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Guideline for Thromboprophylaxis and Treatment of Venous Thromboembolism in Obstetrics

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ABSTRACT

Venous Thromboembolism (VTE) is one of the preventable but poorly reported causes of maternal morbidity and mortality in developing countries. Data on the prevalence of VTE in obstetric population in Nigerian is scanty, attributable to low index of clinical suspicion as well as paucity of diagnostic capability. The aim of this guideline is to provide clinical guidance based on the best available evidence in the prevention and treatment of venous thromboembolism in the Nigerian obstetric population. Certain innate and acquired factors have been found to increase the risk of developing VTE. These risk factors have enabled the development of risk assessment tools for prophylaxis. It is recommended that VTE risk assessment should be done for all pregnant women at booking for antenatal care, whenever they are admitted into the hospital and during vaginal delivery, emergency and elective Caesarean section, and also in the pueperium. Thromboprophylaxis is centered on the use of Low Molecular Weight (LMWH) or unfractionated heparin (UFH) based on the identified risk factor(s). It is also important to diagnose pregnant women who develop Deep Venous Thrombosis (DVT)and/or Pulmonary Embolism (PE). LMWH or UFH are recommended for treatment of DVT and/or PE with or without certain non-pharmacological methods. A consensual acceptance and utilization of this guideline is expected to change the narrative of VTE in obstetric population in Nigeria and other developing countries.

Keywords: Venous Thromboembolism; Deep Venous Thrombosis; Pulmonary Embolism, Low Molecular Weight Heparin; Unfractionated Heparin

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Introduction

Venous thromboembolism (VTE) is one of the preventable but poorly reported causes of maternal morbidity and mortality in developing countries. Currently in Nigeria, maternal mortality ratio (MMR) is 512 per 100 000.[1] While haemorrhage, sepsis, obstructed labour, unsafe abortion and anaemia are largely responsible for the high MMR. However, interest is beginning to develop in the contribution of VTE to maternal l morbidity and mortality because there is evidence that it is equally prevalent in blacks, if not more than in the Caucasian populations.[2] Studies in predominantly black populations in the United Kingdom (UK) have shown that more younger blacks present with VTE than whites and they have more proximal events compared to whites.[3,4]

Data on the prevalence of VTE in pregnancy in the Nigerian obstetric population is scanty, attributable to low index of clinical suspicion as well as paucity of diagnostic capability. An incidence of DVT in pregnancy of 448 per 100 000,[5] DVT inpuerperium of 380 per 100,0006 and prevalence of PE of 1.4% in pregnant and postpartum women[5] have been reported in North Africa. In the UK and United States of America (USA), incidence of 1-2 per 1000 maternities and 1 in 500 to 2000 deliveries have been reported respectively.[7,8]

While there is paucity of data in Nigeria on the contribution of VTE to maternal mortality and morbidity, in the UKpulmonary embolism is a leading cause of maternal mortality responsible for 0.70 per 100 000 maternities in 2006-2008.[9,10] and the seventh leading causeof death in the USA accounting for 9% of maternal deaths.[11,12] Data from non-obstetric population in local studies suggest that several deaths occur among Nigerians due to complications of VTE that are not diagnosed ante-mortem.[13,14]

VTE is nondiscriminatory and affects people of all ethnicity, ages, races as well as both sexes. Pregnancy and the pueperium are well established risk factors for VTE[15,16] and this risk increase with gestational age, reaching a maximum just after delivery.[7,17,18] However, the absolute risk of VTE in pregnancy is low and this necessitate some form of risk stratification to determine which women will benefit from pharmacological thromboprophylaxis.[19] The National Institute of Health and Care Excellence (NICE) estimates that low molecular weight heparin (LMWH) reduces VTE risk in medical and surgical patients by 60% and 70% respectively.[10] Therefore, it is reasonably assumed that LMWH will reduce the risk of VTE in obstetric patients.

Certain innate and acquired factors have been found to increase the risk of developing VTE. These risk factors have enabled the development of risk assessment tools for prophylaxis. A report from the North Eastern part of Nigeria between 1996 and 1999 involving 22 cases of diagnosed VTE showed obesity, abdominal and pelvic surgery, advancing age and pueperium as the leading predisposing factors.[20] A study in Senegal on VTE found the predisposing factors to include gender, protein S deficiency, surgery, varicosity, non O ABO blood group and presence of anti-phospholipid antibodies.[21] Other risk factors that have been documented include multiple pregnancy, diabetes, hypertension, pre eclampsia, eclampsia, obstetric haemorrhage, postpartum infection, stillbirth, Caesarean section(particularly emergency), hospitalization, increased maternal age of 35 years or more[22-26] and these risk factors are quite prevalent in the Nigerian obstetric population.

The aim of this guideline is to provide clinical guidance based on the best available evidence in the prevention and treatment of venous thromboembolism in the Nigerian obstetric population. A consensual acceptance and utilization of the guideline by practitioners is expected to change the current narrative of VTE in obstetric population in Nigeria and other developing countries.

Methodology

The authors identified the need for a national, and regional guideline for VTE prophylaxis and management in the obstetric population following their attendance at the "2020 Thrombosis in Women" conference from the 22nd to 23rd February, 2020 at Mount Grace, Magaliesburg, South Africa. At the conference, a meeting was held

with the other delegates from Ghana. The Nigerian delegates (the authors) agreed to prepare a national and possibly regional guideline to change the narrative of VTE in obstetrics in the region. The goal is to provide appropriate clinical guidance for thromboprohylaxis and treatment of VTE in obstetrics based on the best available evidence in consonance with local experiences and practices. Simplicity without loss of context and content was a major objective.

To facilitate our goal, we relied on current publications on the area of interest by the Royal College of Obstetrics and Gynaecology (RCOG).[31,33] American College of Obstetrics and Gynaecology (ACOG), National Institute for Health and Care Excellence (NICE),[10] and NSHBT (Nigerian Society for Hematology and Blood Transfusion).[33] Further literature search for recent relevant publications were done using PubMed, Cochrane Library, BioMed Central, Science Direct, and Google Scholar.

The authors were paired to prepare aspects of the guideline with coordination by JT, ABA and OA. Compilation and integration of the submissions to ensure appropriate content and context was done by the coordinators (JT, ABA and OA). Several virtual meetings were held by the authors and their colleagues at Ghana to agree on suitability of the guideline. Some experts in the field, practicing in the local setting kindly obliged their inputs to the guideline.

The final agreed guideline was presented for publicationto ensure wider circulation, peer review, and suggestions for possible improvement.

Pathophysiology of Venous Thromboembolism in Pregnancy

Normal haemostasisis characterized by a balance between procoagulants and anticoagulants. An alteration in this balance could lead to either thrombosis or haemorrhage depending on whether pro or anti-coagulantspredominate.

During normal pregnancy, levels of coagulation factors II, VII, VIII, and X are increased, there is also a progressive fall in Protein S levels as well as an acquired resistance to activated Protein Cwhich leads to an increase in fibrin generation.[27] In addition, there is a decrease in antithrombin and an increase in plasminogen activator inhibitor I and 2 (PAI-1 and PAI-2).[28]

These physiological changes cause disequilibrium between the procoagulants and anticoagulants leading to a hypercoagulable and hypofibrinolytic state that help to protect the mother from haemorrhagic complications at the time of delivery. All of these changes reflect the physiological preparation for the hemostatic challenge of delivery.

The hemostatic activation that occurs in pregnancy is demonstrated by increased markers of hemostatic activation, such as prothrombin fragment F1+2, thrombin antithrombin complex and D-dimer.

All the three components of the Virchow's triad (hypercoagulability, venous stasis and vascular endothelial injury) are affected in pregnancy as shown in Figure 1.

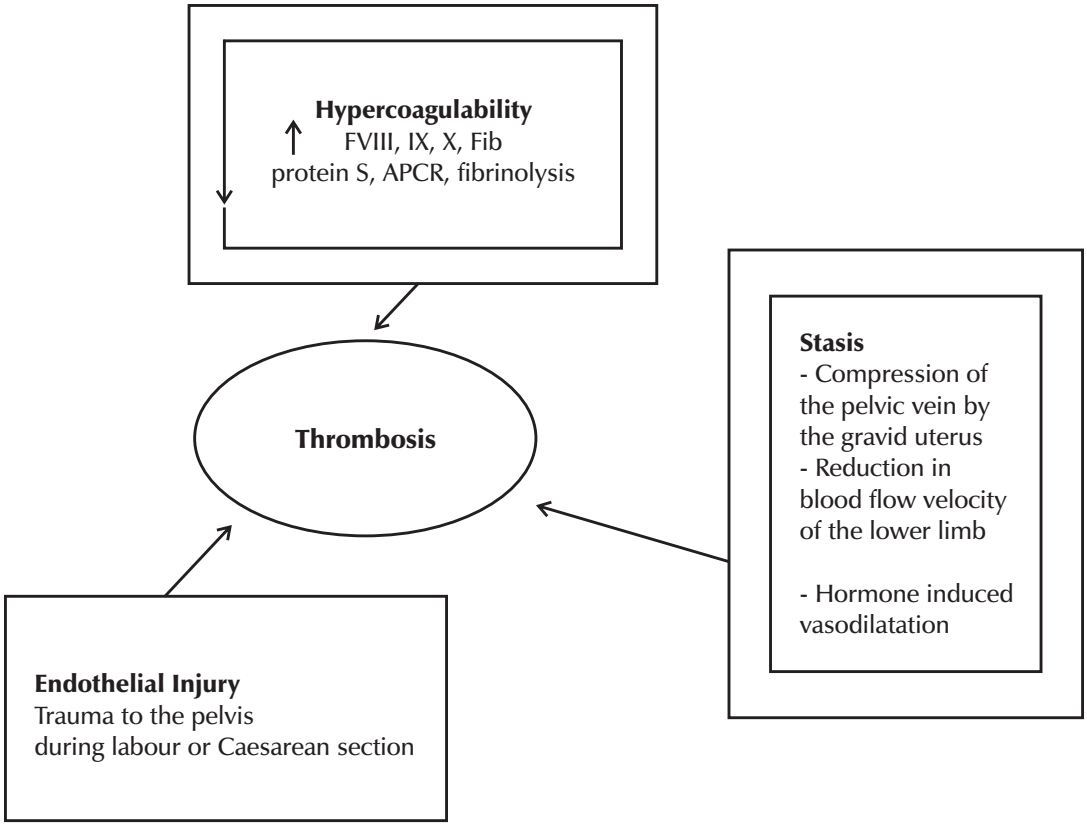


Figure 1: Virchow's triad in pregnancy

Venous stasis results from a hormone induced vasodilatationand decrease in venous tone as well as compression of the pelvic veins by the enlarging uterus. A reduction of venous flow velocity by approximately 50% occurs in the legs by weeks 25 - 29 of gestation which lasts until approximately 6 weeks postpartum.[29] Among pregnant and post-partum women, the left lower extremity is the most common site of DVT (82%), possibly due to compression of the left common iliac vein by the right common iliac artery which is accentuated by the enlarging uterus (May-Turner syndrome). Stasis also occurs by compression of the inferior vena cava by the gravid uterus.[30]

Endothelial damage in pelvic veins may occur through vascular compression at the time of delivery or from assisted and operative deliveries.

Risk factors of VTE in pregnancy

Although pregnancy is an independent risk factor for VTE, certain conditions have been found to increase the risk profile. The Royal College of Obstetrics and Gynecology (RCOG) categorized these factors into:[31]

1. **Preexisting factors**: These include maternal age of 35years and older, multiparity, multiple gestations, obesity, smoking, gross varicosity, comorbidities such as inherited or acquired thrombophilias, a previous history of thrombosis, antiphospholipid syndrome, heart disease, diabetes, inflammatory bowel disease, preeclampsia and sickle cell disease.

2. **Obstetric risk factors**: Preeclampsia, prolonged labour, instrumental deliveries,

Caesarean section, still birth, preterm birth, postpartum hemorrhage.

3. **Transient factors**: Hyperemesis, dehydration, any surgical procedure in pregnancy and pueperium, ovarian hyperstimulation syndrome, invitrofertilisation(IVF) pregnancy, bed rest for more than 3 days and long distance travel of more than 4 hours.

VTE Risk Assessment In Obstetrics

Risk assessment for VTE in obstetrics is individualized and based on the consideration of a number of factors that predispose the patient to the condition. There is therefore no single approach but should be on the assessment of each particular patient. This risk assessment should be conducted at each contact with the patient. It is recommended that VTE risk assessment should be done for all pregnant women as they book for antenatal care, whenever they are admitted into the hospital for surgery, medical comorbidities, disorders of pregnancy, etc, labour and delivery; vaginal delivery, emergency and elective Caesarean section. At the end of the pueperium, it is also important to decide if the woman will need further thromboprophylaxis in which case she is referred to the Physician/ Haematologist for further care.

Use of Anticoagulants in Obstetrics

Anticoagulants, commonly known as blood thinners are chemical substances that prevent or reduce the time it takes for blood to clot. They are used to prevent the formation of new blood clots and to treat existing clots by preventing clot elongation/propagation and distant embolisation.

Anticoagulant therapy is indicated in pregnancy for the treatment of acute VTE and valvular heart disease, as well as for the prevention of pregnancy-related complications in women with antithrombin deficiency, antiphospholipid antibody (APLA) syndrome, or other thrombophilias who have had a prior VTE.

In making a decision to use anticoagulants in obstetrics, the maternal risk of VTE and hemorrhage with the risk of fetal exposure must be safely balanced. The risks of various anticoagulation agents must be acknowledged and duly explained to the patient. The choice of anticoagulant agent must be individualized on the basis of maternal and fetal factors. Factors to consider include cumulative risks of the underlying disease process that warrants anticoagulation, medication side effects, compliance with medical therapy, and physician or patients' choice for mode of delivery.

Types of Anticoagulants

They are generally classified into two groups according to the route of administration and mode of action into parenteral and oral drugs.

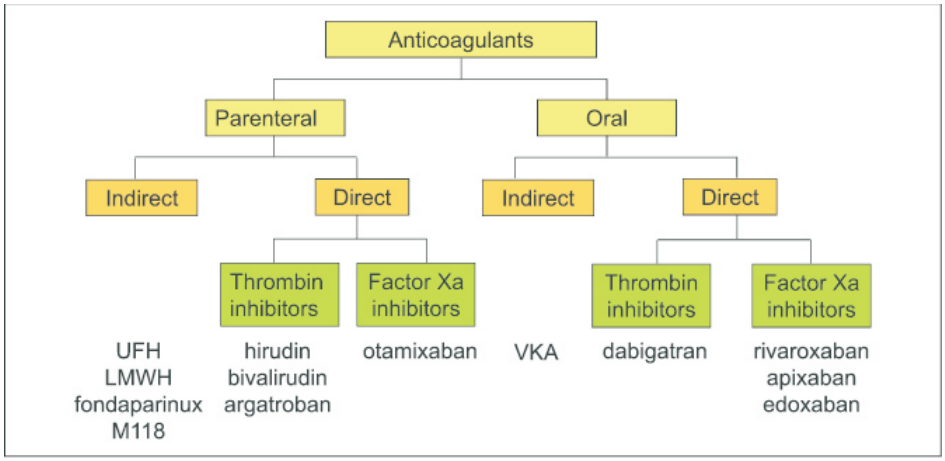
Classification of anticoagulants based on their route of administration and their mode of action.32

1. **Parenteral anticoagulants**
   a) ***Unfractionated heparin (UFH)***

   UFH is very heterogeneous in composition and includes molecules varying in polysaccharide chain length ($\geq$50 saccharide units) with molecular weight between 5,000-30,000 Daltons. It has no direct anticoagulant effect but acts through antithrombin (a serine protease inhibitor whose anticoagulant effect is acceleratedby 1000-fold in the presence of heparin).[33]

   UFH inhibits thrombin by binding to both thrombin and antithrombin (AT) to form a ternary complex. Inhibition of activated factor X (FXa) occurs through binding to heparin-AT complex without requirement of heparin binding directly also to FXa.[33]

   UFH when used in pregnancy does not cross the placenta due to its high molecular weight thus preventing the risk of fetal bleeding and teratogenicity. It is also not secreted in breast milk, hence safe during puerperium. UFH has a very short half-life, thus its reversal with protamine sulphate is usually complete in cases of renal impairment (creatinine clearance <30ml/min) and in those of increased risk



of bleeding.[34] Major adverse effects of UFH include heparin-induced thrombocytopenia (HIT), heparin-induced osteoporosis and bleeding.[35] There is also concern about its monitoring during pregnancy as the activated partial thromboplastin time (APTT) response is blunted in pregnancy because of increased factor VIII levels and increased heparin-binding proteins. This blunted response may lead to heparin overdosing. Measuring anti-activated factor X may obviate the problem.[34]

UFH administration is dose dependent, therefore, variation in weight during pregnancy would require close monitoring of dosages.[34]

b) ***Low molecular weight heparin (LMWH)***
They are produced by treating heparin chemically or enzymatically to decrease the size of the polysaccharide chains to get a product with restricted mean molecular weight distribution of approximately 4000 to 5000 Daltons (range of 1000-10000 Daltons).[33]

LMWH exerts its anticoagulant effects by inactivating factor Xa and to a lesser extent activated factor II (FIIa) because the shorter polysaccharide chain does not allow the formation of necessary ternary complex. LMWH have more predictable pharmacokinetics and a longer half-life than UFH which allows once or twice daily subcutaneous dosing. They are excreted through the kidneys and may accumulate in patients with impaired renal function (enoxaparin >dalteparin>tinzaparin).[33]

As in UFH, LMWH does not cross the placenta and is not secreted in breast milk. HIT and osteoporosis are not as common with LMWH. It also has less non-specific binding to heparin-binding proteins, hence they have more predictable dose response than UFH. 3LMWH is therefore the anticoagulant of choice for VTE treatment or prophylaxis during pregnancy in the absence of severe renal impairment.

Some authors have suggested that LMWH dosing should be evaluated by monitoring anti-Xa level in pregnancy because of the effects of increased plasma volume and glomerular filtration rate on pharmacokinetics.[34]

In a study of 13 pregnancies requiring therapeutic anticoagulation, Barbour et al monitored the patients' peak (2-4 hours after dosing) and trough (pre-dose) levels of anti-Xa while on weight-based dosing of LMWH. They found that 85% of patients required dosing adjustments to maintain peak anti-Xa levels in therapeutic range,

and noted that trough values were therapeutic only 9% of the time.[35] The current RCOG guideline favours weight base dosing.

LMWH is excreted by the kidneys and should not be used if the patient's creatinine clearance is less than 30 mL/min. Weight-based dosing with LMWH is only feasible in patients that weight less than 150kg. For patients, greater than 150kg, UFH maybe preferred or else closer monitoring of anti-Xa levels should be performed to ensure therapeutic effect.[35] Cost and compliance are a major hindrance to use of LMWH.

c) ***Fondaparinux***

It is a heparin-like anticoagulant with selective antithrombin (AT) dependent anti FXa activity. It is a synthetic pentasaccharide (based on heparin structure) that binds reversibly and with high affinity for AT. It has no direct action on thrombin; its mode of action depends on reducing thrombin generation. Indications include acute VTE and patients with previous history of HIT because cross reactivity with the antibodies responsible for HIT does not occur.

Fondaparinux has been reported to pass in-vivo the placental barrier, resulting in low but measurable antifactor Xa activity in umbilical-cord blood, suggesting that a potential hazard cannot be ruled out.[36]

It could be considered when heparin intolerance or HIT occurs in pregnant women who need thromboprophylaxis. However, due to limitations in the available data on its use, it should be used with caution during the first trimester.

2. **Oral anticoagulants**

i) ***Vitamin K antagonist (VKA)***

Warfarin: It is a coumarin derivative. It exerts its anticoagulant effect by inhibiting vitamin K epoxide reductase and vitamin K reductase. There is inhibition of gamma carboxylation required for carboxylation of the coagulation proteins factors II, VII, IX and X, as well as the anticoagulants proteins C and S.

To ensure immediate anticoagulant effect, warfarin therapy must be initiated with a rapidly acting anticoagulant (UFH or LMWH). Anticoagulant effect of warfarin is monitored with the international normalized ratio (INR). Parenteral anticoagulation is continued until a therapeutic INR of 2-3 has been achieved on at least two consecutive times for at least 24 hours apart.[33]

Warfarin freely crosses the placenta and is classified as category X by the Food and Drug Agency of America (FDA).[33] Teratogenic effects such as mid-face hypoplasia, stippled chondral calcification, scoliosis, short proximal limbs, and short fingers have been described when warfarin is given in the first trimester. Other possible effects are CNS abnormalities or fetal/neonatal hemorrhage and death if given at any gestational age.

Other complications include bleeding which is related to patients' characteristics, intensity of anticoagulation and the length of therapy, skin necrosis, purple toe syndrome, rash and hepatitis. Its anticoagulant effect is reversed for episodes of bleeding or drug overdose using factor replacement and or intravenous administration of vitamin K.[33]

Warfarin is rarely used in pregnancy and it is indicated in few cases such as women with prosthetic heart valves. It is minimally excreted in breast milk and could therefore be used in the postpartum period.

ii) ***Direct orally-active anticoagulants***

a) *Rivaroxaban* - Mechanism of action:

Rivaroxaban acts by direct inhibition of factor Xa and achieves maximum plasma levels approximately 3 hours after oral ingestion. Once at steady state, the terminal half-life is 4 to 9 hours (up to 12 hours in patients 75 years old). It has very few significant drug-drug interactions, and food does not affect absorption from the gastrointestinal tract; the oral bioavailability is more than 80%.[33]

b) *Dabigatran* - Mechanism of action: Dabigatran directly inhibits both free and clot-bound thrombin. It is rapidly absorbed orally and reaches peak plasma levels 1.5 hours after ingestion. Once at steady state, dabigatran has a half-life of 14 to 17 hours. With oral treatment, bioavailability is 72%, and dabigatran is predominantly excreted in faeces.[33]

Use of DOAC'S in obstetrics

DOACs are increasingly used for anticoagulation or prevention of thromboembolic events in conditions that may exist with pregnancy. However, evidence regarding efficacy and safety during pregnancy is scarce.[37]

Guideline for VTE Prophylaxis in Nigeria

Figure 2 describes the VTE risk assessment in obstetrics by the Royal College of Obstetrics and Gynaecology (RCOG)[38] while Table 1 is drawn from Fig. 2 and describes the Nigerian recommendation.

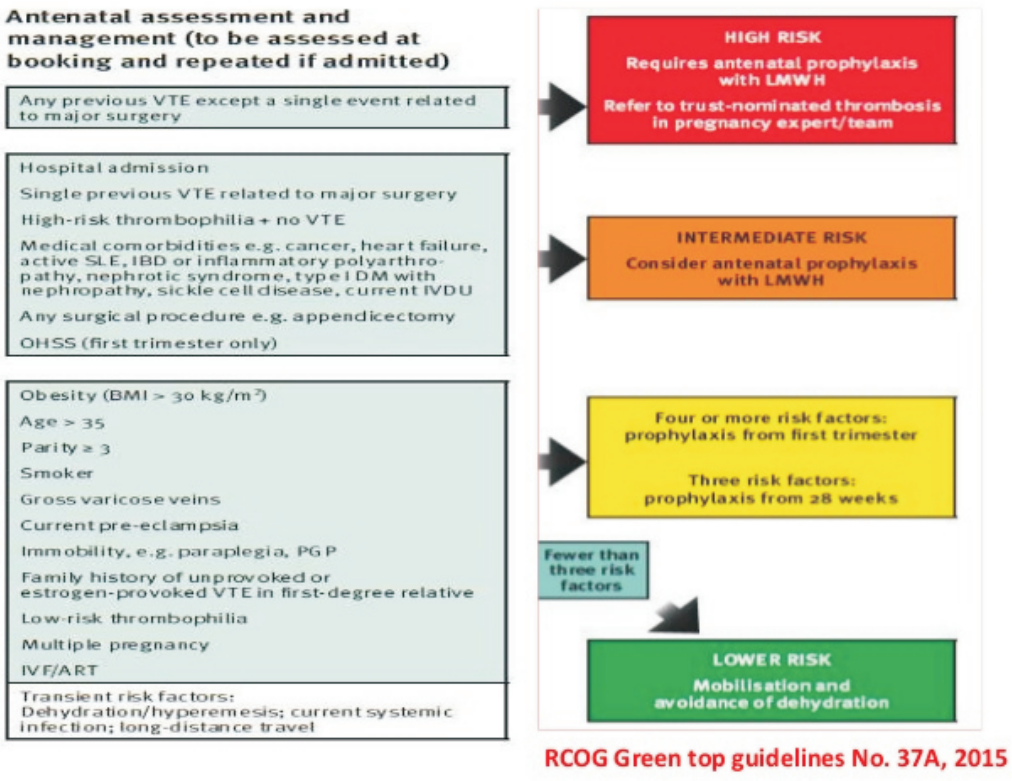


Figure 2: Antenatal Risk Assessment: Adopted from the RCOG Guidelines

Table 1: Recommendation for Thromboprohylaxis in Obstetrics: Nigerian Context

Risk Factor	Level of Risk	Recommendation	Duration	Follow Up Action
Any previous VTE except VTE related to major surgery	Any previous VTE except VTE related to major surgery	Antenatal prophylactic LMWH Recurrent VTE may need higher doses of Heparin may continue Warfarin after delivery	Throughout pregnancy to 6 weeks postpartum	Joint management with a haematologist May need to continue oral anticoagulants after the pueperium
Hospital admission Previous VTE related to surgery High risk thrombophilia with no VTE Medical comorbidities e.g. cancer, Sickle cell disease, Cardiac disease Surgical procedure in pregnancy e.g. Appendectomy	Intermediate risk	Antenatal prophylactic LMWH	Throughout pregnancy to 6 weeks postpartum 1st trimester for ovarian hyperstimulation syndrome (OHSS) Duration of hospital admission for surgical interventions	Joint management with haematologist May need to continue oral anticoagulants after the pueperium
Obesity (BMI.30kg/m2) Age >35years Parity >3 Smoking Gross varicose veins Low risk thrombophilia Pre eclampsia/ Eclampsia Immobility e.g. paraplegia Family history of unprovoked or oestrogen provoked VTE in a 1st degree relative Multiple pregnancy IVF/ ART Transient risk factors: long distance travel >4hours, dehydration/ hyperaemesisgravidarum, current systemic infections	4 or more risk factors	Prophylactic LMWH	From 1st trimester to 6 weeks postpartum	Postnatal risk assessment
	3 risk factors	Prophylactic LMWH	28 weeks to 6 weeks post-partum	Postnatal risk assessment
	2 or less risk factors	Ambulation Avoidance of dehydration	10 days postpartum	Postnatal risk assessment
Emergency Caesarean section	Intermediate	Prophylactic LMWH	10 days postpartum	Postnatal risk assessment
Maternal obesity (>30kg/m^2 either prepregnancy or at booking)	Intermediate	Prophylactic LMWH	10 days postpartum	Postnatal risk assessment
Admission of pregnant woman to hospital including gynaecological conditions, e.g. Hyperaemesisgravidarum	Intermediate	Prophylactic LMWH	Till discharge	Reassess risk at discharge
Ovarian hyperstimulation syndrome (OHSS)	Intermediate	Prophylactic LMWH	1st Trimester	Reassess risk at discharge

Adjustment of Heparin During Labour/ Caesarean Section

Women on heparin injection could bleed if the drug is administered in labour due to its anticoagulant activity. This action could potentially predispose the woman to develop intrapartum or postpartum haemorrhage. They could also bleed from the site of the epidural/spinal injection instituted for analgesia/anaesthesia for labour and/or Caesarean section. For this reason, the following are recommended:[38]

- Women on antenatal LMWH should be educated that when they develop labour pain or vaginal bleeding, they should not inject their medication. They should rather come to the hospital for further assessment
- Regional anaesthesia should be avoided till at least 12 hours after last prophylactic dose of heparin. In case of emergencies where it is not feasible to allow the 12 hours, alternative modes of anaesthesia should be considered.
- LMWH should not be administered until at least 4 hours after epidural/ spinal anaesthesia or removal of epidural/ spinal catheter.
- Elective Caesarean section: For those on antenatal LMWH, the morning dose for the day of the surgery should be withheld.
- After a vaginal delivery, LMWH could be started as soon as it is confirmed that placenta has been delivered and there is no PPH
- After a Caesarean section, LMWH could be started as soon as haemostasis has been achieved and there is no PPH provided the mode of anaesthesia did not involve insertion of an epidural/spinal catheter.
- Where the anaesthesia involved insertion of an epidural/ spinal cathether, LMWH could be started 4 hours after removal of the catheter
- If PPH develops while on LMWH, stop the medication and seek haematological consultation

Dosage of Heparin

The thromboprophylactic dose of heparin is weight based. Figure 3gives a guide on the appropriate dosage of heparins.

Protocols for Prophylaxis

Agent	LMWH Enoxaparin	Dalteparin	Tinzaparin	UFH Unfractionated heparin	
Weight based				*Gestational age-based*	
<50kg	*20mg daily*	*2500 units daily*	*3500 units daily*	*First trimester*	*5000-7500 units Twice daily*
50-90kg	*40mg daily*	*5000 units daily*	*4500 units daily*	*Second trimester*	*7500-10000 units Twice daily*
91-130kg	*60mg daily**	*7500 units daily**	*7000 units daily**	*Third trimester*	*10000 units Twice daily*
131-170kg	*80mg daily**	*10000 units daily**	*9000 units daily*	*Postpartum*	*5000 units twice daily*
>170kg	*0.6mg/kg/day**	*75 units/kg/day*	*75 units/kg/day*		

Hospitalized antepartum patients may receive 5000 units UFH twice daily for prophylaxis to facilitate regional anesthesia

*=may be given in two divided doses

Adapted from ACOG Practice Bulletin 123, ACCP Recommendations , RCOG Green Top Guideline 37a

Safe Motherhood Initiative

ACOG THE AMERICAN CONGRESS OF OBSTETRICIANS AND GYNECOLOGISTS District II

Figure 3: Heparin Dosage guidelines (adopted from RCOG and American College of Obstetrics and Gynaecology)

LMWH (Enoxaparin in particular) is recommended for use in pregnancy and pueperium because itcan easily be self-administered by once daily subcutaneous injections and is safe in pregnancy, pueperium and breastfeeding as it does not require serum monitoring. However, as it is excreted through the kidneys, there is need to use lower dosages in those with renal impairment (creatinine clearance <30ml/min or a serum creatinine> 200umol/ L). It also has a 2% risk of wound haematoma following a Caesarean section. The other forms of LMWH (Dalteparin and Tinzaparin) are also safe to use in pregnancy and pueperium but their availability is currently limited.

Unfractionated Heparin (UFH) can also be used in place of the LMWH. It is also equally effective, safe in pregnancy and pueperium including breastfeeding women. However, unlike LMWH, it requires multiple daily injections and requires monitoring of the platelet count and the activated partial thromboplastin time (APTT). It is also generally cheaper than LMWH. The side effects of UFH include bleeding, heparin induced thrombocytopaenia (HIT), wound haematoma, osteoporosis and allergic reactions. These effects could be reversed by the use of protamine sulphate.

As UFH has a shorter half-life than LMWH, it could be used in women who need anticoagulation and also need regional anaesthesia because the time interval between administration of UFH and insertion of epidural/ spinal cathether is shorter (4 hours)

Oral anticoagulants (such as warfarin) are not safe inpregnancy. Warfarin is known to cause Warfarin embryopathywhen used between the 6th to the 10th week of pregnancy characterized by low birth weight, slowed growth, mental retarda-tion, deafness, small head size, malformed bones, joints and cartilages39. However, it can be used safely in the breastfeeding mother and is best suited for those on long term (includinglifelong) anticoagulation such as those with prosthetic heart valves. In these groups of patients, it is possible to switch from LMWH/ UFH to oral warfarinby the 5th to 7th day postpartum.

Clinical Features and Diagnosis of DVT and PE in Pregnancy and Puerperium Wells' Criteria

Symptoms of DVT and PE may be minimal and non-specific, thus requiring a high index of clinical suspicion as shown in Table 2. The presence of risk factors indicates further diagnostic studies. Individual symptoms and signs are of little value.It is important to remember that some of the physiological changes of pregnancy and the puerperium predispose to DVT ± PE. PE is a complication of DVT. Some haematological conditions peculiar to our region of practice for example Sickle Cell Disease are additional risk factors. It is likely that DVT and PE (i.e. VTE) are underdiagnosed in our practice.

Table 2: Symptoms, Signs and Diagnosis of DVT:

Symptoms	Signs	Diagnosis
Non specific Shortness of breathe Sudden sharp chest pain Cough Unilateral Lower limb: swelling, numbness, heaviness, pain, warm sensation, skin discoloration, wounds/ulcers	Unilateral lower limb: oedema, increase in diameter, local tenderness, skin discoloration, ulcers, positive Homan's sign	d-Dimer test Special tests that can locate blood clots in the veins (Imaging Tests) are diagnostic: - Venography or Ultra-sonography Doppler Studies - CT - MRI

Wells' Scoring Criteria40 (Table 3) is among the screening tools found useful to facilitate the diagnosis of DVT.

It is meant to aid decision making, not force management, and is only applied after detailed history taking plus physical examination. Its application is only when there is risk of DVT; there is no need for risk stratification if no DVT concern. Pregnancy and puerperium are risk factorsfor PTE.

Table 3: Wells Criteria for Deep Vein Thrombosis

Clinical Characteristics	Scores
Active cancer	1
Paralysis, paresis, or recent immobilization of the lower extremities	1
Recently bed ridden > 3 days or major surgery within 4 weeks	1
Localised tenderness along the distribution of the deep venous system	1
Swelling of entire leg	1
Calf swelling by > 3 cm compared to the asymptomatic leg (measured 10 cm below the tibial tuberosity)	1
Pitting oedema (greaterin the symptomatic leg)	1
Swollen unilateral superficial veins (nonvaricose)	1
Alternative diagnosis as likely as or more likely than deep vein thrombosis	-2
Total	**8**

Low probability	≥ 0	>2 Points- DVT likely
Moderate probability	1 - 2	<2 Points- DVT unlikely
High probability	≤ 3	

Table 4: Symptoms, Signs and Diagnosis of PE:
There may **or not be any prior clinical evidence of DVT.**

Symptoms	Signs	Diagnosis
± Symptoms of DVT Pleuritic pain Haemoptysis Dyspnoea with varying degrees of cardiovascular shock including loss of consciousness Some factors have been associated with increased risk of PE: - Increased age and parity - Obesity - Bed confinement - Lactation suppression with oestrogens - C-section, more in pre-eclampsia/ eclampsia - ?Blood groups other than O - Sicke cell disease (SCD)	± Symptoms of DVT Consider PE if there is no any other obvious explanation for tachycardia, pyrexia or bronchospasm	Tests to suggest or diagnose DVT Special tests that can locate blood clots in the lungs (Imaging Tests) are diagnostic: - VCUS/Doppler USS to diagnose - CT - MRI - Ventilation perfusion (V/Q) scan - Pulmonary angiography Other Tests suggestive but not specific: - CXR may be normal - ECG often normal, except when the embolus is large and has produced acute corpulmonale. ECG changes in pregnancy may obscure the changes - Arterial blood gas monitoring

Just as the Wells' Scoring Criteria for DVT facilitate the diagnosis of DVT by the need or not for further testing, the Wells' Scoring Criteria for the probability of PE,41 (Table 5) facilitates its diagnosis.

It clinically stratifies patients, providing an estimated pre-testing probability of PE, and suggestion of the need for further testing for diagnosing PE.

Table 5: Wells Clinical Prediction for Pulmonary Embolism (PE)

Clinical Features	Points
Clinical symptoms of DVT	3
Other diagnosis less likely than PE	3
Heart rate greater than 100 beats per minute	1.5
Immobilization or surgery within past 4 weeks	1.5
Previous DVT or PE	1.5
Haemoptysis	1
Malignancy	1
Total Points	12.5

- > 6 Points: High Risk (78.4%)
- 2 to 6 Points: Moderate Risk (27.8%)
- < 2 Points: Low Risk (3.4%)
- < 4 points- PE unlikely
- >4 points- PE likely

Treatment of DVT and PE in Pregnancy and the Pueperium

Once the diagnosis of DVT or PE is made in pregnancy or in the peurperium, the following should be done:

- Appropriately counsel patient and significant relative/s on the diagnosis, prognosis and possible complications.
- Discuss available treatment options, possible duration, cost and potential challenges, including side effects / complications
- Patients and significant relative/s are allowed to make informed decision on preferred treatment option
- Management is in collaboration with a Haematologist with experience in thrombo-embolism
- Initial care in the acute phase should be in a hospital with appropriate facilities and manpower for care, monitoring and interventions till possibly being sufficiently stable for outpatient care

Treatment

- DVT and PE without haemodynamic changes have essentially the same treatment modalities
- The aim of treatment for DVT is to prevent extension (to PE) and recurrences, prevent or minimize the post thrombotic syndrome and chronic thromboembolic hypertension.
- For PE, the aim is to: prevent recurrence and death
- Consideration of safety of treatment options to the foetus/newborn, pregnant and puerperal women are paramount
- Treatment options are either pharmacological, and non-pharmacological; singly or in combination

Table 6: Outline of treatment options, route of administration and expert opinions on safety in pregnancy and the pueperium

Option	Route	Safety in Pregnancy and Peurperium
a) Pharmacological: Low dose unfractionated heparin (LDUH) Loading dose: 5000 IU followed by 10,000IU 8hrly or 20,000 IU 12 hrly	Intravenous or Subcutaneous	Safe
b) Low molecular weight heparin (LMWH) Enoxaparin Dose: 1mg/kg sc 12hrly Use 1 mg/kg scdly where the Creatinine clearance is <30ml/min or weight of <40kg	Subcutaneous	Safe
c) Non-Pharmacological: Anti-embolism stocking Intermittent pneumatic compression (IPCD) devices Foot pumps or foot impulse devices (FID) Electrical stimulation (including Geko devices) Continuous passive motion Vena cava filters	Above or below knee Above or below knee	All safe

Thrombolysis In Vte

The use of thrombolytic agents is indicated in patients with PE and cardiovascular collapse/ haemodynamic compromise33. It provides a more rapid lysis of PE, restoration of vascular stability, reduce pulmonary resistance thus improving oxygenation and restoration of cardiac function. Thrombolytic agents are best administered intravenously within 30 minutes of admission. The available agents in Nigeria and their dosages are as follows:

- **Streptokinase:** 220,000 International Unit stat then 100,000 IU hourly for 48 hours
- **Urokinase:** 2,000 International Unit stat then 2,000IU hourly for 12 hours

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