understand their treatment regimen and any monitoring or follow up that is required
2. In the majority of cases, initiate treatment and prescribe until the GP formally agrees to share care (as a minimum, supply the first 20 days for antenatal patients and first 6 weeks for postpartum patients)
3. Send a letter to the GP requesting shared care for this patient
4. Evaluation of any reported adverse effects by GP or patient
5. Advise GP on review, duration or discontinuation of treatment where necessary. Where urgent action is required following tests the hospital team will telephone the patient and inform GP
6. Inform GP of patients who do not attend clinic appointments
7. Ensure that backup advice is available at all times

General Practitioner

1. Ensure that the patient understands the nature, effect and potential side effects of the drug before prescribing it as part of the shared care programme and contact the specialist for clarification where appropriate.
2. Report any adverse events to the Doctor where appropriate.
3. Report any adverse events to the MHRA / CHM, where appropriate.
4. Ensure patient is aware of the signs and symptoms of a venous thromboembolic clot and to seek immediate medical attention should they experience this.
5. Prescribe the drug treatment as described.

City and Hackney Medicines Management Team

1. To provide feedback to acute trusts via Joint Prescribing and Medicines Management Group
2. To support GPs to make the decision whether or not to accept clinical responsibility for prescribing.
3. To support acute trusts in resolving issues that may arise as a result of shared care.

Patient/ Carer

1. Report any adverse effects to their GP and/or specialist
2. Ensure they have a clear understanding of their treatment.
3. Alert GP and/or specialist of any changes of circumstance which could affect management of disease e.g. plans for pregnancy
4. Take/ administer the medication as prescribed

RELEVANT CONTACT DETAILS

Doctor via switchboard 0208 510 5555 Registrar on-call out of hours	Maternal Medicine Consultant /Obstetricians Obstetrics bleep 004, Haematology 254
Obstetric query email	huh-tr.obstetricquery@nhs.net
Pharmacy medicines information Pharmacy- out of hours	0208 510 7000 Via switch
Trust Homerton University Hospital NHS Foundation Medicines Information/dispensary	020 8510 7000/7003
City and Hackney Medicines Management Team	020 3816 3224

References

(1) Marian Knight, Manisha Nair, Derek Tuffnell, Sara Kenyon, Judy Shakespeare, Peter Brocklehurst, Jennifer J Kurinczuk (Eds.) Saving Lives, Improving Mothers' Care. Surveillance of maternal deaths in the UK 2012–14 and lessons learned to inform maternity care from the UK and Ireland Confidential Enquiries into Maternal Deaths and Morbidity 2009–14. December 2016.

(2) Thrombosis and Embolism during Pregnancy and the Puerperium Reducing the Risks (Green-Top Guideline No. 37a) 2015.

(3) Joint Formulary Committee. British National Formulary (online) London: BMJ Group and Pharmaceutical Press (http://www.medicinescomplete.com). Date accessed 30/07/2018

With thanks to Barts Health NHS Trust part of UCL Partners for allowing the adoption of the SCG template. NELMMN and Barts Health NHS Trust (updated by JPG February 2015).

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APPENDIX 1[2]

Risk assessment for venous thromboembolism (VTE)

- If total score ≥ 4 antenatally, consider thromboprophylaxis from the first trimester.
- If total score 3 antenatally, consider thromboprophylaxis from 28 weeks.
- If total score ≥ 2 postnatally, consider thromboprophylaxis for at least 10 days.
- If admitted to hospital antenatally consider thromboprophylaxis.
- If prolonged admission (≥ 3 days) or readmission 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.

Risk factors for VTE

Pre-existing risk factors	Tick	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		3
OHSS (first trimester only)		4
Current systemic infection		1
Immobility, dehydration		1
TOTAL		

Abbreviations: ART assisted reproductive technology; IVF in vitro fertilisation; OHSS ovarian hyperstimulation syndrome; VTE venous thromboembolism.

[a] If the known low-risk thrombophilia is in a woman with a family history of VTE in a first-degree relative postpartum thromboprophylaxis should be continued for 6 weeks.

[b] BMI ≥ 30 = 1; BMI ≥ 40 = 2