INCIDENCE AND CLINICAL PROFILE OF VENOUS THROMBOEMBOLISM IN PREGNANCY AND PUERPERIUM AT KENYATTA NATIONAL HOSPITAL BETWEEN JANUARY 2013 AND DECEMBER 2017.

(A FIVE YEAR RETROSPECTIVE DESCRIPTIVE COHORT STUDY)

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A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE AWARD OF THE DEGREE IN MASTER OF MEDICINE IN OBSTETRICS AND GYNAECOLOGY OF THE UNIVERSITY OF NAIROBI.

2019

DECLARATION

I hereby declare that this research is my own work and has not been accepted for the award of any other degree or diploma at the University of Nairobi or any other educational institution

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ACKNOWLEDGEMENTS

I wish to thank my supervisors Dr. Alfred Osoti and Dr. Lydia Okutoyi for their constant supervision throughout this study.

I would like to acknowledge the Department of Obstetrics and Gynecology, University of Nairobi.

I would like to thank Kenyatta National Hospital for allowing me to conduct the study and for funding the study.

I would like to thank Wycliffe Ayieko for his valuable work with data analysis and presentation.

I acknowledge my research assistant Beatrice Ngila (Registered Clinical Officer) for her efficiency with data collection.

I acknowledge my family The Micheni's for their unwavering support.

Lastly I would like to thank Dr. Odera and Dr. Kibe for the support and encouragement to keep on going on.

LIST OF ABBREVIATIONS

BMI	Body Mass Index
CTP/A	Computed Tomography Pulmonary Angiography
CUS	Compression Ultrasonography
CVS	Cardiovascular System
CXR	Chest X Ray
DVT	Deep Venous Thrombosis
ECG	Electrocardiograph
ECHO	Echocardiograph
IVC	Inferior Vena Cava
ICU	Intensive Care Unit
KNH	Kenyatta National Hospital
LMWH	Lower Molecular Weight Heparin
NOAC	Newer/Novel Oral Anticoagulants
PE	Pulmonary Emboli
PTS	Post Thrombotic Syndrome
SPE	Surgical Pulmonary Embolectomy
UFH	Unfractionated Heparin
VTE	Venous Thromboembolism
VWF	Von Wille Brand Factor

DEFINITION OF TERMS

Hemostasis: it is the normal physiological response after a vascular injury that prevents significant blood loss thereby maintaining the integrity of the circulatory system. It involves platelets and coagulation factors.

Coagulation cascade: a process involving coagulation factors and a complex set of reactions that leads to hemostasis.

Coagulation factors: plasma proteins in the coagulation system that circulate as inactive enzymes or co factors which when activated form complexes that ultimately produce a fibrin clot. Given roman numeral designation.

Thrombus: a collection of fibrin and platelets, often contains red and white cells that occur within a blood vessel. It occurs in areas with slow flow due to stasis or associated with endothelial injury.

Embolus: a piece of thrombus that has broken off and moved to other parts of the circulatory system causing partial or complete obstruction of blood flow.

Anticoagulants: naturally occurring proteins within the circulatory system or medications which inhibit abnormal thrombus formation

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ABSTRACT

BACKGROUND: Venous thromboembolism (VTE) is associated with severe morbidity and is currently among the leading causes of maternal mortality in the high income countries. Pregnancy increases the risk of venous thromboembolism in women by 4 to 5 times compared to that of age-matched non-pregnant women. Presentation of VTE in pregnancy is nonspecific as most of the signs and symptoms tend to overlap with some of the normal physiological changes associated with pregnancy which further poses a challenge in diagnosis. Management of VTE in pregnancy is also challenging due to the fetal safety concerns of the medications used. The burden and management of obstetric VTE in Kenya has not been recently evaluated despite the ongoing changes in the diagnosis and management

STUDY OBJECTIVE: To evaluate the incidence and clinical profile of venous thromboembolism during pregnancy and puerperium in Kenyatta National Hospital between January 2013 and December 2017.

STUDY DESIGN: The study was a 5-year retrospective descriptive cohort study from January 2013 to December 2017 conducted at Kenyatta National Hospital.

RESULTS: The 5-year incidence of obstetric VTE in KNH was 1.8 per 1,000 deliveries. DVT accounted for 94.9% of all obstetric VTEs while pulmonary embolism accounted for 5.1% of the cases. 74.5% of obstetric VTEs occurred in the antenatal period while 25.5% occurred in the post-natal period. In the antenatal period the third trimester had the highest number of cases 39.2%, second trimester had 32.4% and first trimester 28.4% of the cases. The left lower limb was the commonly affected limb with pain and swelling being the most common presenting symptoms occurring in 96.4% and 95.6% of the cases respectively. For patients with pulmonary embolism chest pain and dyspnea were the commonest presenting symptoms reported in 100% and 71.4% of patients respectively. All patients were managed medically and there was 1(1.7%) maternal death.

CONCLUSION AND RECOMMENDATION: The incidence of obstetric VTE in KNH is similar to that reported in similar studies. There should be a high index of suspicion of VTE in obstetric patients presenting with lower limb swelling, pain, chest pain and dyspnea.

KEYWORDS: Venous thromboembolism, deep venous thrombosis, pulmonary embolism, pregnancy, puerperium

1.0 INTRODUCTION

Venous thromboembolism (VTE) is a clinical term that encompasses deep venous thrombosis and pulmonary embolism. Thrombosis is described as abnormal clot formation within a blood vessel causing partial or complete obstruction within the circulatory system. It occurs when the balance between coagulation and natural anticoagulation/fibrinolytic mechanisms become disrupted. DVT involves abnormal clot formation in the deep veins of the lower limbs which if untreated or unrecognized can break off, follow the natural course of venous blood flow by traversing the vena cava to the right heart chambers and ultimately to the pulmonary artery where they lodge to become pulmonary emboli. The embolus can cause partial or complete obstruction of the pulmonary circulation which can be fatal. It is associated with significant morbidity and mortality. (1,2)

Venous thrombi usually arise at the site of vessel damage or areas of stasis such as venous sinuses or valve cusps. Small DVT undergo spontaneous lysis while others may extend to the proximal veins. Proximal, larger clots are more likely to embolise than isolated distal clots. DVT causes vascular congestion and may present symptomatically as leg swelling and pain though the symptoms maybe nonexistent or subtle. (3)

In PE the emboli obstruct the pulmonary artery resulting in some degree of vascular occlusion leading to varying degrees of ventilation perfusion mismatch. It can range from small thrombi which only obstruct segmental or sub segmental arteries to large emboli which straddle the bifurcation of pulmonary arteries or obstruct the entire pulmonary outflow tract. Development of symptoms depends on the extent of the thrombus, occlusion, adequacy of collaterals and the severity of the vascular occlusion.(3,4)

VENOUS THROMBOEMBOLISM AND PREGNANCY

Pregnancy and puerperium is a physiological state during which the woman exhibits each element of the Virchow's triad i.e. hypercoagulability, stasis and endothelial injury which increases the risk of VTE (3).

Pregnancy is marked by an alteration in the coagulation and anticoagulation system leading to a hypercoagulable state whose physiological aim is to protect the woman from any catastrophic bleeding that may occur after delivery or in the event of an abortion. Pregnancy is a classical hypercoagulable state marked by the increase of clotting factors ii, vii, viii, ix, x, xii, VWF and fibrinogen. The anticoagulation system is affected by a decrease in the free levels of protein S due to an increase in its binding globulin, a resistance to activated protein C and a decline in fibrinolytic activity. The net effect of all these changes is a preponderance towards clot formation. (5)

Venous stasis in pregnancy is due to physiological and anatomical factors. Physiologically it is due to the dilatation of the venous system as a result of the influence of progesterone which causes vasodilation. There is a reduction in the venous flow velocity by about 50% starting from about 25 weeks of gestation up to 6 weeks post-delivery when it goes back to its pre pregnancy state(5). Anatomically it is due to the pressure effect of the gravid uterus on the inferior vena cava (IVC) and the pelvic veins which results in stasis below the level of the obstruction. The compression of the left iliac vein by the right iliac artery (May-Thurner syndrome) is more exaggerated during pregnancy which explains the propensity of DVT to occur more in the left lower limb compared to the right lower limb in pregnancy(6).

The risk of developing VTE in the puerperium has been found to be higher by about 20 fold and this has been attributed to endothelial injury of the pelvic veins during delivery(7). Endothelial injury occurs during the delivery process and it involves the pelvic vessels. It occurs in both operative and vaginal deliveries but it tends to be more marked after a cesarean delivery and operative vaginal delivery. This may explain why the incidence of VTE is higher post caesarean delivery, almost double compared to a vaginal delivery (7)

About 80% of the VTE events in pregnancy are DVT and while PE accounts for about 20% of the events(8). A third of the pregnancy related DVTs and about a half of pregnancy related PE have been found to occur after delivery(6,8–10).

Presentation of venous thromboembolism in pregnancy is nonspecific as most of the signs and symptoms tend to overlap with some of the normal physiologic process of pregnancy which

poses a challenge in diagnosis. Delayed diagnosis, delayed or inadequate treatment, and inadequate thromboprophylaxis account for many of the deaths due to venous thromboembolism(5).

2.0LITERATURE REVIEW

2.1 PREVALENCE OF VTE IN PREGNANCY

Most of the studies done on VTE in pregnancy and postpartum period have been conducted in the west. In Africa there is paucity of data on the subject with only two known published studies on the subject both from North Sudan.

The global incidence of VTE in pregnancy is estimated at 1-2/1,000 deliveries with pulmonary embolism as one of the leading cause of maternal deaths in the high income countries with an estimated mortality rate of 1.1-1.5 deaths/ 100,000 deliveries(5,11–13). A thirteen-year study in 11 Norwegian counties put the incidence of VTE at 1.0/ 1,000 deliveries. A 26-year population based study in Scotland found the incidence of pregnancy related VTE to be 13.6/10, 000 deliveries. (4) In Canada the incidence of pregnancy related DVT was 12.1/10,00 women and pulmonary embolism was 5.4/ 10,000 women (5). A study done in Saudi Arabia estimated the incidence at 1.25/ 1,000 deliveries(14). The incidence of VTE in the Norwegian countries and from the middle east study are similar.

In Africa the incidence of DVT from the only 2 published papers available which were done in North Sudan estimates the incidence at 380-448/ 100,000 deliveries (7,8). A one year prospective study done in KNH in 2010 looking at the risk factors of DVT during pregnancy and puerperium found that DVT accounted for 0.61 % of admissions during pregnancy and the puerperium giving an incidence of 6/1000 deliveries (15).

The two published studies in Africa are limited by the fact that they were conducted in North Sudan whose population is mainly made up of people of Arabic descent and may not be a true representation of the indigenous African population. The studies focused mainly on DVT and did not look into pulmonary embolism.

The local study done in KNH only looked at the incidence and risk factors of DVT during the pregnancy and postpartum period and did not look at pulmonary embolism. If both DVT and PE are looked together as one entity the incidence of VTE may be higher than what is reported in the other studies. VTE is not a common occurrence in pregnancy and a retrospective study covering 5 years may give us a better estimate of the incidence and its clinical profile.

While PE is among the leading cause of maternal deaths in the high income countries, the leading cause of death in the low and middle income countries is postpartum hemorrhage (2,3). The incidence of VTE has been noted to be increasing due to the increased diagnosis, availability and increased utilization of imaging(16).

2.2CLINICAL PRESENTATION OF DEEP VENOUS THROMBOSIS

DVT presents with lower limb swelling and pain which is experienced by almost 80% of pregnant women especially as the pregnancy progresses although few of them are diagnosed with DVT. Most common symptoms of DVT in pregnancy are swelling- 88%, difficulty in walking- 21% and erythema in 26%. In puerperium 95% present with swelling, 32% have difficulty in walking and 26% have erythema. Patients with isolated DVT of the iliac veins may present with abdominal pain. Back pain and swelling of the entire leg.(5,16)

DVT in pregnancy has a predilection for the left lower limb compared to that in the general population which has an almost equal distribution among both limbs.(17) More than 80% of the cases of DVT in pregnancy occur in the left lower limb and this has been attributed to the compression of the left iliac vein by the right iliac artery (May-Thurner syndrome) which is more pronounced during pregnancy (11,14,16,18,19). DVT in pregnancy tends to affect the proximal veins compared to the non-pregnant women who tend to have more of distal DVT. Most of the DVT cases in pregnancy involve the ilio-femoral veins rather than the calf veins.(15–17,20). A calf circumference difference of 2cm or more is suggestive of lower extremity DVT(21)

2.3 CLINICAL PRESENTATION OF PULMONARY EMBOLISM

The classic symptoms of PE are dyspnea, chest pain of abrupt onset and cough. On clinical examination some of the findings include tachypnea, tachycardia and crackles. The signs and symptoms are rarely encountered together and they are common physiological changes that occur in pregnancy making the diagnosis challenging. Up to 70% of women in pregnancy experience dyspnea although a few have PE. One study done in Canada found PE in pregnancy presented with dyspnea in 61.9%, pleuritic chest pain 46.4% or non-pleuritic chest pain in 18.4% of the women. The symptoms were either alone or in combination(22). Another study looking at 38 pregnant women with objectively confirmed PE found the most common features of PE were dyspnea- 62%, pleuritic chest pain-55%, cough 21% and sweating-18% (10). Patients with

massive PE may present with dyspnea, tachycardia, cyanosis, tachypnea, hypoxemia, acute respiratory distress, and palpitations. The symptoms usually occur in combination(23)

2.4 DISTRIBUTION OF VTE IN PREGNANCY AND PUERPERIUM

The incidence of VTE has been found to be highest in the third trimester compared to the other trimesters (11,12,17,19,24) but some studies have shown the incidence to be equally distributed among all the trimesters(1,25) while others have found the risk to be highest in the first trimester.(6,14,16) The incidence of VTE has been shown to be higher in the antenatal period compared to the post-natal period(16) while other studies have shown the incidence to be higher in the postpartum period compared to the antenatal period.(9,19,26,27). During the postpartum period the incidence of VTE has been found to be highest in the first two weeks after delivery with the incidence being higher in patients who underwent a caesarean section due to greater endothelial injury to the pelvic vessels that occurs during a caesarean section (17,24,26)

2.5DIAGNOSIS OF DEEP VENOUS THROMBOSIS

Compression ultrasonography is the primary diagnostic modality for DVT. It is preferred as it is non-invasive, does not involve the use of radiation thus is safe for the fetus and it is widely available. It has a sensitivity of 94% for DVT involving the popliteal and femoral veins but it is less sensitive for isolated calf vein DVT(28). When iliac thrombosis is suspected i.e. in patients with back and gluteal pain and swelling of the entire limb, Doppler ultrasonography, MR venography or contrast venography may be considered.(29,30)

2.6 DIAGNOSIS OF PULMONARY EMBOLISM

2.6.1 CT P/A AND V/Q SCANNING

For patients presenting with symptoms of PE without symptoms of DVT, CT PA or V/Q scanning can be used depending on their local availability but the V/Q scanning is the preferred imaging modality(23,31) though it has increased radiation exposure to the fetus compared to the mother which has been shown to increase the risk of childhood malignancy. CT PA and V/Q scanning have been shown to have a comparable negative predictive value of 99% and 100% respectively

2.6.2 CHEST X RAY

A chest x-ray is recommended before further diagnostic testing. It will help rule out pulmonary pathologies like pneumonia, lobar collapse or pneumothorax which may present in the same manner as a PE. The CXR is normal in more than 50% of pregnant patients with objectively proven PE. Some of the abnormal CXR features that have been found in patients with PE include pulmonary oedema, effusion, atelectasis, focal opacities and regional oligaemia(32)

2.7 MANAGEMENT OF VENOUS THROMBOEMBOLISM

Management of VTE in pregnancy is challenging because of the potential maternal and fetal complications. The treatment of VTE in pregnancy is largely based on observational studies, case series and data extrapolated from the non-pregnant population. Anticoagulation is the mainstay of treatment of VTE in pregnancy. Other forms of management may also include thrombolysis and surgical management which involves IVC filter insertion and embolectomy.

2.7.1 MEDICAL MANAGEMENT

Medical management involving the use of anticoagulants is the mainstay of management of VTE in pregnancy. Different classes of anticoagulants are used in the management VTE with some being preferred over others due to fetal safety concerns.

HEPARINS

It consists of UFH and LMWH with the LMWH being more preferred to the UFH. Both UFH and LMWH do not cross the placental barrier to the fetus. LMWH is preferred to UFH as it has a lower rate of VTE recurrence or extension, less hemorrhage during the initial treatment, less overall mortality, less heparin associated osteoporosis and HIT. (8,33–36)

Other advantages of LMWHs over UFH include a stable and predictable pharmacokinetics with increased bioavailability and half-life, allowing less frequent fixed or weight-based dosing without the need for monitoring. The main disadvantage of LMWH is the long half-life which is a challenge during delivery and it may accumulate in patients with renal insufficiency therefore needing dose adjustments to match the creatinine clearance (37).The cost of LMWH may limit its accessibility to some patients.

A major concern with the widespread use of UFH in pregnancy has been the 2% risk of symptomatic heparin induced osteoporotic fracture in pregnancy which is lower with

LMWH(38) UFH heparin requires constant monitoring through use of aPTT to ensure that the drug levels are within the therapeutic levels.

VITAMIN K ANTAGONISTS

The use of vitamin k antagonists like warfarin is contraindicated in pregnancy except in the cases of patients with mechanical valves where the use of LMWH and UFH is associated with a risk of thrombosis(31).

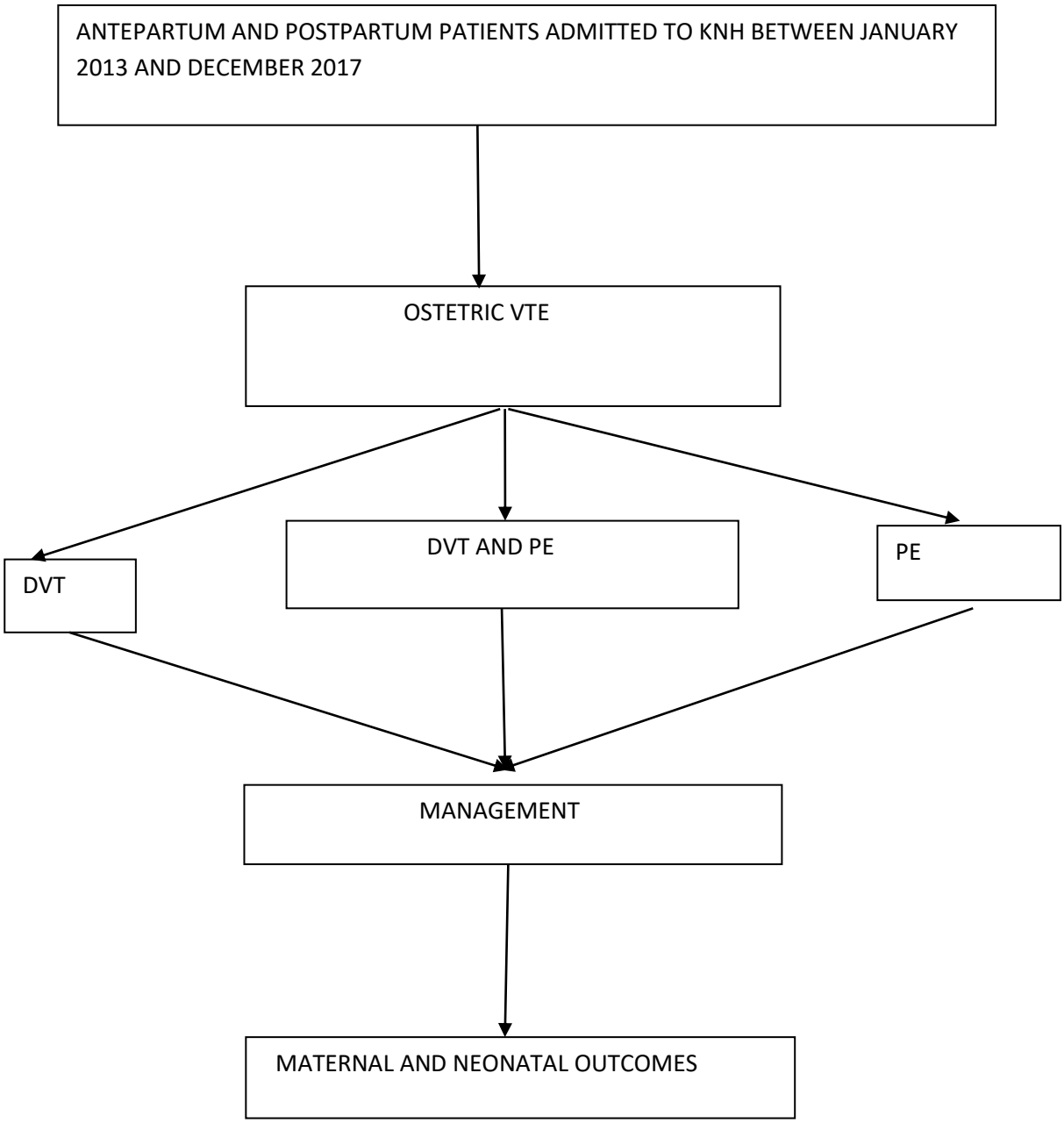
Warfarin is classified by the FDA as a category D drug. It crosses the placenta and it is teratogenic especially when used in the period of organogenesis between 6 and 12 weeks. It is associated with a 30% risk of congenital anomalies (warfarin embryopathy) when used during this time. The use of warfarin in the first trimester has also been associated with a 14-56% risk of first trimester miscarriage. Later use in pregnancy is associated with risk of placental and fetal hemorrhage, stillbirth, low birth weight and neurodevelopmental deficits. Discontinuation of VKAs before 6 weeks of gestation eliminates the risk of warfarin embryopathy. (8,33–35,39)

The use of warfarin is safe during the breastfeeding period as the drug is not secreted in breastmilk.

The recommended duration of treatment by most guidelines is a minimum of 3 months and once the diagnosis has been made during pregnancy treatment should continue up to 6 weeks postpartum and until at least 3 months of treatment have been given.(21,31)

The various peer reviewed guidelines on medical management of obstetric VTE recommend the use of LMWH(clexane) or UFH as they have better fetal side effect profile. Use of warfarin in the antenatal period is contraindicated except in patients with mechanical valves as they are better at preventing thrombi compared to the LMWH and UFH (16,31,35).

1.0 CONCEPTUAL FRAMEWORK



4.0 STUDY JUSTIFICATION

Venous thromboembolism is an important cause of maternal morbidity and mortality with lifelong post treatment complications, it is therefore important to be able to make a timely diagnosis, treat and also identify those at risk and provide prophylactic measures. Most of the literature available on the subject is from studies conducted in the West.

In Africa there is paucity of data on the subject and to the best of our knowledge Africa has two known published studies on the subject. The 2 studies were conducted in North Sudan and they focused primarily on DVT in pregnancy and puerperium.

Locally the two available studies were done more than 10 years ago and they focused on DVT during pregnancy, the puerperium and in women on oral contraceptives but they did not evaluate PE in the obstetric population. At the time the studies were conducted use of LMWH which has a better safety profile had not been effected in KNH and the study will evaluate if there has been a shift towards use of LMWH during pregnancy.

The study will evaluate if the incidence and presentation of obstetric VTE in our population is comparable to that of other populations. The study will also inform us if the management of obstetric VTE in KNH is in line with peer reviewed obstetrics guidelines.

It will help identify gaps in the management that need to be changed or improved. It will also help identify areas for additional studies in the future.

The study will add to the pool of knowledge on the subject of obstetric VTE locally, regionally and globally.

5.0 RESEARCH QUESTION

What is the incidence and clinical profile of venous thromboembolism in pregnancy and puerperium in KNH between January 2013 to December 2017?

6.0STUDY OBJECTIVES

6.1BROAD OBJECTIVE

To evaluate the incidence and clinical profile of venous thromboembolism among the obstetric population in KNH between January 2013 to December 2017.

6.2SPECIFIC OBJECTIVES

Among the pregnant or postpartum women who received antepartum or postpartum care in KNH between January 2013 to December 2017 at KNH

1. To determine the incidence of VTE in the obstetric population at KNH between January 2013 to December 2017
2. To describe the clinical presentation of VTE in pregnancy and puerperium
3. To evaluate the clinical management of VTE in pregnancy and puerperium

7.0 STUDY METHODOLOGY

7.1STUDY DESIGN

The study was a 5-year retrospective descriptive cohort study from January 2013 to December 2017. The 5-year period was used as obstetric VTE is not a common diagnosis hence the 5-year period was used so as to get a significant number of cases.

7.2 STUDY AREA/ STUDY SITE

The study was conducted at the Kenyatta National hospital (KNH) the largest teaching and referral hospital in Kenya and the East and Central Africa region. It is located in the capital city Nairobi about 3-4 kilometers from the city center and has a bed capacity of 1,800 beds with a high patient turnover. KNH is a teaching hospital for the University of Nairobi, Faculty of Medicine and visiting students from other institutions.

The hospital has an obstetrics and gynecology department, with a maternity wing that conducts approximately 10,000 deliveries per year. As a referral facility KNH receives a large number of high risk patients from hospitals country wide hence accumulation of patients with obstetric VTE to attain a sample size. Data were collected in April and May 2019 at the records department.

7.3STUDY POPULATION

The study population was made up of pregnant women and women in the postpartum period (up to 6 weeks post-delivery) who were admitted in KNH between 1st January 2013 and 31st December 2017. The 5-year period was used as VTE in pregnancy is not a common diagnosis in KNH. For the determination of incidence which was the first aim of the study all pregnant and postpartum women admitted in KNH during this five-year period were recruited to the study. For

the description of clinical presentation, management and outcome all pregnant and postpartum patients with a diagnosis of VTE that met the inclusion criteria will be included in the study.

7.4 INCLUSION AND EXCLUSION CRITERIAS

7.4.1 INCLUSION CRITERIA

1. All obstetric patients without diagnosis and treatment for VTE at the onset of index pregnancy
2. Any obstetric patient with a first time episode of VTE that has been objectively diagnosed through imaging i.e. Doppler/compression ultrasound for DVT or CT PA for PE.
3. Patients with a diagnosis of VTE based on clinical findings

7.4.2 EXCLUSION CRITERIA

1. Patients on prophylactic anticoagulants due to history of VTE in previous pregnancy and cardiac disease.
2. Files missing more than 40% of the critical data. Critical data in the study means there is no justification as to how the diagnosis of VTE was arrived at. Patients with no clinical signs suggestive of VTE and no investigations that arrived at the diagnosis of VTE.

7.5 SAMPLE SIZE DETRMINATION

Sample size calculation for the records to be reviewed was calculated using Cochrane's formula of proportions:

$$n = \frac{Z^2_{1-\alpha/2} \times p(1-p)}{d^2}$$

Assumptions were derived from a study by Anne Flem Jacobsen et al[1] who found the incidence of VTE to be 1 per 1,000 deliveries.

- n= sample size
- Z= level of statistical difference = 1.96
- P = proportion that developed VTE (0.1)
- d= Estimated error, taken as 0.05

Substituting this in the formula gave a sample size of **139** as shown below:

$$n = \frac{1.96^2 \times 0.736(1-0.736)}{0.05 \times 0.05}$$

= 139

To compensate for missing entries, a 10% adjustment was applied to arrive at a recalculated sample size of 153 as follows:

100/90*139 = **153**

7.6 SAMPLING PROCEDURE

All files of patients diagnosed with obstetric VTE in KNH between 1st January 2013 and 31st December 2017 that fulfilled the inclusion criteria formed the study target population. During the study period we found 206 files had been listed as having obstetric VTE but only 137 met the inclusion criteria against our sample size of 153. Our sample size of 153 was not met due to missing files, some files were missing critical data and some files had been misclassified. We proceeded with data collection and analysis as the number would not influence the outcome of analysis. Once the ERC had given us approval, we sought written authorization form the head of the Department of reproductive health, KNH and the head of KNH Records department before proceeding with the data collection. All the records were retrieved from the KNH Records department and the retrieval of data was carried out in the reading rooms within the KNH records department. Data extraction was done by the principal investigator and one other research assistants and entered into a structured data extraction tool.

7.7 DATA VARIABLES

The study outcome was defined as any obstetric patient listed in the KNH health records register as having had a clinical diagnosis of and /or treatment for VTE between January 2013 and December 2017. Obstetric patients were defined as antenatal patients and post-natal patients. The postnatal period was defined as a period of up to six weeks post-delivery.

Data variables for the sociodemographic characteristics were; age, marital status, level of education and the employment status.

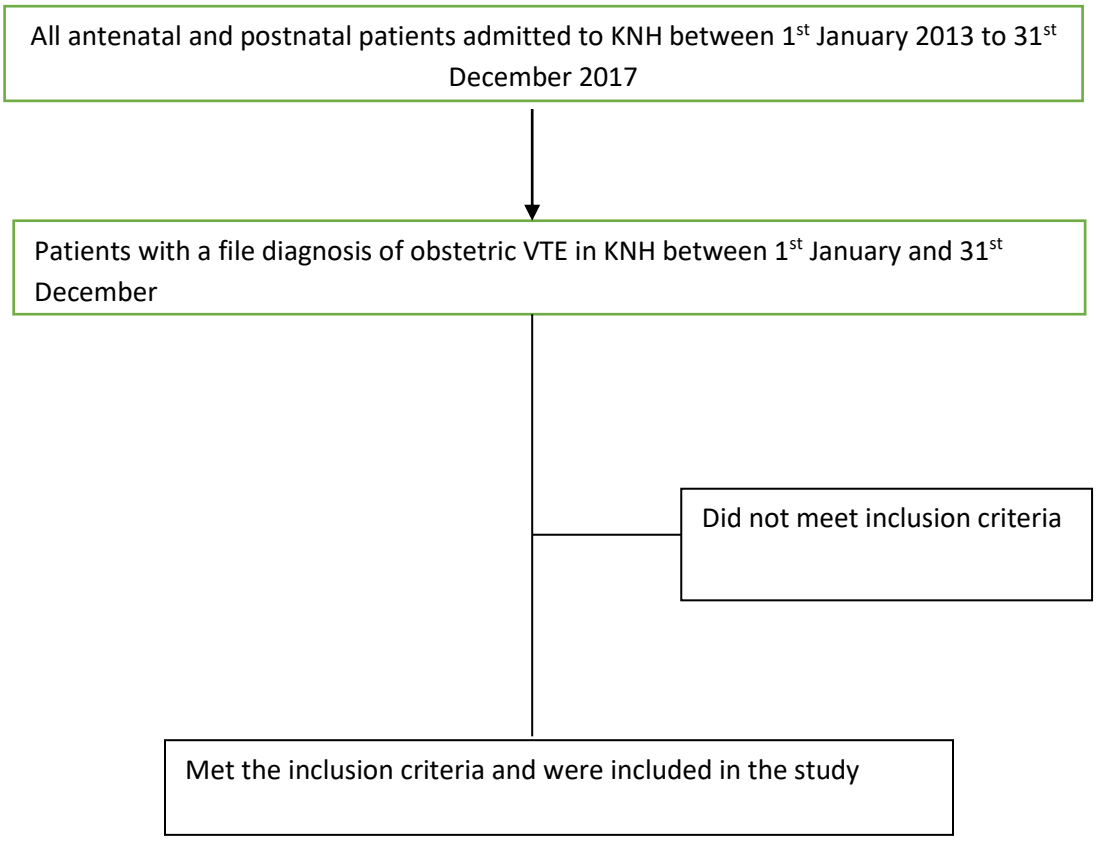
Data variables for obstetric characteristics were: parity, gestational age, gravidity, type of gestation.

The clinical profile variables were the signs and symptoms at presentation, imaging modality to confirm the diagnosis and the findings. The management of the patients whether surgical or medical. For medical management the drugs used in the initiation and maintenance phase.

7.8 STUDY FLOW CHART

The study flow chart was as shown in figure 1 below.

Figure 1: selection of patient files for inclusion in the study to describe the incidence and clinical profile of patients with obstetric VTE at KNH from 1st Jan 2013 to 31st Dec 2017



7.9 STUDY MATERIALS

Materials used for this study included stationery, data retrieval forms, storage files, flash drives, hard drives and password protected computers.

7.10 TRAINING PROCEDURES

The research assistants, a registered clinical officer received the appropriate training and a piloting of the data collection tool was done before data collection commenced.

7.11 QUALITY ASSURANCE PROCEDURE

The following measures were taken for quality assurance through all the stages of the study.

1. Data obtained from the records and files was counterchecked by an independent research assistant to ensure it was correct.

2. Data was stored in password protected computers, hard drives and flash drives that were only accessible to the principal investigator, supervisors and statistician to ensure confidentiality was maintained.

7.12DATA MANAGEMENT AND ANALYSIS

The collected data was transcribed to a password protected excel sheet that was accessible to the primary investigator and the statistician. Data were cleaned and verified by the principle investigator before being analyzed. The analysis was done using SPSS version 23 software. There was an initial analysis and presentation of data in different formats before the final format and outcome of the analysis was agreed on by the principal investigator and the supervisors. The incidence of VTE across the 5-year period was calculated and expressed as number of VTE cases per 1000 deliveries with the denominator being the total number of deliveries in the 5-year period. The sociodemographic characteristics and obstetric characteristics data were analyzed and presented in tables as proportions. The clinical profile data which included the clinical presentation and management were analyzed and presented in tables as frequency and proportions.

8.0ETHICAL CONSIDERATIONS

Approval was obtained from Kenyatta National Hospital/ University of Nairobi ethical review committee, ERC approval number KNH-ERC/A/116.Permission was also sort from the Department of Obstetrics and Gynecology University of Nairobi and the KNH administration to carry out the study. Since the study was retrospective a waiver of consent for the study was given by the ethics and research committee. Patients data was also de identified to maintain confidentiality.

9.0 STUDY RESULTS DISSEMINATION

The final results were presented to the Department of Obstetrics and Gynecology both KNH and University of Nairobi. The results will also be presented in other fora like conferences or seminars and to health care workers involved in the management of obstetric patients. The study will also be published in an obstetric or fetomaternal journal.

10.0 STUDY LIMITATIONS

The study was limited by the misclassification of data with some of the patients being listed as obstetric patients yet they were pediatric cases, orthopedic and medical cases and they were not included in the study.

Some files were missing and others were missing critical data hence they were not included in the study.

Incomplete documentation of the medical examination findings of the patients hence the study was not able to describe the most common clinical examination findings in patients who had obstetric VTE.

The study was a descriptive study hence it was not able to analyze for any risk factors or associations regarding VTE in the obstetric period.

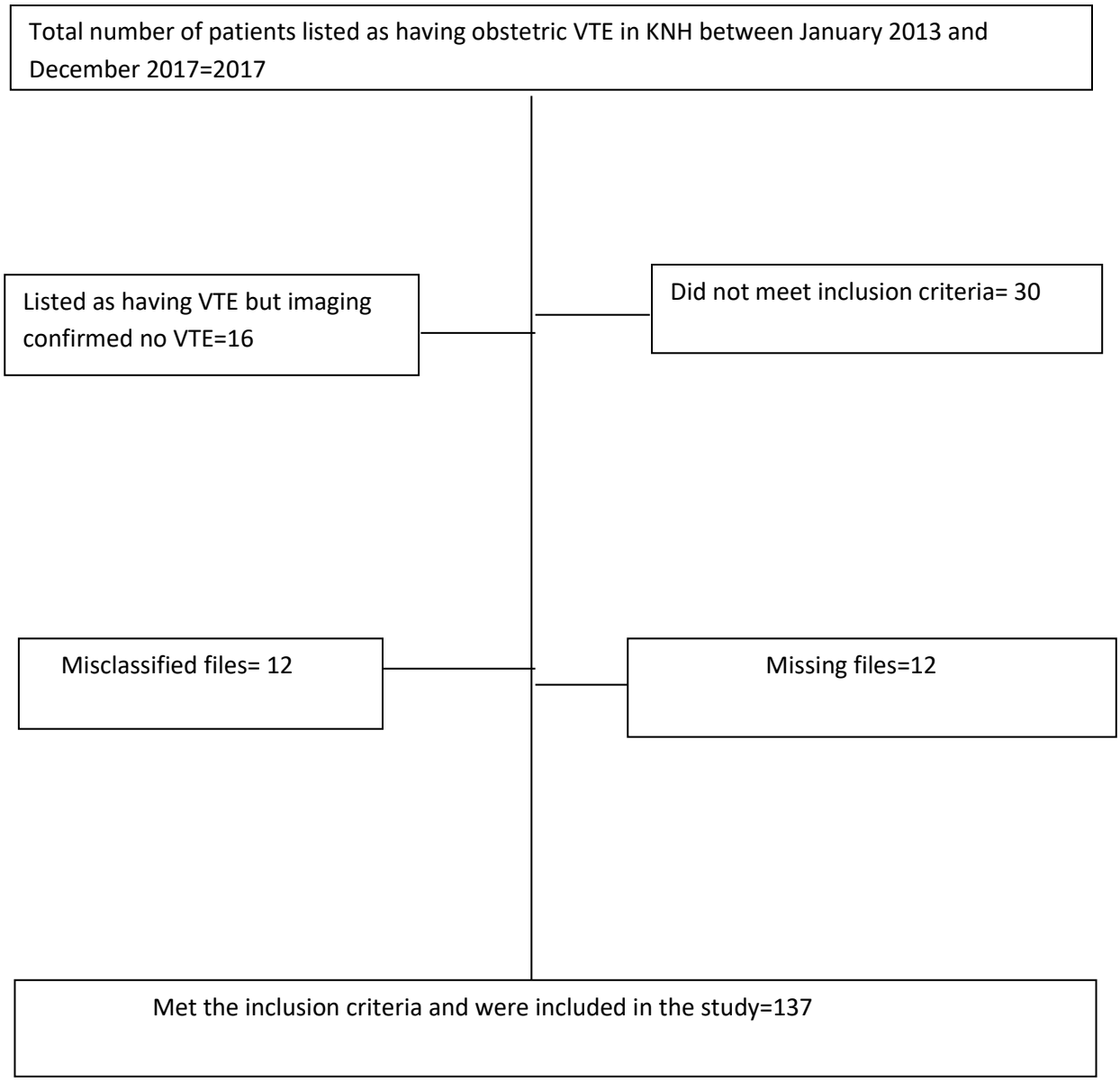
There was loss of follow up of a significant number of patients that were diagnosed in the antenatal period hence it was not possible to know what the maternal and fetal outcomes were.

There was also loss of follow up in the post-natal period after discharge hence the study could not establish how long the patients were on anticoagulation for.

11.0 RESULTS

For the 5-year period 207 patients were listed as having obstetric VTE using the ICD 10 code but only 137 files met the inclusion criteria and include in the study as shown in figure one below.

Figure 2: Selection of patients for inclusion in a study to evaluate the clinical profile of obstetric VTE in KNH between January 2013 and December 2017



SOCIODEMOGRAPHIC AND OBSTETRIC CHARACTERISTICS

The commonest age group in the study was 18-25 years 61(44.5%) with a mean age of 27.2 years, most of the patients were married 85(62%), most had attained at least secondary level 51(41.6%) of education and most were unemployed79(57.7%). Majority of the women were multigravida 92(67.2%) and singleton gestation was the commonest at 123(89.8%). The sociodemographic and obstetric characteristics of patients with obstetric VTE are as shown in table 1.

Table 1; Frequency distribution of sociodemographic and obstetric characteristics of women with obstetric VTE at KNH (N=137)

Characteristic	No. (%)
Sociodemographic	
Age	
<18 years	2(1.5)
18-25 years	61 (44.5)
25-35 years	58 (42.3)
>35 years	16 (11.7)
Marital status	
Single	52 (38)
Married	85 (62)
Level of education	
None	7 (5.1)
Primary	37 (27)
Secondary	57 (41.6)
Tertiary	36 (26.3)
Employment status	
Employed	58 (42.3)
Unemployed	79 (57.7)
Obstetric characteristics	
Gravidity	
Primigravida	45 (32.8)
Multigravida	92(67.2)
Pregnancy	
Singleton	123 (89.8)
Multiple	14 (10.2)

INCIDENCE

The incidence of obstetric VTE in KNH between January 2013 to December 2017 was 1.8 per 1000 deliveries as shown in Table 1.

Table 2: Incidence of obstetric VTE in KNH between Jan 2013 and December 2017

Year	No. of VTE* cases	No. of deliveries	incidence/ 1000 deliveries
2013	24	13 060	1.8
2014	42	15 097	2.9
2015	21	17 331	1.2
2016	23	16 488	1.4
2017	27	15 872	1.7
Total	137	77 848	1.8

***Venous thromboembolism**

Table 3: Type of obstetric VTE cases at KNH between Jan 2013 and Dec 2017 (N=137)

Type of VTE*	No. of cases	%
Deep venous thrombosis	130	94.9
DVT* AND PE*	5	3.6
Pulmonary embolism	2	1.5

***venous thromboembolism *deep venous thrombosis *pulmonary embolism**

DVT was the most common type of VTE with 130(94.9%), DVT & PE occurred in 5(3.6%) and PE alone occurred in 2 (1.5%) of the cases, shown in table 3. The antenatal period recorded the highest VTE cases 102(74.5%) while the postnatal period had 35(25.5%) cases.

In the antenatal period most of the patients 40(39.2%) presented in the third trimester, 33(32.4%) in the second trimester and 29(28.4%) in the first trimester as shown in table 4.

Table 4: Number of obstetric venous thrombosis embolism cases by trimester at presentation at Kenyatta National hospital between Jan 2013 and December 2017 (N=102)

Trimester at presentation	n (%)
1st trimester	29 (28.4)
2nd trimester	33 (32.4)
3rd trimester	40 (39.2)

In the postnatal period most of the patients 18(51.4%) presented in the first fourteen days after delivery, this is shown in table 5.

Table 5: Number of postnatal days at presentation in patients with obstetric venous thromboembolism at Kenyatta National Hospital between Jan 2013 and Dec 2017 (N=35)

Number of postnatal days at presentation	n (%)
< 7 days	6 (17.1)
7-14 days	12 (34.3)
>14 days	17 (48.6)

In patients presenting with DVT the most affected limb was the left lower limb 112(81.8%) followed by the right lower limb 21 (15.3%) and only a minority had bilateral DVT 4(2.9%). The commonest presenting symptoms in patients who had DVT was pain and swelling occurring in more than 95% of the cases. Table 6 summarizes the presenting symptoms in patients with DVT which occurred in combination.

Table 6: Presenting symptoms of deep venous thrombosis in the obstetric period at Kenyatta National Hospital between Jan 2013 and Dec 2017 (N=135)

Symptoms of DVT	**n (%)**
Pain	132(96.4)
Swelling	131(95.6)
Difficulty in walking	31(22.6)
Inability to walk	5(3.6)
Erythema	1(0.7)
Warmth	1(0.7)

All the patients in our study had objectively diagnosed DVT using Doppler ultrasound and the veins that were commonly affected were femoral 89(65.9%), iliac 59(43.7%), popliteal 58(43%) while 20 (14.8%)were unspecified as shown in figure 3.

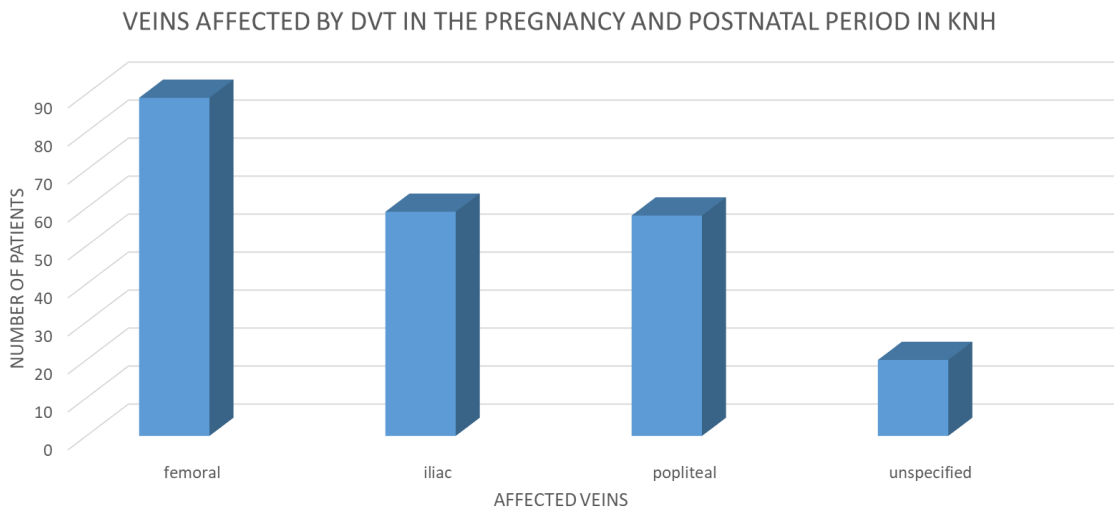


Figure 3: Veins affected by DVT in patients with obstetric VTE at Kenyatta National Hospital between January 2013 and December 2017

All the patients with pulmonary embolism in the study had an imaging modality done to confirm the diagnosis; 6(85.7%) had CT PA while 1(14.2%) was diagnosed through an echocardiogram. The commonest presenting symptoms of PE in the study were chest pain 7(100%) and dyspnea (71.4%) followed by cough, hemoptysis and syncope which occurred in equal frequency. The symptoms of presentation are as summarized in table 7.

Table 7: Presenting symptoms of pulmonary embolism in obstetric patients at Kenyatta National Hospital between Jan 2013 and December 2017 (N=7)

Symptoms of pulmonary embolism(PE)	**n (%)**
Dyspnea	5 (71.4)
Cough	3 (42.9)
Hemoptysis	3 (42.9)
Syncope	3 (42.9)

All the patients who had obstetric VTE during the study period were managed medically with no surgical intervention like embolectomy or IVC filter placement. The classes of drugs used were the LMWH (clexane), UFH (heparin) and VKAs(warfarin).

During the initiation phase of treatment LMWH (clexane) was the most commonly used drug in 75(54.7%) of the cases, UFH used in 60(43.8%) of the cases while 2(1.5%) of the patients received both UFH and LMWH. During the maintenance phase 35(25.5%) of the patients received LMWH while 102(74.5%) received warfarin, this is shown in table 8. In the antenatal period 67.6% of the patients received warfarin in the maintenance phase of treatment while 32.4% received clexane. This is shown in table 9.

For the 5-year study period there was one (0.7%) recorded maternal death.

Table 8: Drugs used in the management of obstetric venous thromboembolism at Kenyatta National Hospital between January 2013 and December 2017 (N=137)

Type of medication used in obstetric VTE	**n (%)**
Initiation phase	
Low Molecular weight Heparin (Clexane)	75 (54.7)
Unfractionated heparin	60 (43.8)
LMWH* & UFH*	2 (1.5)
Maintenance phase	
LMWH*	35 (25.5)
Warfarin	102(74.5)

*Low Molecular Weight Heparin *Unfractionated Heparin

Table 9: Drugs used in the management of venous thromboembolism in the antenatal period at Kenyatta National Hospital between Jan 2013 and Dec 2017 (N=102)

Type of medication	**n(%)**
Initiation phase	
Low Molecular Weight Heparin	70 (68.6)
Unfractionated heparin	32 (31.4)
Maintenance phase	
Warfarin	69 (67.6)
Low molecular weight heparin	33 (32.4)

DISCUSSION

In this first retrospective cohort study conducted at the Kenyatta National Hospital we found the incidence of obstetric VTE to be 1.8/1000 deliveries with the incidence of DVT at 1.6 per 1000 deliveries and that of PE 0.8 per 1000 deliveries. Majority of the obstetric VTE was DVT which accounted for 94.9% of the cases while PE accounted for the rest of the cases. Three quarters of the obstetric VTE cases occurred in the antenatal period while the rest of the cases occurred in the post-natal period. In the antenatal period majority of the cases occurred in the third trimester while in the postpartum period majority of the cases presented in the first two weeks after delivery. The left lower limb was the most affected limb by DVT with pain and swelling being the most common presenting symptoms. The femoral veins and the iliac veins were the commonly involved veins in DVT. In patients who had PE chest pain and dyspnea were the most common presenting symptoms. All the patients were managed medically with LMWH being the most commonly used drug in the initiation phase of treatment while warfarin was the most commonly used drug in the maintenance phase of treatment in both the antenatal and postnatal phase of treatment. There was one recorded maternal mortality in relation to obstetric VTE.

The incidence of obstetric VTE in our study was similar to the global incidence that has been estimated at 1-2 per 1000 deliveries from a meta-analysis and systematic reviews done by Meng K and Kourlaba (11,12). Compared to figures from other countries the incidence in our study was similar to that described by Heit (USA) and Jacobsen (Sweden) at 1-2/1000 pregnancies but lower than that described by Simpson(UK) and Andersen(Denmark)(7,9,24,40). Regionally the incidence was similar to what was reported in Middle Eastern study which placed the incidence between 1-2 per 1000 deliveries(14,24). Compared to the two published studies from Africa that were done in North Sudan the incidence in our study was lower at 180/100,000 cases compared to their incidence of 380-448/100,000 deliveries(18,19). The incidence of DVT in the study was lower than that described in a previous local study done at KNH which found the incidence at 6/1000 deliveries(15), this may be attributed to missing files in our study and probably the low denominator in the previous study as it covered a period of one year.

Majority of the obstetric VTE cases were DVT which accounted for more than 90% of the cases in our study while the rest were PE. This differed from what was reported by James et al who found about 80% of obstetric VTEs to be DVT while the rest were PE(13,16). In the study

conducted this may have been due to under diagnosis of PE in our setting which may be due to under recognition of symptoms and delays experienced carrying out imaging for PE.

More than 70% of obstetric VTE occurred in the antenatal period and the rest in the postnatal period similar to what was reported by Ray JG et al and James AH who found more than two thirds of obstetric VTE occurred in the antenatal period while a third occurred in the postnatal period(6,13). The findings differed from those of Simpson EL et al (London) and Pomp ER who found the incidence of obstetric VTE to be higher in the postpartum period compared to the antenatal period while Anne FJ found the incidence of obstetric VTE to be similar in the antenatal and postnatal period(9,17,24).

In the antenatal period most of the cases presented in the third trimester similar to what was reported by Pomp ER, Jacobsen AF, Meng and Kourlaba which may be due to mechanical compression of the iliac veins by the distended uterus.(11,12,17,24).

Jacobsen(Sweden) and James AH(USA) found more than half of VTE in the postnatal period presented within the 1st two weeks of delivery comparable to what the study found. More than half of the patients presenting during puerperium in the study had delivered vaginally and the rest by caesarean section, differing from studies which found that most of the patients presenting with obstetric VTE in the puerperium had delivered by caesarean section (7,17,24).

Swelling and pain were the commonest presenting symptoms in the study similar to what was reported by James AH et al and Marik PE who found pain and swelling occurred in more than 80% of patients who had DVT (5,7). The left lower limb was the most affected similar to what was reported by two Sudanese studies and a study in KNH (15,18,19). The commonly affected veins were femoral and iliacs similar to what was reported in a meta-analysis by Meng K and a study by Pomp ER(11,17) This is also in keeping with the May-Thurner syndrome(compression of the left common iliac by the right common iliac) that predisposes the left lower limb to DVT during pregnancy(8,14).

In patients who had PE, chest pain and dyspnea were the commonest presenting symptoms while cough, hemoptysis and syncope occurred in equal proportions. The findings differed from what

was reported by Chan WS et al and Gherman RB who in their studies reported dyspnea as the most common symptom followed by chest pain (10,22).

All the patients in the study were managed medically. The use of warfarin in the antenatal period was found to be common in the study with more than half of the patients in the antenatal period receiving warfarin during the maintenance phase of treatment. This is not in line with peer reviewed guidelines which recommend the use of LMWH(clexane) or UFH as they have a better safety profile.(21,31,35) The use of warfarin in the antenatal period in our setting was widespread because of ease of availability, ease of administration(oral compared to clexane which is administered subcutaneously) and warfarin is cheaper compared to LMWH(clexane).

The maternal death reported in the study occurred in the postpartum period in a patient who had multiple comorbidities. There was no documented postmortem report therefore the study could not attribute the cause of death entirely to the VTE.

13.0CONCLUSION

VTE is an important cause of morbidity associated with pregnancy and a high index of suspicion is required in patients presenting with lower limb pain, swelling, chest pain and difficulty in breathing.

Incidence of obstetric VTE is similar to what has been described in other studies

DVT accounted for majority of obstetric VTE similar to what was reported in other studies.

Use of warfarin in the antenatal period is still a common practice in our setting which is not in line with the peer reviewed guidelines.

14.0 RECOMMENDATIONS

A high index of suspicion for VTE should be maintained in a patient presenting with lower limb swelling and pain and/or chest symptoms like chest pain and difficulty in breathing.

There is need for KNH to standardize the management of obstetric VTE to be in line with that in peer reviewed guidelines

There is need for a prospective study with prospective data collection to avoid missing data and records.

There is also need for a prospective case control study to analyze the risk factors for obstetric VTE in our setting.

15.0STUDY TIMELINE

	ACTIVITY	DURATION	TIMELINE
1.	Proposal development	4 months	January- August 2018
2.	Ethical approval	3 months	September 2018 to April 2019
3.	Data collection	1 month	April 2019
4.	Data analysis	1 month	June 2019
5.	Thesis write up	2 months	July 2019
6.	Manuscript development	2 months	August 2019

16.0 BUDGET

	ITEM	UNIT COST KSHS	UNITS	TOTAL COST KSHS
1.	Research assistant per diem	15,000	1	15,000
2.	Printing, photocopying and binding	10,000		10,000
4.	Flash drives and stationery	5000		3,000
5.	Communication/ airtime	1000	2	1,000
6.	Statistician/ data analysis	40000		30,000
7.	Miscellaneous	5000		2,000
	TOTAL COST			61,000

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18.0 APPENDICES

APPENDIX 1: ERC APPROVAL LETTER

APPENDIX 2:DATA COLLECTION TOOL

SERIAL NO.

DEMOGRAPHICS

1. What is the patients age?
2. What is the patient's Marital status?
   - Single
   - Married
   - Divorced
   - Separated
3. What is the patients level of education?
   - None
   - Primary
   - Secondary
   - College/university
4. What is the patients' employment status?
   - None
   - Casual
   - Business
   - Permanent

OBSTETRICS

When was the patients Last Normal menstrualPeriod(LNMP)…… when is the expected due date (EDD)……

What was the Gestation By Dates (GBD)?……

What was the Gestation by Ultrasound (GB U/S) (if a scan was done)?……

What is the patients' Parity?……

What is the patients' gravidity?……

Is the pregnancy a singleton? …. multiple pregnancy……..

What Trimester was the patient in at the time of diagnosis 1st …… 2nd ……. 3rd …….

Did the patient have a previous scar yes…….. no……...

If yes, how many previous scars 1……. 2……. 3……. more than 3…….

ANTENATAL PROFILES

Did the patient have ANC profiles? YES…… NO…….. if yes please indicate the results of the tests done:

1.Hemoglobin levels-

2.Blood group- Rhesus

3.Human immunodeficiency virus (HIV) status- POSITIVE…….. NEGATIVE…….

4.Venereal disease research lab status(VDRL) POSITIVE…… NEGATIVE……

5.Random blood sugar(RBS) value…….

6.Hepatitis b surface antigen (Hep BsAg Positive…….. negative……

7.urinalysis

FOR PATIENTS PRESENTING IN THE POSTPARTUM PERIOD

How many Days after delivery did the patient present?.....

What was the patient's mode of delivery?

- Spontaneous Vertex Delivery(SVD)
- Assisted vaginal delivery
- Emergency Caesarean Section
- Elective Caesarean Section

Where did the patient deliver?

- Kenyatta National Hospital

- Other facility
- Home

CLINICAL PRESENTATION

FOR PATEINTS PRESENTING WITH DEEP VENOUS THROMBOSIS(DVT)

Which Limb was involved?

- Right lower limb
- Left lower limb
- Both

What Symptoms did the patient present with?

- Pain
- Swelling
- Inability to walk
- Difficulty in walking
- Warmth
- Erythema

What examination findings were present?

- Swelling
- Warmth
- Erythema
- tenderness

What was Limb circumference measurements of both the involved and non-involved limb?

- Above knee……
- Below knee…..

What Imaging was done?

- Doppler ultrasound
- Venography
- Magnetic resonance Imaging (MRI)
- Computed pulmonary angiogram (CTPA)

What was the location of thrombus?

- INFERIOR VENA CAVA (IVC)
- Iliac vein
- Femoral vein
- Popliteal vein
- Infrapopliteal veins
- unspecified

FOR PATIENTS PRESENTING WITH PULMONARY EMBOLISM

What symptoms did the patient present with?

- difficulty in breathing
- chest pain
- cough
- haemoptysis
- syncope

What were the examination findings?

- respiratory rate……. below 18……. above 18
- chest expansion equal…… reduced……if reduced indicate the involved side…….
- percussion note……. resonant……dull
- rhonchi present……. Absent……..

- rales present……. Absent…….
- absent breath sounds

Was imaging done? Yes……. No……. If yes indicate which modalities were used and the findings

- Computed Tomography Pulmonary Angiogram (CT P/A)
- Chest X-Ray (CXR)
- Electrocardiograph (ECG)
- Echocardiogram (ECHO)

Where was Location of the clot in the pulmonary circulation?

MANAGEMENT

Was the patient managed medically or surgically?

FOR MEDICAL MANAGEMENT INDICATE THE DRUGS AND DOSAGES USED IN THE TABLE BELOW

DRUG	DOSAGE	DURATION OF TREATMENT	GESTATIONAL AGE AT INITIATION OF TREATMENT
Warfarin			
Unfractionated heparin			
Low molecular weight heparin			

FOR PATIENTS MANAGED SURGICALLY WHAT WAS DONE

- Inferior Vena Cava (IVC) filter placement
- embolectomy

MATERNAL OUTCOMES

- What was the Gestational age at delivery?
- Was the delivery spontaneous or induced?
- What was the Mode of delivery?

  Vaginal delivery

  Assisted vaginal delivery

  c/section…….. for patients who had a c/section what mode of anaesthesia used?

  General anaesthesia yes…… no…….. spinal anaesthesia yes…… no……..
- What was the Outcome of the delivery

  Live birth …… still birth……
- What was the birth weight……. Apgar score……...
- Hemorrhage purpura yes…. no…….
- Thrombocytopenia yes…… no……

Did the patient have Post-partum hemorrhage (PPH) yes…… no……

If yes what was the estimated blood loss

- 500-1000 mls
- 1000- 1500 mls
- More than 1500mls

Was the patient admitted to Intensive Care Unit? Yes……. No…… If yes how long was the duration of stay in the ICU?

FETAL OUTCOMES

What was the birth weight?

What was the APGAR score?

Was the fetus born prematurely? yes…… no…….

Did the neonate have any congenital anomalies? yes…… no……. If yes indicate the anomalies that were present…….

Did the neonate have any bleeding abnormality? Yes…….. no……. If yes indicate the sites

Did the neonate have any Intra ventricular hemorrhage (IVH) yes…… no……...

Was the neonate admitted to the new born unit? Yes……. No…… If yes, what was the length of stay in the NBU?.....