Chapter

76

Deep Venous Thrombosis in a Young Woman

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INTRODUCTION

Venous thrombosis is relatively under-diagnosed condition with a potential for significant morbidity and mortality. It is under-diagnosed because in many individuals it may be asymptomatic and the signs and symptoms when present are non-specific. Most episodes of venous thrombosis occur in the deep veins of lower limbs, though venous thrombosis is known to occur at other sites. The morbidity in Deep venous thrombosis (DVT) is related to local effects that may be: (i) immediate such as pain and swelling, (ii) delayed as a result of post-phlebitic syndrome (swelling, skin changes, venous stasis ulcers etc.) or recurrent DVT. However, it is the tendency of these thrombi to embolize into the pulmonary circuit that results in mortality (venous thromboembolism: VTE) as well as significant long-term morbidity in the form of chronic thromboembolic pulmonary hypertension. Treatment with anticoagulants or thrombolytics may itself rarely be the cause of morbidity.

Currently DVT is thought to be a multicausal disease. Though, Virchow had proposed the role of vascular damage, stasis and hypercoagulability of the blood in causing venous thrombosis way back in 1884, our understanding of pathogenesis of these factors and interplay of the genetic and acquired factors has improved tremendously in the last 20-30 years. Moreover, improvements in imaging techniques have improved the recognition of DVT. Venous thrombosis is known to occur in association with both acquired as well as heritable risk factors (Table 1). It may occur in absence of an obvious risk factor I Idiopathic DVT/VTE). Epidemiological studies suggest that DVT occurs in approximately 1/1000 persons per year in the west.

Table 1: Factors predisposing to DVT. Those in bold are important in causation of DVT in young women

Congenital	*Acquired*
Activated protein C resistance (Factor V Leiden)	Increasing age
Antithrombin (AT) deficiency	Cancer
Protein C deficiency	**Pregnancy**
Protein deficiency	**Post operative state/ prolonged immobilization**
Prothrombin G20210A	**Oral contraceptives** and HRT
Hyperhomocysteinemia (MTHFR mutation)	**Antiphospholipid/anticardiolipin antibody syndrome**
Hyper/dysfibrinogenemia	Nephrotic syndrome
Heparin co-factor II deficiency	Myeloproliferative disorders
High concentration of factor VIII	Paroxysmal nocturnal hemoglobinuria
Tissue plasminogen activator deficiency	Hyperhomocystinemia
Factor XII deficiency	High levels of factor VIII
	Heparin induced thrombocytopenia
	Hyperviscosity
	Obesity

Though exact incidence of DVT in Indian context is not known, it is now being recognized to be a significant problem in our hospitals. Incidence of DVT increases with age and spontaneous DVT is relatively uncommon in the young.

DVT IN YOUNG WOMEN

Even though DVT is predominantly a disease of the elderly, it is known to occur in the young, especially

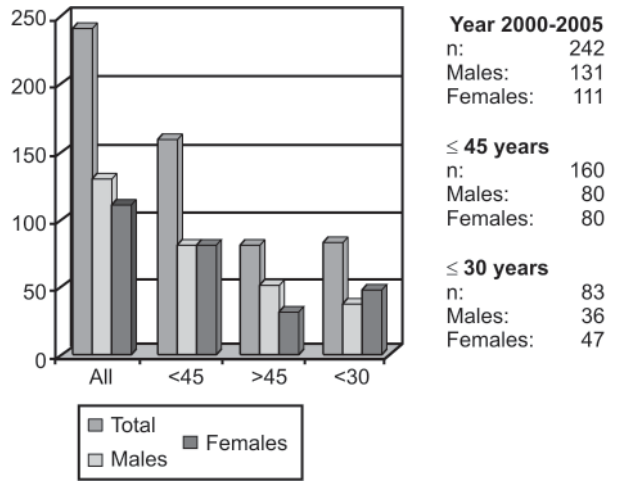

Fig. 1: Unpublished data of adult hematology clinic showing altered male female ratio in DVT patients at age 30 years or less

those with more than one risk factor. The effect of gender has been studied by several investigators. North American studies have shown that males have slightly higher incidence of asymptomatic DVT (RR 1.2-1.4). Males are also known to have higher risk for recurrent DVT. However, females in the child bearing age i.e. young females are at risk for DVT due to hypercoagulable state associated with pregnancy and puerperium or use of hormones as contraception or part of treatment for other associated disease such as carcinoma breast. Thus, a young woman of say thirty years is at an additional risk for developing DVT. Unpublished data of patients followed up in our adult hematology clinic suggest that more women than men had been diagnosed to have DVT at age 30 or less (Fig. 1). Important issues relate to the use of drugs for treatment and prophylaxis, advice about contraception in individuals with history of idiopathic DVT or a strong family history of DVT or that of thrombophilia screen prior to use of oral contraceptives.

PREGNANCY AND DVT

Data from various studies suggest that pregnancy and puerperium are associated with 5 times or more risk of DVT and that VTE resulting in pulmonary embolism remains to be an important cause of maternal mortality in the developed nations. Left sided DVT is more common. Proximal DVT involving ileofemoral system occurs in a greater proportion that may increase the chances of pulmonary thromboembolism. Though absolute risk of clinically significant DVT in pregnancy and puerperium is low, it is estimated in the developed nations that acute ante-partum DVT occurs in approximately 1.2 per one thousand pregnancies above the age of 35 and 0.6 per one thousand below it and that fatality as a consequence of PE occurs in 1 in 100,000 births. Women in the postpartum period are said to be at maximum risk whereas the risk in the first trimester of pregnancy is lower and remains constant for the rest of the pregnancy ®. Data from CDC showed that pulmonary embolism was the cause of death in 20% of all pregnancy related deaths (Rochat et al).

PATHOGENESIS OF DVT IN PREGNANCY AND POSTPARTUM PERIOD

Development of DVT involves all three mechanisms proposed by Virchow. Venous stasis occurs as a result of pressure of gravid uterus and changes in venous capacitance, endothelial injury may play a part during delivery when instrumentation or cesarean section is involved and hypercoagulable state due to a physiological increase in several coagulation factors, such as factors I, II, VII, VIII, IX, and X, along with a decrease in protein S in pregnancy is along with a progressive increase in resistance to activated protein C from the second trimester and an increase in the activity of plasminogen activator inhibitor. Moreover patients with inherited thrombophilic states are at an increased risk. Gerhardt et al reported 6.5 times increased risk in carriers of factor V Leiden and 9.5 fold RR in prothrombin mutations. James et al reported that of medical disorders predisposing to pregnancy-related venous thromboembolism, known thrombophilia had the highest odds ratio (51.8) whereas other conditions included history of thrombosis (OR 24.8), antiphospholipid syndrome (OR 15.8), lupus (OR 8.7)), heart disease OR (7.1), and sickle cell disease, OR (6.7)®.

THROMBOPHILIA AND PREGNANCY OUTCOME

Hereditary thrombophilic states are not only associated with an increased risk of DVT but are also related to poor pregnancy outcomes as has been shown by case control and cohort studies. Though the risk of fetal loss is increased throughout the pregnancy, it is higher in second and third trimesters. Thrombophilia screen is therefore advised in women with 3 or more pregnancy losses in the first and two or more pregnancy losses in the second trimester. In addition intra uterine fetal growth retardation, intra uterine death and eclampsia have been reported to occur with higher frequency. However evidence for higher incidence of eclampsia has not been shown consistently.

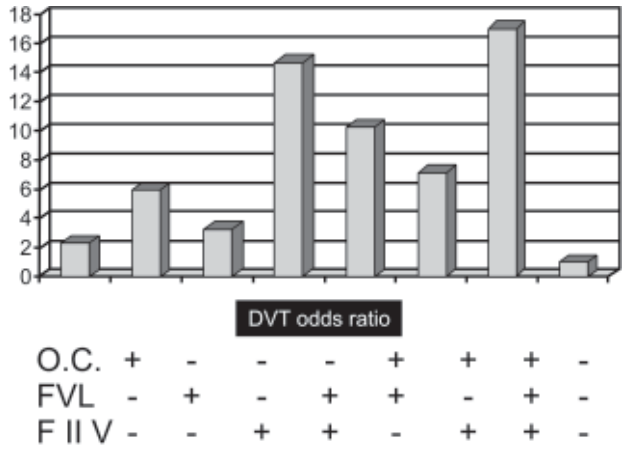

Fig. 2: Odds ratio for the development of DVT with oral contraceptive use in the absence or presence of inherited thrombophilia due to factor V Leiden or prothrombin variant singly or in combination. + denotes presence and – denotes absence of given risk factor. Data adapted from Emmerich, et al. Thromb Hemostasis 2001; 86:809

ORAL CONTRACEPTION AND DVT

Association of oral contraceptives (OCP) with an increased incidence of thromboembolic events has been known ever since their introduction. Oral contraceptives possibly mediate their effects through an increase in procoagulant proteins (prothrombin, factors VII, VIII and fibrinogen), a fall in natural anticoagulants (free protein S and AT) and acquired resistance to activated protein C. The risk in users of third generation OCP has been reported to be approximately twice higher than that in second generation OCP users. OCP used in women with congenital thrombophilia is associated with higher risk of DVT/VTE (Fig. 2). DVT risk in OCP use has been related to estrogen in these pills. Since pregnancy itself carries a risk for DVT in patients with thrombophilic states, if so desired, progesterone only contraceptives (though not completely free of risk) or intra-uterine devices may be used to avoid pregnancy.

THROMBOPHILIA AND IDIOPATHIC DVT IN THE YOUNG

DVT occurring without an inciting event or with a very weak predisposing factor in a young person should raise the suspicion of one or more heritable risk factors for DVT and currently these can be demonstrated in over 50% of such cases. Generally congenital thrombophilic states could either be related to a loss of physiological anticoagulant system (either a qualitative or quantitative deficiency of Protein C, S or antithrombin) or a gain of procoagulant function (activated Protein C resistance as a consequence of Factor V Leiden, increase in factor VIII levels, or Prothrombin variant). Though 'gain in function' thrombophilic states occur more frequently in populations compared to 'loss of function' related thrombophilia, the later are associated with higher relative risk for DVT. A strong family history of VTE is indicative of inherited thrombophilic disorders. Young women could also be at an increased risk for DVT as a result of antiphospholipid syndrome or hyperhomocystinemia either due to an inherited enzyme deficiency or nutritional vitamin B_{12} or folate deficiency. These are also related with higher chances of arterial disease. The indicators of thrombophilia in a young woman are shown in Table 2.

DIAGNOSIS OF DVT/VTE

A detailed discussion on the diagnosis of DVT is out of the scope of this write up. Since the signs and symptoms may be non-specific or DVT in hospital settings may be asymptomatic, a high index of suspicion is needed. Wells et al had suggested the use of a clinical score to determine pretest probability of DVT (Table 3). Diagnosis of venous thrombosis depends upon the territory involved. Most patients present with leg vein thrombosis, which may lead to pulmonary embolism especially with the involvement of proximal leg veins. Clinical signs of pain and limb swelling are unreliable and a high index of suspicion is needed to initiate investigations and treatment. Compression ultrasonography is the initial investigation for the diagnosis of proximal DVT. It can be repeated if the suspicion is high and at times venography either direct or CT/MR venography may be used. Other tests used for the

Table 2: Indications for investigating for thrombophilia in young women

1. Recurrent venous thromboembolism
2. First episode of venous thromboembolism with at least one of the following:
   - Positive family h/o venous thromboembolism
   - Thrombosis at unusual site
   - Massive venous thrombosis
3. In a woman with:
   - Recurrent fetal loss especially second trimester pregnancy loss
   - Severe/ recurrent pre-eclampsia
   - Intrauterine growth restriction
   - Before starting oral contraceptives with family H/O thrombophilia
4. Warfarin induced skin necrosis

diagnosis are impedance plathysmography and D dimer assay. D dimer assay has a high negative predictive value and can be used in the diagnostic algorithm as shown in Table 3. The diagnosis of pulmonary embolism also requires a high index of suspicion. Radionuclide lung imaging, whereever available is the investigation of choice though some patients may have a non-diagnostic scan. Echocardiography, pulmonary angiography, digital subtraction angiography, spiral CT scan and MR imaging can be used whereever indicated. Involvement of other veins like that of upper limb, cerebral or abdominal visceral veins would result in clinical findings related to the area involved.

Various risk factors should be looked for when a diagnosis of venous thrombosis is made. Indicators for thrombophilic states are as shown in Table 2. Recurrent fetal loss has been shown to be related mainly to antiphospholipid antibody syndrome (APLA) and occasionally to the presence of factor V Leiden or deficiency of proteins C and S. Superficial venous thrombosis, coumarin induced skin necrosis and purpura fulminans (in neonates with homozygous defect) are other manifestations of protein C deficiency. Concomitant arterial thrombosis is a feature of APLA syndrome, vasculitis, heparin-induced thrombocytopenia (HIT), hyperhomocystinemia and rarely Protein C deficiency.

MANAGEMENT ISSUES

Treatment of an established episode of DVT or PTE necessitates the use of anticoagulation initially with low molecular weight heparin or unfractionated heparin with use of vitamin K antagonists within 24 hours. Heparin is overlapped for a period of 3-4 days and target INR with oral anticoagulants is between 2 to 3. LMWH has the advantage of ease of use because as opposed to unfractionated heparin mandatory laboratory monitoring is not required. A regular monitoring of INR is required while the patient is receiving oral anticoagulants and appropriate dose adjustments to maintain target INR are needed. Duration of treatment is dependent upon the risk factors. For those with transient risk factors three months of anticoagulation may suffice but for most patients with proximal venous thrombosis at least 6 months of anticoagulation is required. Indefinite anticoagulation is recommended only in patients with hereditary thrombophilia with:

- Two or more spontaneous thrombosis.
- One spontaneous life threatening thrombosis.
- Spontaneous thrombosis at unusual site.
- One spontaneous thrombosis in presence of multiple genetic risk factors.

Table 3: Well's clinical model for predicting pretest probability for DVT and use of pretest probability for diagnostic algorithm

Clinical feature	*Score*
• Active cancer within 6 mo	1
• Paralysis, paresis, or cast of lower extremity	1
• Recently bedridden > 3 d or major surgery within 4 week	1
• Localized tenderness along deep vein system	1
• Calf diameter > 3 cm larger than opposite leg†	1
• Pitting edema	1
• Collateral superficial veins (non-varicose)	1
• Alternative diagnosis as ≥ likely than that of DVT	–2
• †10 cm below the tibial tuberosity	

Score	*Probability*	*Frequency of DVT (%)*	
0	Low	03	
1-2	Medium	17	
≥ 3	High	75	
Score 0-1	D-Dimer estimation		
	Negative		DVT unlikely
	Positive	Compression US	DVT if positive
Score ≥2	Compression US		
	Positive		DVT
	Negative		Repeat 7-14 days

Pregnancy and Puerperium

Since oral anticoagulants are associated with risk of embryopathy, either adjusted dose LMWH or unfractionated heparin through subcutaneous route is preferred in pregnancy. Patients who are on coumadin anticoagulants need to switch to heparin when the pregnancy is diagnosed. The latest ACCP consensus guidelines suggest the following options:

i. Aggressive adjusted-dose unfractionated heparin every 12 hours subcutaneously throughout the pregnancy; heparin to keep the mid-interval aPTT at least twice the control, or an anti-Xa heparin level of 0.35 to 0.70 U/mL. After a stable dose is achieved, the aPTT should be measured at least weekly.

ii. LMWH throughout the pregnancy in doses adjusted according to weight or to keep a four hour postinjection anti-Xa heparin level at approximately 1.0 to 1.2 U/mL.

iii. Heparin therapy as above till the 13th week, a change to warfarin until the middle of the third trimester, followed by unfractionated or low molecular weight heparin till the delivery.

iv. Long-term anticoagulation should be resumed postpartum regardless of the regimen used. In absence of significant bleeding heparin can be restarted 12 hours post-cesarean delivery and 6 hours post-vaginal birth. Heparin may be continued, or replaced with warfarin for six weeks postpartum.

Thrombophilia Screening in Young Women

Routine thrombophilia screening in pregnancy is not advised. However it should be carried out in young patients with unprovoked DVT, a strong family history of DVT in a woman before OCP use, recurrent fetal loss or venous thrombosis at an unusual site.

Conclusions

Venous thrombosis in young women is uncommon but potentially lethal condition. Young women are at higher risk as a result of pregnancy or oral contraceptive related hypercoagulability. It is important to understand the interaction of congenital thrombophilia, use thromboprophylaxis in higher risk groups and treat with heparin in the event of an established episode to minimize the morbidity and mortality.

SUGGESTED READING

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