



ST. PAUL'S HOSPITAL MILLENNIUM MEDICAL COLLEGE

**PREGNANCY-RELATED VENOUS THROMBOEMBOLISM:
ASSESSMENT OF PREVALENT PERIOD, ASSOCIATED
FACTORS AND ITS OUTCOME IN ST. PAUL'S HOSPITAL
MILLENNIUM MEDICAL COLLEGE**

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SEPTEMBER 2021

ADDIS ABABA, ETHIOPIA



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List of acronyms and Abbreviations

APS -	Antiphospholipid syndrome
CTPA -	Computed tomographic pulmonary angiography
CUS -	Compression ultrasonography
CVD -	Cardiovascular disease
CVT -	Cerebral venous sinus thrombosis
DVT -	Deep venous thrombosis
INR -	International normalized ratio
HIT -	Heparin-induced thrombocytopenia
HIV/AIDS -	Human Immunodeficiency Virus
LMWH -	Low molecular weight heparin
PTE -	Pulmonary embolism
RCOG -	Royal College of Obstetricians and Gynecologists
RVI -	Retroviral infection
VTE -	Venous thromboembolism
UFH -	Unfractionated heparin
SLE -	Systemic lupus erythematosus
SPHMMC -	St. Paul's Hospital Millennium Medical College

List of tables and figures

List of tables

Table 1: Sociodemographic characteristics of patients, SPHMMC, Addis Ababa, 2021.....	12
Table 2: Medical history of Patient with VTE, SPHMMC, Addis Ababa, 2021.....	13
Table 3: Other risk factors of VTE identified among patients, SPHMMC, Addis Ababa, 2021.....	13
Table 4: Pregnancy information Gravida in number, SPHMMC, Addis Ababa, 2021.....	14
Table 5: Pregnancy information Abortion in number, SPHMMC, Addis Ababa, 2021.....	15
Table 6: Pregnancy information Stillbirth (dead fetus >28 weeks) in number, SPHMMC, Addis Ababa, 2021.....	15
Table 7: Trimester of pregnancy (from LNMP or Obstetric U/S) and VTE diagnosis, SPHMMC, Addis Ababa, 2021.....	17
Table 8: Post-partum who delivered within 6 weeks and VTE diagnosis, SPHMMC, Addis Ababa, 2021.....	18
Table 9: Characteristic of DVT in pregnant and post-partum who delivered within 6 weeks, SPHMMC, Addis Ababa, 2021.....	19
Table 10: Characteristic of PTE in pregnant and post-partum who delivered within 6 weeks, SPHMMC, Addis Ababa, 2021.....	20
Table 11: CVT diagnosed tool in pregnant and post-partum who delivered within 6 weeks, SPHMMC, Addis Ababa, 2021.....	20
Table 12: Management of VTE in pregnancy and the postpartum period, SPHMMC, Addis Ababa, 2021.....	21
Table 13: Management with an oral anticoagulant in pregnancy and the postpartum period, SPHMMC, Addis Ababa, 2021.....	21
Table 14: Management with parenteral anticoagulant in pregnancy and the postpartum period, SPHMMC, Addis Ababa, 2021.....	21
Table 15: Duration of treatment in pregnancy and the postpartum period, SPHMMC, Addis Ababa, 2021.....	22
Table 16: Complication of VTE and management in pregnancy and the postpartum period, SPHMMC, Addis Ababa, 2021.....	23
Table 17: Recurrent VTE in pregnancy and the postpartum period, SPHMMC, Addis Ababa, 2021.....	23

List of figures

Figure 1: Diagnosis of VTE in pregnancy and the postpartum period, SPHMMC, Addis Ababa, 2021...	16
Figure 2: Type of VTE in pregnancy and the postpartum period, SPHMMC, Addis Ababa, 2021.....	16
Figure 3: Diagnosis of VTE & Trimester of pregnancy, SPHMMC, Addis Ababa, 2021.....	17
Figure 4: Diagnosis of VTE & Post-partum period (delivered within 6 weeks), SPHMMC, Addis Ababa, 2021.....	18
Figure 5: Post-partum who delivered within 6 weeks diagnosed with VTE and stay day after delivery, SPHMMC, Addis Ababa, 2021.....	19

List of Appendices

Appendix 1	Questionnaire	31
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Contents

Chapter 1: Introduction	1
1.1. Background	1
1.2. Statement of the problem	2
1.3. Significance of the study	3
Chapter 2: Literature review	4
Chapter 3: Objectives	7
3.1. General objectives	7
3.2. Specific objectives	7
Chapter 4: Methods	8
4.1. Study area and study period	8
4.2. Study design	8
4.3. Source population	8
4.4. Study population	8
4.4.1 Inclusion criteria	8
4.4.2. Exclusion criteria	9
4.5. Sample size and sampling method	9
4.6. Study variables	9
4.7. Data collection method and tool	9
4.8. Operational definitions	10
4.9. Data quality control	11
4.10. Method of statistical analysis	11
4.11. Ethical consideration	11
4.12. Dissemination of results	11
Chapter 5: Results and Discussion	12
5.1. Results	12
5.2. Discussion	24
Chapter 6: Conclusions and recommendations	26
References	27
Annex	30

Abstract

Background: Pregnancy and the puerperium are well-established risk factors for deep vein thrombosis (DVT) and pulmonary embolism (PE), which are collectively referred to as venous thromboembolic disease (VTE). The need for thromboprophylaxis should be assessed antepartum, postpartum, and at any time the patient transitions from the outpatient to the inpatient setting. The clinical features of DVT in pregnancy overlap with many of the features of normal pregnancy. A high index of clinical suspicion and a low threshold for the use of objective confirmatory testing are required to accurately diagnose DVT during pregnancy.

Method: A hospital-based descriptive cross-sectional study was conducted at SPHMMC from September 2017 to February 2021 by using a retrospective chart review of eligible pregnant and postpartum women with VTE having follow-up at the Hematology referral clinic. 84 pregnant and post-partum VTE patients were included, assessment of the prevalent period of VTE, associated factors, and its outcome was done.

Results: The highest prevalent period for VTE was the post-partum period with 51 (60.7%) patients of which 27 (52.9%) modes of delivery were spontaneous vaginal delivery (SVD) and 24 (47.1%) were cesarean sections (C/S), with the day of stay after delivery 3-7 days 38 (74.5%). The most common VTE diagnosed was DVT alone 59 (70.2%), PTE alone 14 (16.7%) then CVT 6 (7.1%) and last is DVT with PTE 5 (6%). All the 64 DVT diagnoses are lower extremity 58 (90.6%) are left extremities while 6 are right extremities. From the 19 PTE diagnoses, 13(68.4%) are mild PTE. The most frequently identified medical history that the patient with VTE had is a history of hypertension 15 (83.3%). Other risk factor for VTE besides pregnancy the most frequently identified risk is preeclampsia 12 (66.7%). Out of 84 patients with VTE 67 (79.7%) completed their management with no complication related to the disease or management.

Conclusions: From this study, the post-partum period which is within 6 weeks after delivery is the high likely prevalent time for VTE to occur and needs careful follow-up. And preeclampsia patients have a high chance to develop VTE as compare to other comorbid conditions. The outcome of VTE in pregnancy from this study is good with appropriate management using anticoagulants for a specific period.

Chapter 1: Introduction

1.1. Background

The risk of venous thromboembolism increases significantly during pregnancy, peaks during the postpartum period, and is one of the leading causes of maternal mortality in developed countries. VTE is the third most common cause of CVD globally ^[1-4] Recommendations for thromboprophylaxis among a large proportion of postpartum women with only one or more "low to moderate" risk factors (such as obesity, cesarean section, and postpartum hemorrhage) are inconsistent across countries^[1].

Venous thromboembolism, including deep vein thrombosis and pulmonary embolism, remains an important cause of maternal mortality and severe maternal morbidity, despite recent advances in thromboprophylaxis. Pulmonary embolism continues to be one of the most common causes of maternal death following childbirth in developed countries ^[2].

In addition to the mortality and short-term morbidity, women who have experienced venous thromboembolism during pregnancy may develop long-term sequelae that are associated with a post-thrombotic syndrome, ranging from edema and skin changes to recurrent thromboses and ulceration ^[1,2].

Pregnant women, in general, are four to five times more likely to develop venous thromboembolism than women who are not pregnant. This predisposition of pregnant women is attributed to the hypercoagulable state of pregnancy that protects women from hemorrhage during miscarriage and delivery ^[2,3]. Venous thromboembolism is both more common and more complex to diagnose in patients who are pregnant than in those who are not pregnant ^[3].

Better quantification of risk factors can help target women who are most likely to benefit from postpartum thromboprophylaxis with heparin ^[1,2,5].

Venous thromboembolism also complicates low-risk pregnancies in the postpartum period, with the risk of VTE being 2.2-fold higher after planned Caesarean section than after planned vaginal delivery ^[2].

The prevalence of deep vein thrombosis (DVT) in Africa varied between 2.4% and 9.6% in postoperative patients and between 380 and 448 per 100 000 births per year in pregnant and postpartum women. The prevalence of VTE and associated mortality are high following surgery, and in pregnant and postpartum women in Africa ^[4].

Two-thirds of cases of deep-vein thrombosis occurred in the antepartum period and were distributed relatively equally among all three trimesters. In contrast, 43 to 60% of pregnancy-related episodes of pulmonary embolism appear to occur in the puerperium ^[3,4]. Delayed diagnosis, delayed or inadequate treatment, and inadequate thromboprophylaxis account for many of the deaths due to venous thromboembolism ^[3-5].

1.2. Statement of the problem

Pregnancy is classically thought to be a hypercoagulable state. Fibrin generation is increased, fibrinolytic activity is decreased, levels of coagulation factors II, VII, VIII, and X are all increased, free protein S levels are decreased, and acquired resistance to activated protein C is common ^[3].

Uncomplicated pregnancy is accompanied by substantial hemostatic activation as indicated by increased markers of coagulation activation, such as prothrombin fragment F1+2 and d-dimer. Also, a reduction in venous flow velocity of approximately 50% occurs in the legs by 25 to 29 weeks of gestation and lasts until approximately 6 weeks after delivery, at which time it returns to normal nonpregnancy flow-velocity rates. In addition, the presence of inherited thrombophilia and the antiphospholipid syndrome, as well as a previous history of thrombosis, increase the risk for venous thromboembolism during pregnancy and the postpartum period ^[1,3,4,6,7].

Additional risk factors include black race, heart disease, sickle cell disease, diabetes, lupus, smoking, multiple pregnancies, age greater than 35 years, obesity, and cesarean delivery ^[2,3,5]

There is a striking predisposition for deep-vein thrombosis to occur in the left leg (approximately 70 to 90% of cases), possibly because of exacerbation of the compressive effects on the left iliac vein due to its being crossed by the right iliac artery.

The incidence of isolated deep-vein thrombosis in the iliac vein is thought to be higher in pregnant women than in nonpregnant women. This complicates the diagnosis of deep-vein thrombosis in symptomatic pregnant women because compression ultrasonography does not reliably detect iliac deep-vein thrombosis.

Isolated iliac-vein thrombosis may present with abdominal pain, back pain, and swelling of the entire leg; however, patients may also be asymptomatic and have no findings on physical examination ^[3,4]

Clinical suspicion is critical for the diagnosis of venous thromboembolism. However, many of the classic signs and symptoms of deep-vein thrombosis and pulmonary embolism, including leg swelling, tachycardia, tachypnea, and dyspnea, may be associated with a normal pregnancy.

Treatment with low-molecular-weight heparin or unfractionated heparin is recommended until the diagnosis is ruled out by objective testing unless treatment is strongly contraindicated.

So far, in our country, despite knowledge related to VTE and its risk factors, poorly known regarding VTE disease related to pregnancy. In light of the paucity of literature, this study will serve as a starting point by filling knowledge gap on pregnancy related VTE.

1.3. Significance of the study

Knowing the characteristic of VTE in pregnancy is an important tool in the early diagnosis and management of the scenario. The diagnosis and management of VTE in pregnancy are challenging, and many diagnostic tests are less accurate in pregnant than non-pregnant patients, and the available options are suboptimal.

Developed countries have promulgated guidelines for risk assessment and prevention of maternal VTE, and standardized management has led to a significant reduction in maternal mortality. However, there is a paucity of relevant research related to pregnancy and puerperal VTE in Ethiopia even at wide-angle in developing countries. This research tries to bump some ideas on the characteristic of pregnancy-related venous thromboembolism.

This study will help in identifying which pregnancy time is highly influenced to have VTE and compare the pregnancy time to the post-partum aspect and tries to see the outcome regarding the management and complication of the disease.

Chapter 2: Literature review

VENOUS THROMBOEMBOLISM AND PREGNANCY

A population-based cohort study, using 30-year data, detected an overall incidence of VTE of 200 per 100,000 women per year. Venous thromboembolism was 5 times more likely in the postpartum period than during the pregnancy, and DVT was 3 times more common than pulmonary embolism [1].

Venous thromboembolism, including deep vein thrombosis and pulmonary embolism, remains an important cause of maternal mortality and severe maternal morbidity, despite recent advances in thromboprophylaxis. Pulmonary embolism continues to be one of the most common causes of maternal death following childbirth in developed countries [1,2]. Pulmonary embolism is 15 times more likely to occur in the postpartum period than during pregnancy. Lower extremities deep venous thrombosis (DVT) during pregnancy occurs at a rate of 0.13-0.61 per thousand pregnancies. The risk of DVT is approximately twice as high after cesarean delivery than vaginal birth [2,4,8].

A population-based cohort study (N = 3,852,569) done in Canada. All women with pregnancy-related hospitalizations in Canada were identified. DVT and PE rates were calculated using the number of hospital deliveries as the denominator for the antepartum and peripartum (labour and delivery) hospitalizations and for postpartum readmissions. Risk factors for DVT/PE were identified using logistic regression. The strongest risk factors for DVT occurrence during the peripartum period were thrombophilia (95% CI 10.8–22.0), a past history of circulatory disease, and major puerperal infection, whereas those for PE were previous DVT (CI 40.9–79.1), heart disease (CI 35.0–53.9), antiphospholipid syndrome, past history of circulatory disease and major puerperal infection [2]

Pregnant and puerperal women face a higher risk for venous thromboembolism (VTE) than that of non-pregnant women due to their specialized physiologic changes, including hypercoagulation, venous stasis, and vascular endothelial injury [2,3].

Venous stasis of the lower extremities occurs during pregnancy because of two factors: pregnancy-associated changes in venous capacitance and compression of large veins by the gravid uterus. The lower extremity veins of pregnant patients appear to be subject to increased stasis even before the

uterus has enlarged substantially. Although blood volume and total venous return are supernormal in pregnancy, the linear flow velocity in the lower extremity veins is decreased due to hormonally induced dilation of capacitance veins, leading to venous pooling and valvular incompetence [3,9,10].

Delivery is associated with vascular injury and changes at the uteroplacental surface, which probably contribute to the increased risk of VTE in the immediate postpartum period. Forceps, vacuum extraction, or surgical delivery can exaggerate vascular intimal injury and amplify this phenomenon as well [11,12].

Pregnancy is a hypercoagulable state associated with progressive increases in several coagulation factors, including factors I, II, VII, VIII, IX, and X, along with a decrease in protein S [11,12]. A progressive increase in resistance to activated protein C is normally observed in the second and third trimesters, and high resistance to activated protein C was shown in one study to be associated with an increased risk for pregnancy-related venous thrombosis. The activity of the fibrinolytic inhibitors PAI-1 and PAI-2 is increased during pregnancy, although total fibrinolytic activity may not be impaired patients [9,11,12].

Compression ultrasonography is a noninvasive test with a sensitivity of 97% and a specificity of 94% for the diagnosis of symptomatic, proximal deep-vein thrombosis in the general population. This test is without risk and is the test of choice in pregnant patients with suspected venous thromboembolism. Compression ultrasonography is less accurate for isolated calf- and iliac-vein thrombosis [3,4].

Patients with suspected pulmonary embolism and normal findings on compression ultrasonography require additional diagnostic imaging. A chest radiograph should be obtained to rule out alternative diagnoses and to guide further diagnostic testing. Ventilation-perfusion lung scanning or computed tomographic pulmonary angiography (CTPA) should be performed [3].

Management of VTE in pregnancy and postpartum period

Current guidelines from the Royal College of Obstetricians and Gynecologists (RCOG) recommend that antenatal pharmacological thromboprophylaxis should be considered in pregnant women during admissions to hospital for stays of three or more days if they also have two or more risk factors [13].

The options for prophylaxis include mechanical methods (e.g. mobilization, compression stockings, calf stimulation, or intermittent pneumatic compression) or pharmacologic agents (low molecular weight heparin [LMWH] and unfractionated heparin [UFH]). Mechanical methods are suitable for women who are at low risk or for those in whom pharmacologic prophylaxis is contraindicated (e.g. acute hemorrhage or impending surgery). Low molecular weight heparin is used in preference to UFH for pharmacologic prophylaxis, and measurement of anti-Xa levels is not required. In the absence of compelling evidence, it seems premature to recommend an increased dose of LMWH for thromboprophylaxis in pregnancy for all women weighing more than 90 kg, but a reasonable threshold for considering higher doses is not clear^[7,14,15].

The preferred agents for anticoagulation in pregnancy are heparin compounds. Neither heparin nor LMWH crosses the placenta, and both are considered safe in pregnancy. Unique aspects of anticoagulation in pregnancy include an increase in maternal blood volume of 40% to 50% and an increase in the volume of distribution. An increase in glomerular filtration results in increased renal excretion of heparin compounds, which are eliminated by this route^[14-16].

During pregnancy, both UFH and LMWH have shorter half-lives and lower peak plasma concentrations, usually necessitating higher doses and more frequent administration^[7,8,17].

Disadvantages of UFH include the necessity of parenteral administration, risk of major bleeding, risk of reduced bone density, risk of vertebral fracture, and risk of heparin-induced thrombocytopenia (HIT). Although the risk of HIT is low in pregnancy and may be lower than in nonpregnant patients the actual risk is unknown^[17].

Cutaneous allergic reactions to low-molecular-weight heparin are rare and include pruritus, urticarial rashes, erythematous plaques, and very rarely, skin necrosis^[18]. These reactions are reported to be more common during long-term use in pregnant women than during short-term use in nonpregnant persons^[17-19].

Warfarin is known to cross the placenta. Warfarin embryopathy is characterized by midface hypoplasia, stippled chondral calcification, scoliosis, short proximal limbs, and short phalanges; it affects 5% of fetuses that are exposed to the drug between 6 and 9 weeks of gestation. The use of warfarin in the second trimester and early in the third trimester is associated with fetal intracranial hemorrhage and schizencephaly^[20].

Chapter 3: Objectives

3.1. General objectives

To describe the characteristics of pregnancy-related venous thromboembolism and its outcome in the hematology unit of the internal medicine department at St. Paul's Hospital Millennium Medical College from September 1/2017 to February 28/2021

3.2. Specific objectives

- To determine the prevalent period for VTE in pregnancy at the hematology unit of the internal medicine department in SPHMMC from September 1/2017 to February 28/2021
- To describe the associated factors for VTE in pregnancy at the hematology unit of the internal medicine department in SPHMMC from September 1/2017 to February 28/2021
- To assess the complications related to VTE in pregnancy at the hematology unit of the internal medicine department in SPHMMC from September 1/2017 to February 28/2021
- To measure the outcome of VTE management in pregnancy and postpartum period at the hematology unit of the internal medicine department in SPHMMC from September 1/2017 to February 28/2021

Chapter 4: Methods

4.1. Study area and study period

The study was conducted in St. Paul's Hospital Millennium Medical College (SPHMMC) located in Addis Ababa, Ethiopia. SPHMMC is a referral and teaching hospital established in 2007 after a medical college was opened in a Hospital built by Emperor Haile Selassie I in 1969 with the help of the German Evangelical Church aiming to serve the poor. It has a catchment population of more than 5 million.

The department of internal medicine has 7 subspecialty clinics. The hematology unit is one of them. Under the hematology unit around 5500 patients per year are seen at the OPD level.

The pregnant and postpartum women who have been seen in hematology unit OPD clinic between September 2017 to February 2021 with a diagnosis of venous thromboembolism (VTE)

4.2. Study design

A descriptive cross-sectional study was conducted.

4.3. Source population

The source population were pregnant women who had VTE during pregnancy and the postpartum period within 6 weeks having a follow up at the hematology unit of internal medicine from September 2017 to February 2021 in the past 3 years and 6 months.

4.4. Study population

The study population were all pregnant women who had VTE during pregnancy and the postpartum period within 6 weeks, aged ≥ 18 years having a follow up at the hematology unit of internal medicine.

4.4.1 Inclusion criteria

The inclusion criteria included

- all aged 18 years and above
- who are diagnosed with VTE (DVT, PTE, or CVT) during pregnancy or within 6 weeks post-partum period and who started treatment and stayed on follow up until the date of accomplishment at the hematology unit.

4.4.2. Exclusion criteria

- Patients with incomplete records and
- patients who lost on follow-up from hematology unit were excluded.

4.5. Sample size and sampling method

The study included all pregnant women who had VTE during pregnancy and the postpartum period within 6 weeks having a follow up at the hematology unit of internal medicine during the study period

4.6. Study variables

VTE include DVT, PE, or CVT in a pregnant woman or postpartum woman who give birth within 6 weeks, sociodemographic variables including (age, gender, race, and marital status), diabetes, obesity, family history of the same disease, smoking, renal disease, mode of delivery, number of parities, number of abortions, preeclampsia, Hyperemesis gravidarum, post-partum hemorrhage, and serology status to HIV/AIDS

4.7. Data collection method and tool

Data gathered was secondary data obtained by using a structured data extraction checklist from the chart review of VTE patients at the hematology unit. The data collection format includes different sections these are socio-demographic characteristics, behavioral assessment, medical history assessment, pregnancy information, trimester of pregnancy (from LNMP or Obstetric U/S), mode of delivery (if post-partum delivered within 6 weeks), stay days after delivery, diagnosis of VTE, other causes of VTE, management of VTE and complication of management

4.8. Operational definitions

The following operational definitions were used in the study.

Proximal deep venous thrombosis (DVT): is located in the popliteal, femoral, or iliac veins.

Isolated distal DVT: is located below the knee, and is confined to the calf veins (peroneal, posterior, anterior tibial, and muscular veins)

Sub massive (or intermediate-risk) PE: refers to those patients with acute PE without systemic hypotension but with evidence of either right ventricle (RV) dysfunction or myocardial necrosis.

Massive (or high-risk) PE: is a term used to designate patients with sustained hypotension, pulselessness, or persistent profound bradycardia.

CVT: Cerebral venous sinus thrombosis is the presence of a blood clot in the dural venous sinuses, which drain blood from the brain.

HIT: Heparin-induced thrombocytopenia (HIT) is a life-threatening complication of exposure to heparin (i.e., unfractionated heparin or low molecular weight heparin/ LMWH)

Targeted INR (Therapeutic INR): an INR ranges from 2.0 to 3.0 for a patient taking warfarin for disorders of blood clots in the body.

Recurrent VTE: DVT or PE occurring after successful acute treatment.

Post-thrombotic syndrome: refers to symptoms and signs of chronic venous insufficiency that develop following deep vein thrombosis (DVT)

4.9. Data quality control

Data was collected by the researcher and data collectors. The data collectors were trained about the contents of the questionnaires and to collect the data compassionately and accurately manner. Immediately after the administration of the questionnaires, each paper was checked for completeness. It was checked again during and after the feeding of data.

4.10. Method of statistical analysis

Different statistical analysis methods were used ranging from frequency count of each variable to estimation of relative frequency, cross-tabulation between variables and descriptive statistical tests including estimation of mean and percentage. Paragraphs, tables, graphs, charts were used to illustrate findings using the statistical package for social sciences (SPSS) software version 25.

4.11. Ethical consideration

Before conducting the research, ethical clearance was obtained from the Institutional Review Board of St. Paul's Hospital Millennium Medical College, and then permission was sought from the school administration through the academic provost of the school to carry out the study. Each data was collected using a structured checklist. The collected data was only use for this particular study and was kept confidential.

4.12. Dissemination of results

At the end of the research, the findings will be distributed to the health care providers, hospital quality control bodies, administrators, policymakers directly affected by the results by publishing the results in a journal and making presentations on a research symposium.

Chapter 5: Results and Discussion

5.1. Results

Out of the 86 questionnaires filled 2 lacks complete records and patients were lost on follow-up from the hematology unit. And therefore, not included in the study. From the questionnaires, all included patients were married and were Ethiopians by nationality. The youngest age was 19, oldest was 38 with a mean age of 28.29 with 46.4% belonging to the 26-30 years age group. 67.9% have attained primary school and 69% were unemployed and 75% live in an urban area as shown in Table 1 below.

Table 1: Sociodemographic characteristics of patients, SPHMMC, Addis Ababa, 2021

Characteristics	Number	Percent
Age Group		
18-20	3	3.6
21-25	23	27.4
26-30	39	46.4
31-35	9	10.7
36-40	10	11.9
Marital status		
Married	84	100.0
Total	84	100.0
Education level		
Illiterate	7	8.3
Primary (1-8th Grade)	57	67.9
Secondary (9-12th Grade)	15	17.9
Higher education	5	6.0
Total	84	100.0
Occupation		
Employed	5	6.0
Unemployed	58	69.0
Private business	21	25.0
Total	84	100.0
Residence		
Urban	63	75.0
Rural	21	25.0
Total	84	100.0

Associated factors for VTE in pregnancy

The most frequently identified medical history that the patient with VTE had is a history of hypertension 15 (83.3%), followed by connective tissue diseases such as SLE 2 (11.1%) and Diabetes 1 (5.6%). There was no medical history of obesity with BMI > 30 Kg per m² and there was no identified behavioral risk factors history of smoking and alcohol consumption. From other risk factors of VTE besides pregnancy the most frequently identified risk factor is preeclampsia 12 (66.7%) followed by RVI 4 (22.2%) and history of Hyperemesis gravidarum and history of renal disease (i.e., Nephrotic syndrome) each 1 (5.6%) respectively. None of the patients have a family history of VTE.

Table 2: Medical history of Patient with VTE, SPHMMC, Addis Ababa, 2021

Diagnosis	Frequency	Percent
Diabetes	1	5.6
Hypertension	15	83.3
Connective tissue disease (i.e., SLE)	2	11.1
Obesity (BMI > 30 Kg per m ²)	0	0
Total	18	100

Table 3: Other risk factors of VTE identified among patients, SPHMMC, Addis Ababa, 2021

Other risk factors of VTE	Frequency	Percent
Air travel history > 8 hr.	0	0
Preeclampsia history	12	66.7
Hyperemesis gravidarum history	1	5.9
Renal disease (i.e., Nephrotic syndrome)	1	5.9
GI disease (i.e., Crohn's disease)	0	0
RVI serostatus Reactive (+)	4	23.5
Family history of VTE	0	0
Total	18	100

The prevalent period for VTE in pregnancy

The maximum number of gravidas a patient had was 7 (3%) while the minimum was 1 (24.2%) also the maximum number of abortions a patient had was 5 (1.2%). There was only 1 (8.3%) stillbirth record in 7 patients.

The highest prevalent period for VTE was the post-partum period with 51 (60.7%) patients with 27 (52.9%) modes of delivery spontaneous vaginal delivery (SVD) and 24 (47.1%) cesarean sections (C/S) with the day of stay after delivery 3-7 days 38 (74.5%) followed by >7 days 9 (17.6%) and < 3 days 4 (7.8%)

The next most prevalent period was the third trimester of pregnancy 28 weeks to 42 weeks with 15 (17.9%) followed by the second trimester 16 weeks to 28 weeks 12 (14.3%) next is the first trimester <16 weeks 4 (4.8%) and last is post-term >42 weeks 2 (2.4%)

The most common VTE diagnosed was DVT alone 59 (70.2%) PTE alone 14 (16.7%) then CVT 6 (7.1%) and last is DVT with PTE 5 (6%). All the 64 DVT diagnoses are lower extremities and 58 (90.6%) are left extremities while 6 (9.4%) are right extremities. 61 (95.3%) are proximal DVT 2 (3.1%) are both proximal and distal DVT and 1 (1.6%) is distal DVT.

All the 19 PTE were diagnosed with either signs and symptoms, ECG or CT-Scan of the chest. From the 19 PTE diagnoses, 13(68.4%) are mild PTE, 4 (21.1%) are submassive PTE and 2 (10.5%) are massive PTE.

Among the 6 CVT diagnoses, 4 (66.7%) were diagnosed using MRI of the brain and 2 (33.3%) were diagnosed using a CT-Scan of the brain. From the 6 CVT patients 5 were diagnosed during post-partum period whom all delivered with C/S and 1 was during third trimester of pregnancy.

Table 4: Pregnancy information Gravida in number, SPHMMC, Addis Ababa, 2021

Gravida in number	Frequency	Percent
1	8	24.2
2	10	30.3
3	6	18.2
4	4	12.1
5	3	9.1
6	1	3.0
7	1	3.0
Total	33	100

Table 5: Pregnancy information Abortion in number, SPHMMC, Addis Ababa, 2021

Abortion in number	Frequency	Percent
0	64	76.2
1	12	14.3
2	5	6.0
3	1	1.2
4	1	1.2
5	1	1.2
Total	84	100

Table 6: Pregnancy information Stillbirth (dead fetus >28 weeks) in number, SPHMMC, Addis Ababa, 2021

Stillbirth (dead fetus >28 weeks) in number	Frequency	Percent
0	77	91.7
1	7	8.3
Total	84	100

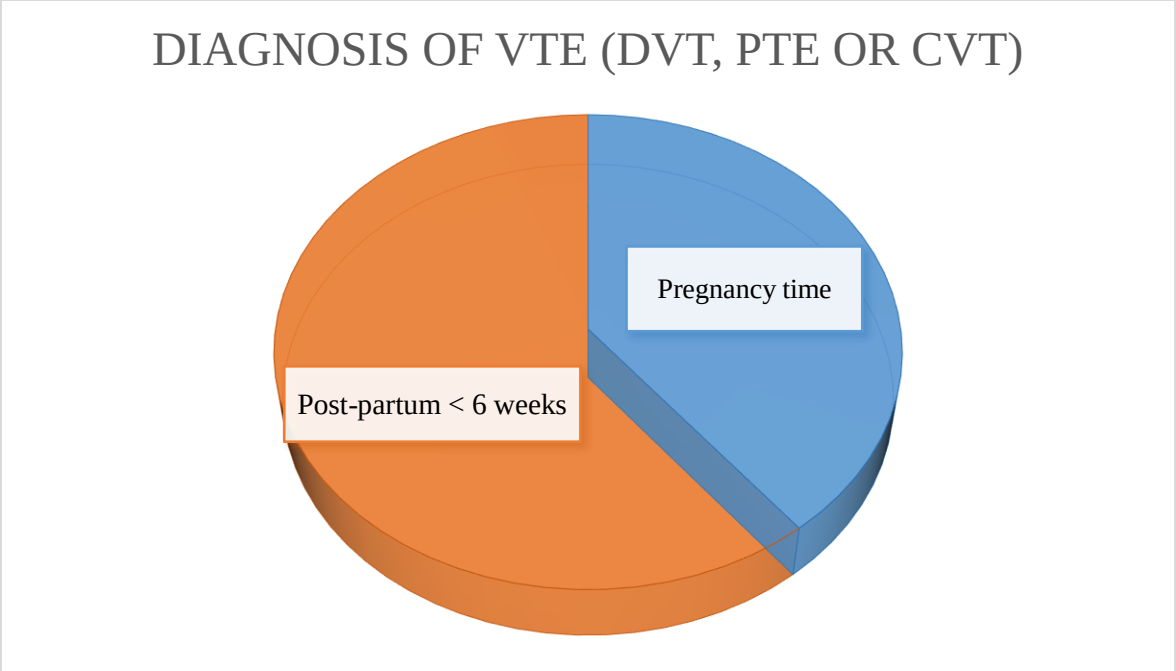


Figure 1: Diagnosis of VTE in pregnancy and postpartum period, SPHMMC, Addis Ababa, 2021

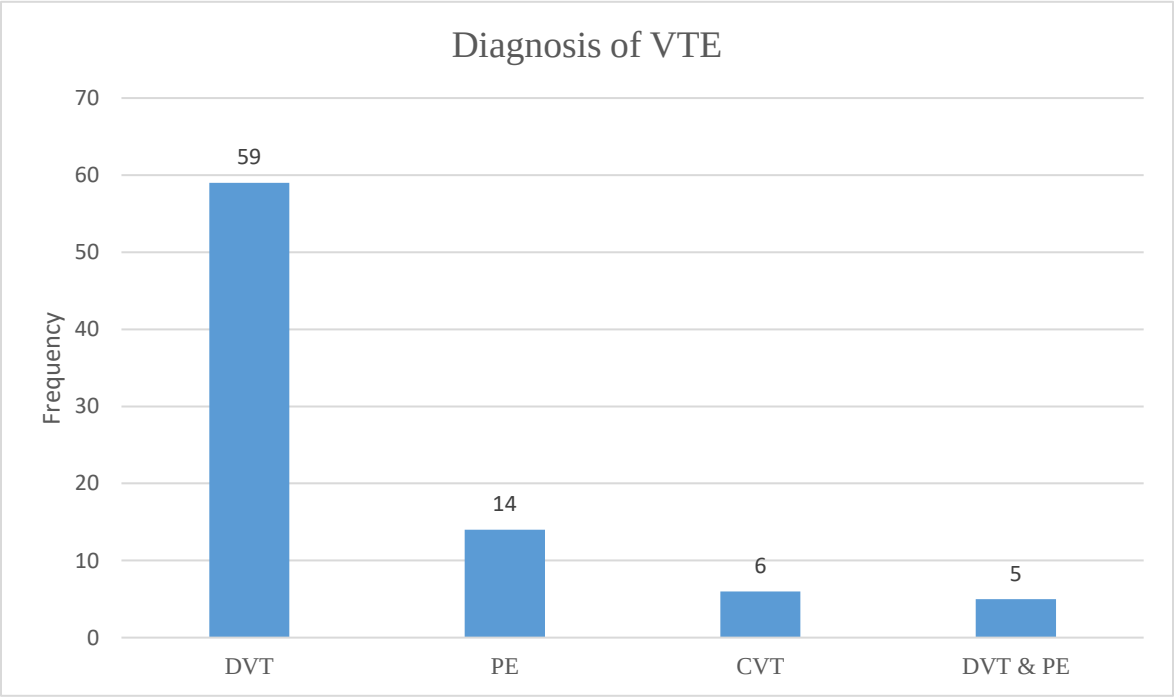


Figure 2: Types of VTE in pregnancy and postpartum period, SPHMMC, Addis Ababa, 2021

Table 7: Trimester of pregnancy (from LNMP or Obstetric U/S) and VTE diagnosis, SPHMMC, Addis Ababa, 2021

		Diagnosis of VTE				
		DVT	PE	CVT	DVT & PE	TOTAL
Trimester of pregnancy (From LNMP or Obstetric U/S)	Less than 16 weeks	3	1	0	0	4
	16 to 28 weeks	10	2	0	0	12
	28 to 42 weeks	8	4	1	2	15
	>42 weeks	0	2	0	0	2
Total		21	9	1	2	33

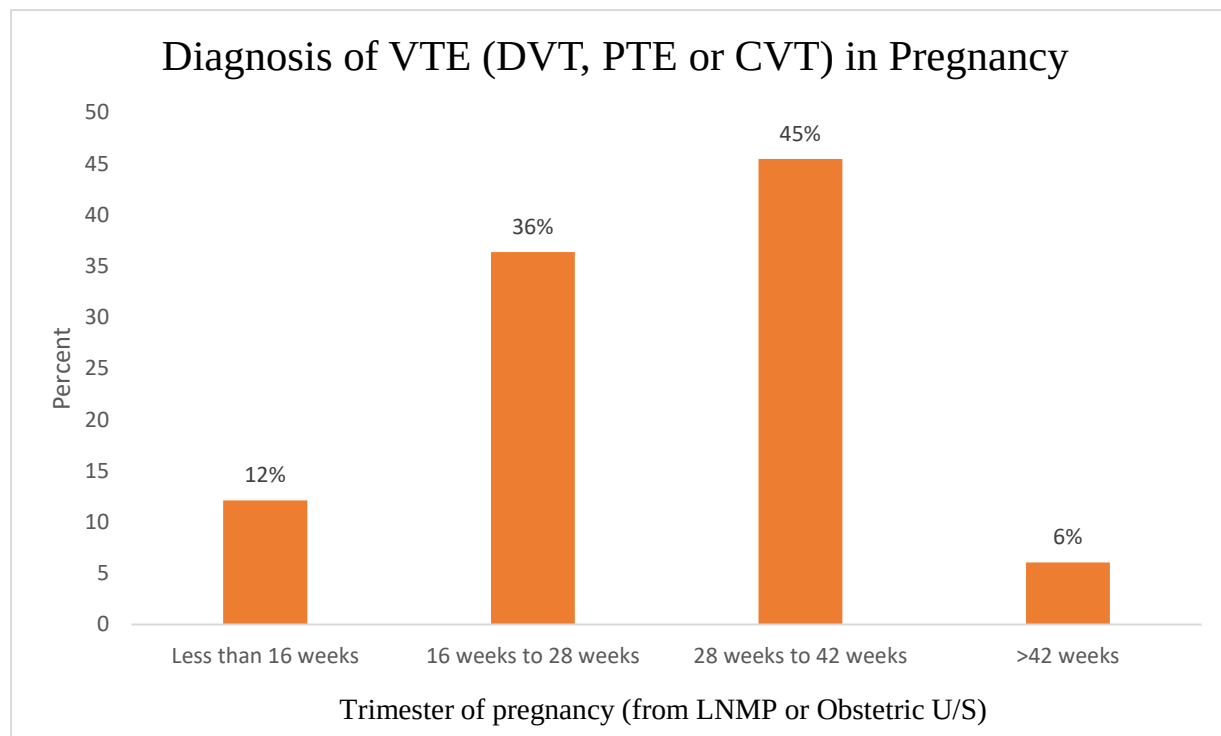


Figure 3: Diagnosis of VTE & Trimester of pregnancy, SPHMMC, Addis Ababa, 2021

Table 8: Post-partum who delivered within 6 weeks and VTE diagnosis, SPHMMC, Addis Ababa, 2021

		Diagnosis of VTE				TOTAL
		DVT	PE	CVT	DVT & PE	
Mode of delivery (If post-partum delivered within 6 weeks)	Spontaneous vaginal delivery (SVD)	24	1	0	2	27
	Cesarean section (C/S)	14	4	5	1	24
Total		38	5	5	3	51

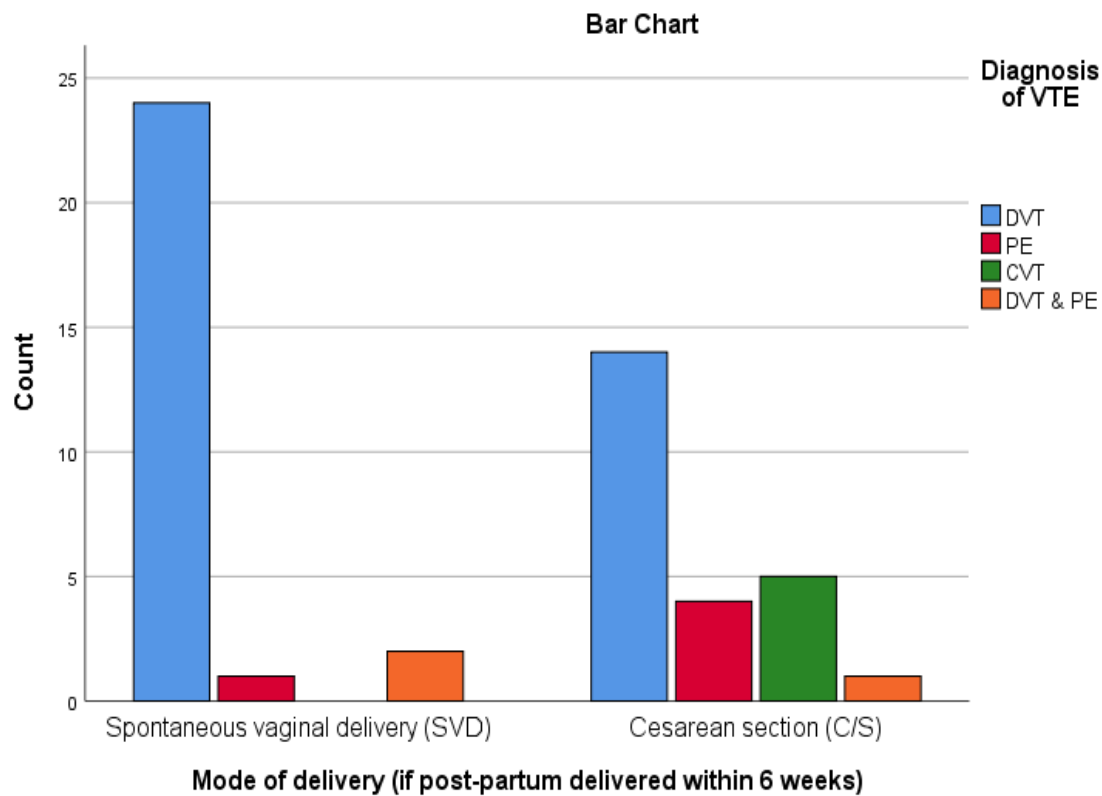


Figure 4: Diagnosis of VTE & Post-partum period (delivered within 6 weeks), SPHMMC, Addis Ababa, 2021

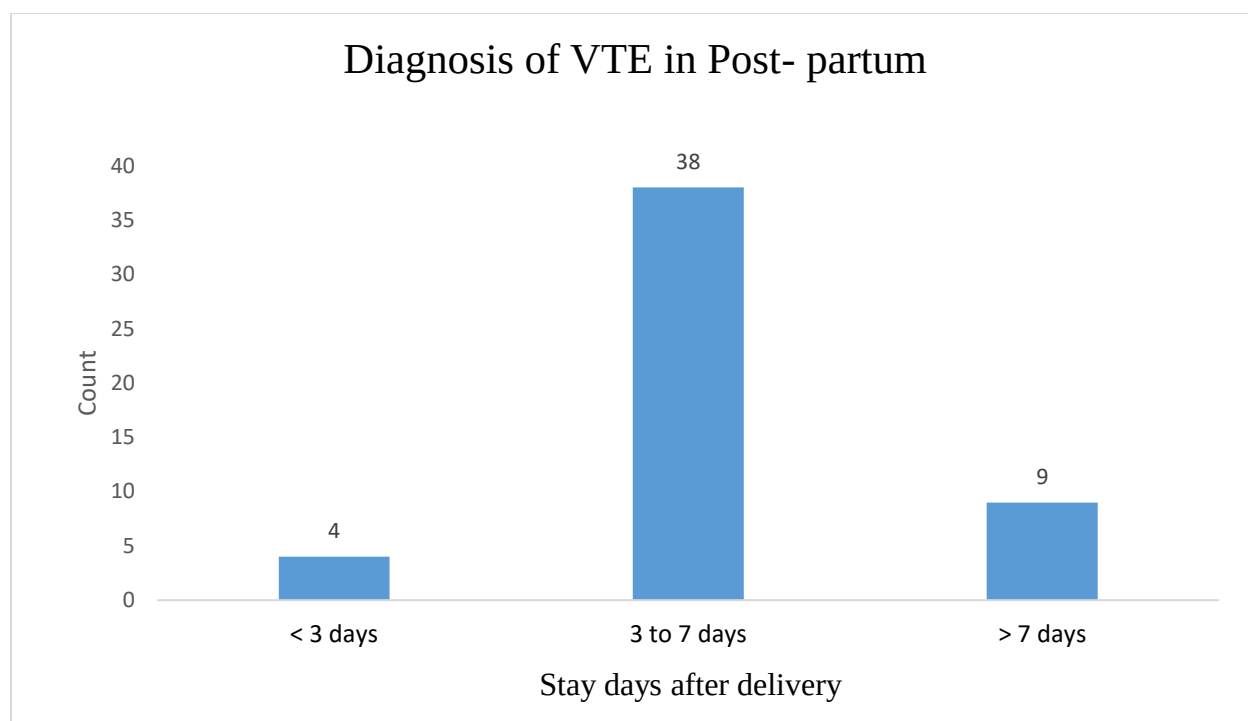


Figure 5: Post-partum who delivered within 6 weeks diagnosed with VTE and stay day after delivery, SPHMMC, Addis Ababa, 2021

Table 9: Characteristic of DVT in pregnant and post-partum who delivered within 6 weeks, SPHMMC, Addis Ababa, 2021

			DVT proximal or distal area			Total
DVT upper or lower extremity			Proximal	Distal	Proximal & Distal	
Lower extremity	DVT left or right extremity	Left extremity	55	1	2	58
		Right extremity	6	0	0	6
	Total		61	1	2	64

Table 10: Characteristic of PTE in pregnant and post-partum who delivered within 6 weeks, SPHMMC, Addis Ababa, 2021

Type of PTE	Frequency	Percent
Mild PTE	13	68.4
Sub massive PTE	4	21.1
Massive PTE	2	10.5
Total	19	100.0

Table 11: CVT diagnosed tool in pregnant and post-partum who delivered within 6 weeks, SPHMMC, Addis Ababa, 2021

CVT diagnosed by	Frequency	Percent
CT-Scan of the brain	2	33.3
MRI of the brain	4	66.7
Total	6	100.0

The outcome of VTE management in pregnancy and postpartum period

Of 84 VTE patients 81 (96.4%) were managed using oral anticoagulant where 79 took warfarin and 2 take new oral anticoagulant which is rivaroxaban. From 84 patients 73 (86.9%) were managed using parenteral anticoagulant 62 took unfractionated heparin (UFH) and 11 took low molecular weighted heparin (LMWH)

Table 12: Management of VTE in pregnancy and the postpartum period, SPHMMC, Addis Ababa, 2021

VTE management	Frequency	Percent
Management with Oral anticoagulant (i.e., Warfarin or NOAC)	81	96.4
Management with a parenteral anticoagulant (i.e., UFH or LMWH)	73	86.9

Table 13: Management with an oral anticoagulant in pregnancy and the postpartum period, SPHMMC, Addis Ababa, 2021

Management with oral anticoagulant	Frequency	Percent
Warfarin	79	97.5
New oral anticoagulant (Rivaroxaban, Apixaban, Edoxaban, etc.)	2	2.5
Total	81	100.0

Table 14: Management with parenteral anticoagulant in pregnancy and the postpartum period, SPHMMC, Addis Ababa, 2021

Management with a parenteral anticoagulant	Frequency	Percent
Unfractionated heparin (UFH)	62	84.9
Low molecular weight heparin (i.e., Enoxaparin)	11	15.1
Total	73	100.0

The most frequent duration of management was 6 months 26 (31%) followed by 7months 20 (23.8%). The maximum duration of treatment is 4 years 4 (4.8%) and the minimum duration of treatment is 4 months 1 (1.2%)

Table 15: Duration of treatment in pregnancy and the postpartum period, SPHMMC, Addis Ababa, 2021

Duration of treatment	Frequency	Percent
4 months	1	1.2
5 months	1	1.2
6 months	26	31
7 months	20	23.8
8 months	8	9.5
9 months	4	4.8
1 year	6	7.1
1 year & 2 months	2	2.4
1 year & 3 months	2	2.4
1 year & 6 months	1	1.2
2 years	2	2.4
2 year & 6 months	1	1.2
3 years	6	7.1
4 years	4	4.8
Total	84	100.0

Out of 84 patients with VTE 67 completed their management with no complications related to the disease or management.

Complications related to VTE in pregnancy and post-partum period

The frequent complication is a recurrence of VTE 12 patients in number and specifically, 8 were DVT diagnosed, 3 were PTE patients and 1 was both DVT and PTE diagnosed. The other complication found was post-thrombotic syndrome (PTS) in 5 patients in which all the patients presented with skin ulceration. There was no complication of heparin-induced thrombocytopenia (HIT) related to management with a parenteral anticoagulant.

Table 16: Complication of VTE and management in pregnancy and postpartum period, SPHMMC, Addis Ababa, 2021

The complication of VTE and management	Frequency	Percentage
Heparin-induced thrombocytopenia (HIT)		
Yes	0	0
No	84	100.0
Post-thrombotic syndrome (PTS) i.e., skin ulceration		
Yes	5	6.0
No	79	94.0
Recurrent VTE (DVT, PTE, CVT)		
Yes	12	14.3
No	72	85.7

Table 17: Recurrent VTE in pregnancy and the postpartum period, SPHMMC, Addis Ababa, 2021

		Recurrent VTE (DVT, PTE, CVT)		
		Yes	No	Total
Diagnosis of VTE	DVT	8	51	59
	PE	3	11	14
	CVT	0	6	6
	DVT & PE	1	4	5
Total		12	72	84

5.2. Discussion

The highest occurrence of post-partum VTE in this study 51 (60.7%) is consistent with other studies which suggest the risk of VTE in pregnancy time reaches its peak in the post-partal period [1-4,11,12]. In this study, the number of patients who delivered by spontaneous vaginal delivery (SVD) 27 (52.9%) and cesarean section (C/S) 24 (47.1%) was nearly comparable, unlike other studies that show more prevalence of VTE is seen in those who undergo C/S [2,4,8]. The day of stay after delivery in most cases was 3-7 days both for SVD and C/S 38 patients and this could be the high likely factor for VTE as support from other studies that bedridden for more than 3 days predispose to VTE [13]. The prevalence of VTE during the time of pregnancy in this study is comparable in third trimester and second trimester 15 (17.9%) and 12 (14.3%) respectively. This study also shows VTE during first trimester 4 (4.8%) and also post-term period 2 (2.4%) similar to other studies that prevalence of VTE is evenly distributed in all trimesters that it could happen in any trimester of pregnancy [3,4].

The most frequent VTE was DVT 59 (70.2%) which is highly prevalent in both pregnancy and post-partum time, unlike other studies in which PTE is most prevalent during the post-partum period. And the left lower proximal extremity 55 was the most common area to occur which is similar compared to other studies [3,4].

All PTE are diagnosed using either sign & symptoms, ECG or CT-Scan of the chest of which the most frequent one is mild PTE 13 (68.4%) compare to studies done in developed countries most common PTE during pregnancy and post-partum period which result increase maternal mortality is massive PTE [1,2].

In this study CVT was also seen in 6 (7.1%) of the VTE in which 5 were post-partum who delivered with C/S and 1 was third trimester pregnant similar to other studies in which CVT is rare but seen in the third trimester of pregnancy and puerperium. In this study, C/S was found to be a risk factor.

Multiple risk factors often co-exist in women who develop VTE in pregnancy in this study most frequent associated medical history was hypertension 15 (83.3%), connective tissue disease which is SLE 2 (11.1%), and diabetes 1 (5.6%) and another frequent factor was preeclampsia 12 (66.7%), RVI seropositive 4 (23.5%), hyperemesis gravidarum 1 (5.9%) and renal disease which is nephrotic syndrome 1 (5.9%). As compared to other studies obesity with BMI >30 Kg per m² was not found to be a risk factor since all of the patients in this study had no documentation of obesity with BMI >30 Kg per m² [2,3,5]. In this study 20 patients with VTE had a history of abortion 1 or more times but were no documented workup for a possible cause such as antiphospholipid syndrome (APS) this may underestimate the possible risk factors in these patients.

In this study, most patients were managed with either oral anticoagulant or parenteral anticoagulant or both and the most frequent duration of time of anticoagulation was 6 months 26 (31%) which is recommended in most studies but some patients were given for prolonged time than the recommendation from other studies.

Among 84 VTE patients in this study 12 had a complication which is a recurrence of VTE specifically 8 were DVT diagnosed, 3 were PTE patients and 1 was both DVT and PTE diagnosed. And 5 had post-thrombotic syndrome (PTS) were presented with skin ulceration. This is similar to other studies that recurrence is the most common complication of VTE in pregnancy^[3,4]. Unlike other studies which show complications related to parenteral anticoagulants such as heparin-induced thrombocytopenia (HIT) in this study no single patient was found to have this complication^[7,8,17]

Strengths

As to the investigator's knowledge, there are no studies done on the subject particularly in internal medicine in general at a country level. It serves as a very important starting point for other institutions and other departments to take initiatives on this important issue.

Limitations

A small number of patients were included in the study and it may not show the general population condition. Wider studies at other hospitals should be done to properly know the magnitude of the problem. A critical limitation of this study was the absence of a control group to compare and contrast the risk factors found in VTE patients. Another risk factor that is common in VTE is inherited thrombophilia such as Factor V Leiden mutation, Antithrombin deficiency, Protein C deficiency, and Protein S deficiency these factors were not assessed in this study.

Chapter 6: Conclusions and recommendations

Conclusions

From this study, the post-partum period which is within 6 weeks after delivery is the high likely prevalent time for VTE to occur and needs careful follow-up. The day of stay after delivery is the other attributing factor in which more than 3 days of stay was seen in the most post-partum period who delivered either SVD or C/S. Another attributing factor was preeclampsia those patients have a high chance to develop VTE as compare to other comorbid conditions.

The outcome of VTE in pregnancy from this study is good with appropriate management using anticoagulants for a specific period. Though there was no standard duration of time used for anticoagulation most patients were given anticoagulants for 6 months. The most common complication in this study was a recurrence of VTE.

Recommendations

- Awareness should be created to physicians and pregnant woman's that there is a risk of developing VTE more during the post-partal period as to this study especially with a day of stay after delivery more than 3 days and those vulnerable groups should have a means of prevention with either mechanical method (e.g., early mobilization, compression stockings, calf stimulation, or intermittent pneumatic compression) or pharmacologic agents (low molecular weight heparin [LMWH] and unfractionated heparin [UFH]) should be given as thromboprophylaxis.
- There should be enhanced risk assessment and documentation on history and workup of possible causes for VTE in pregnancy such as thrombophilia including antiphospholipid syndrome (APS) in selected cases.
- There should be a standard guideline on the management of VTE in pregnancy and the post-partum period. A 6 month of anticoagulation is an appropriate time. This should be the responsibility of healthcare institutions, hospital administrators, quality assurance offices, healthcare consultants, and major regulators like the Ministry of health.

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Annex

Annex 1: The written consent form

How do you do? My name is _____. I am a medical resident. This questionnaire is designed for research work on the characteristics of pregnancy-related venous thromboembolism and its outcome. I want to inform you that you have been selected conveniently for the purpose of the study and you have the right to withdraw from participation at any time during the interview. The information you give will be kept confidential and your name will not be used in the analysis. The fact that you have participated in the study will not interfere with the service you are going to receive here. If you wish to participate in the study, please affirm it with your signature on the area provided below

I place my signature as a sign of agreeing to participate_____

Thank you for your participation and cooperation!

የጥናቱ መግለጫ

ጤና ይስጥልኝ። ይህ መጠይቅ የተዘጋጀው በቅዱስ ጳውሎስ ሚሊኒየም ሜዲካል ኮሌጅ በዉስጥ ደዌ የትምህርት ክፍል ለድህረ ምረቃ ዲግሪ መመረቂያ የደም መርጋት በሽታ ባህሪና አይነት በነፍሠጡር እናቶች እንዲሁም በወላድ እናቶች (የወላድ ጊዚያቸው ከ6 ሳምንት በታች የሆነ) ላይ ለሚደረግ ጥናት ነው። እነዚህን ሁኔታዎች ማወቃችን ችግሩን ለመቀነስ ምን መደረግ እንዳለበት አመለካከት ይሆናል።ክቡር መላሻችን ለጥናቱ የሚረዱ የተለያዩ ጥያቄዎች ይጠየቃሉ።

በዚህ ጥናት ላይ ተሳታፊ እንዲሆኑ የተደረገው የደም መርጋት በሽታ ህመምተኛ በመሆኖ ሲሆን ጥናቱ ላይ የሚሳተፉት ፈቃደኛ ከሆኑ ብቻ ነው። ይህን ቃለ መጠይቅ ሲሞሉ ስምዎን እንዲጽፉ አይፈለግም።በመሆኑም ለሚያደርጉልን ቀና ትብብር በቅድሚያ ከልብ እናመሰግናለን።

የፈቃደኝነት መግለጫ

እኔ የጥናቱ ተሳታፊ የጥናቱን አላማ እና ጥቅም እንዲሁም ከእኔ የሚጠበቁትን ነገሮች ተረድቼአለሁ። ስሜ እና የምሰጣቸው መረጃዎች ለሶስተኛ ወገን ተላልፈው እንደማይሰጡም ተረድቼአለሁ። ስለዚህም በጥናቱ ላይ ለመሳተፍ ፈቃደኛ ነኝ፡

የተሳታፊው ፊርማ _____ ቀን _____

የመረጃ ሰብሳቢው ስም _____ ፊርማ _____ ቀን _____

Section I: Socio-demographic characteristics

Card no. _____ Age _____ Nationality _____

1. Sex: Male ☒ Female ☐

2. Marital status: Single ☐ Married ☐ divorced ☐ widower ☐

3. Educational level:

Illiterate ☐ Primary (1-8th grade) ☐ Secondary (9-12th grade) ☐ Higher education ☐

4. Employment status: Employed ☐ Unemployed ☐ Private business ☐
Retired ☐

5. Area of residence: Urban ☐ Rural ☐

II. behavioral assessment

1. History of smoking ☐ Yes ☐ No
2. If yes, number of packs per year _____
3. History of alcohol consumption ☐ Yes ☐ No
4. If yes, amount of drink per week _____

III. Medical history assessment

1. History of Diabetes (DM) ☐ Yes ☐ No
2. History of Hypertension (HTN) ☐ Yes ☐ No
3. History of Connective tissue disease (i.e. SLE) ☐ Yes ☐ No
4. History of Obesity (BMI > 30 Kg per m²) ☐ Yes ☐ No

IV. Chart review

1. Pregnancy information (each questionnaires' in number)
 - a. Gravida _____
 - b. Para _____
 - c. Abortion _____
 - d. Still birth (dead fetus >28 weeks) _____
2. Trimester of pregnancy (from LNMP or Obstetric U/S)
 - a. Less than 16 weeks
 - b. 16 weeks to 28 weeks
 - c. 28 weeks to 42 weeks
 - d. > 42 weeks
3. Mode of delivery (if post-partum delivered within 6 weeks)
 - A. Spontaneous vaginal delivery (SVD)
 - B. Cesarean section (C/S)
 - C. Assisted Delivery (forceps or vacuum)
4. Stay days after delivery ☐ < 3 days ☐ 3 to 7 days ☐ > 7 days
5. Diagnosis of VTE (can select more than one)
☐ DVT ☐ PE ☐ CVT Other _____
6. If DVT
 - A. Upper extremity ☐ Lower extremity ☐
 - B. Left ☐ Right ☐
 - C. Proximal ☐ Distal ☐
7. If PTE
 - A. Diagnosed by ☐ CT-Scan of chest ☐ ECG ☐ CXR
 ☐ Sign and Symptom Other _____
 - B. Type of PTE
 ☐ Mild ☐ Submassive ☐ Massive
8. CVT Diagnosed by ☐ CT Scan of the brain ☐ MRI of the brain ☐ Other _____

9. Other causes of VTE

- | | | |
|--|---------------------------------------|---|
| A. Air travel history > 8 hr. | ☐ Yes | ☐ No |
| B. Preeclampsia history | ☐ Yes | ☐ No |
| C. Hyperemesis gravidarum history | ☐ Yes | ☐ No |
| D. Renal disease (i.e. Nephrotic syndrome) | ☐ Yes | ☐ No |
| E. GI disease (i.e. Chrons disease) | ☐ Yes | ☐ No |
| F. RVI serostatus | ☐ Reactive (+) | ☐ Non-reactive (-) |
| G. Family history of VTE | ☐ Yes | ☐ No |

10. Management

a. Oral anticoagulant

- ☐ Warfarin
- ☐ New oral anticoagulant (Rivaroxaban, Apixaban, Edoxaban, etc.)

b. Heparin

- ☐ Low molecular weight heparin (i.e. Enoxaparin)
- ☐ Unfractionated Heparin (UFH)

c. Duration of treatment _____

11. Complication of management

- | | | |
|---|------------------------------|-----------------------------|
| A. Heparin-induced thrombocytopenia (HIT) | ☐ Yes | ☐ No |
| B. Skin ulceration or necrosis | ☐ Yes | ☐ No |
| C. Recurrent VTE (DVT or PE or CVT) | ☐ Yes | ☐ No |