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Venous Thrombosis could be Gender Specific, Women Beware!

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ABSTRACT

Venous thrombosis (VT) is the third major cause of mortality in the world after heart attack and stroke. Its two major clinical manifestations are deep vein thrombosis (DVT) and pulmonary embolism (PE) which are serious medical conditions but often remain under-diagnosed. Although rate of occurrence of venous thrombosis in men is slightly higher, a number of studies have pointed out that woman poses higher risk of venous thromboembolism (VTE) compared to men at various stages of life. Risk of VTE increases in women's life particularly with use of oral contraceptives, during pregnancy and with exogenous administration of hormones like in post-menopausal hormone therapy. Various reports show that these factors increase risk of DVT and PE by several folds. DVT is considered as an important cause of maternal death in western countries. It is often asymptomatic and its signs and symptoms are similar to those of normal pregnancy. The hormonal changes at various stages of life and less physical activity increase the risk of VTE by blood flow stasis. It is extremely important for women to know the stages of life when they are prone to develop VTE, about its prevention and treatment. Detailed studies on differences in clinical manifestations of VTE between men and women are lacking. This review focusses on assessing the increased risk of VTE and its prognosis in women based on available literature.

Keywords: Venous thromboembolism; Risk factors; Women

1. INTRODUCTION

Venous thromboembolism (VTE) is a complex multi-factorial disease which is fairly common in many populations and has high rate of recurrence. Annual incidence of VTE ranges from 1 per 1000 to 3 per 1000 in normal populations[1]. Recurrence rates of this disease are higher ranging from 3 per cent to 5 per cent, which mostly occurs in close proximity after stopping anti-coagulant treatment[2]. While deep vein thrombosis (DVT) refers to a clot formed in the vein of calf region deep in the leg which can block the flow of blood in the vein, PE present a more serious condition wherein the blood clot breaks off and travels in the lung resulting in sudden cough, tightness in chest with pain and shortness of breath. Pulmonary embolism is a potentially fatal condition and can lead to sudden death of an individual. Approximately 20 per cent - 25 per cent of all PE cases result in sudden death[3].

Although such blood clots can occur in both men and women, there are many reports which cite the reasons of higher incidences of VTE in women. Although the overall rate of VTE incidence is higher in men compared to women, but the rate is significantly increased during the reproductive phase[4]. Women possessing gender specific risk factors show better prognosis of cerebral venous and sinus thrombosis (CVST) compared to men[5]. One recent study from Indian subcontinent revealed higher incidence of cerebral venous thrombosis (CVT) even in non-pregnant women[6]. Life cycle of women is divided into three phases; pre-reproductive, reproductive and post-reproductive phase. They are exposed to several risk factors for VTE pre-disposition in all three stages of life (Fig. 1). Many recent studies have shown the increased occurrence of various clinical manifestations of VTE in women on fertility treatment, during pregnancy and those undergoing hormone replacement therapy. Some of such recent studies and their key findings are as listed in Table 1.

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2. COMMON RISK FACTORS FOR VTE

Venous thrombosis is believed to be a result of complex interaction between genetic and environmental risk factors. Apart from ethnicity and family history, risk of developing VTE increases with age. Risk of VTE increases rapidly after 45-50 years of age and annual incidences rises to 5-6 per 1000 by the age of 80. With advancing age, there is a sharp rise in incidence of PE compared to DVT[7]. Major risk factors apart from age comprise of exogenous factors like surgery, immobility, trauma, long distance travel, hospitalisation etc.[8] and endogenous factors like obesity, cancers, hyper-coagulation and genetically inherited risk factors. Exogenous factors restricted to women include pregnancy, use of oral contraceptives, hormones for infertility, and menopause related problems.

3. GENDER SPECIFIC RISK FACTORS FOR VTE

Influence of age and sex on VTE susceptibility has not been fully established, it has been reported that overall incidences of both DVT and PE markedly increases with age in both men and women[9]. Relatively higher risk of VTE has been

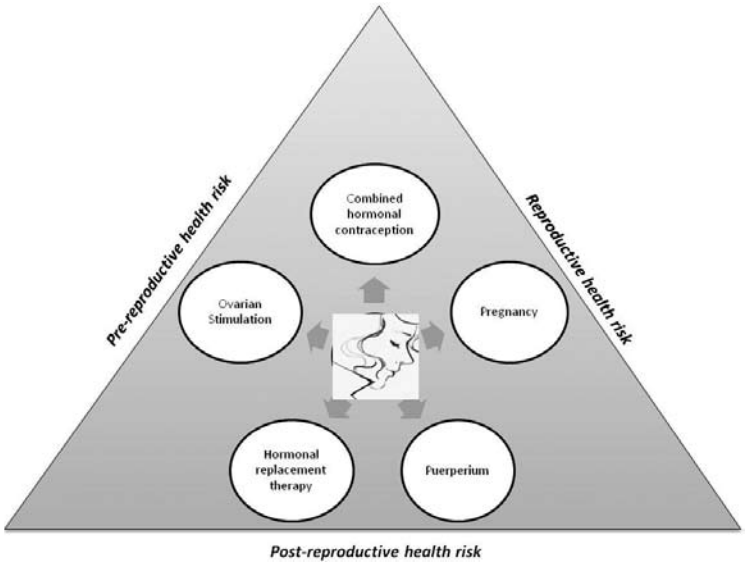

Figure 1. Acquired risk factors for VTE development in women at various stages of life.

Table 1. Major Finding in relation to venous thromboembolism (VTE) and its clinical manifestations (DVT/PE/CVT/SVT)

Key observations	Citation
Incidences of cerebral venous thrombosis (CVT) significantly higher in non-pregnant women	[6]
Higher Cerebral thrombosis and sinus thrombosis (CVST) prognosis in women with gender specific risk factors	[5]
Increase in coagulation factors and reduction in anti-coagulation factors in women during ovarian stimulation	[16]
~10 times higher VTE risk after ovarian stimulation and conceiving through IVF ~100 higher risk of VTE in women conceiving through IVF and developing OHSS	[18]
Incidences of DVT are ~3 fold higher in pregnant women	[19]
Oral Contraceptive users has 6.3 fold increased risk of VTE Oral hormone therapy increase risk by ~4folds	[50]
Relative risk of VTE increases in hormone users with factor V Leiden, prothrombin G20210A or blood group non-O and with family history	[52]

observed in women on oral contraceptives, those undergoing fertility treatment, during pregnancy and post partum period and in those undergoing hormone replacement therapy (as illustrated in Fig. 1).

3.1 Use of Oral Contraceptives

Modern oral contraceptives are very effective. However, use of oral contraceptives may be associated with occurrence of VTE. Use of hormonal oral contraceptives increase the risk of VTE from 5 in 10,000 woman in non-users to 9-10 in 10,000 woman in users[10]. Oral contraceptives were introduced in market as early as in 1960s. These contained high doses of hormones; estrogens and progesterone. First case of PE after use of oral contraceptives was observed in a nurse[11]. After this, several cases of myocardial infarction and ischemic stroke were reported in oral contraceptive users[12].

Levels of estrogen and progesterone hormone content in the drugs affects risk levels. The concentration of procoagulant factors in blood of an individual rise with increase in the levels of hormones. Contraceptives used decades ago had higher doses of estrogens and hence the risk of developing VTE was also higher. Modern available drugs contain <50 µg of ethinyl estradiol and have a lower risk of developing VTE[13]. In a European study, when oral contraceptives (OCs) containing 30 µg ethinyl estradiol was compared with those containing 20 µg, a non-significant decline in VTE was observed[10].

During 1990s, third generation pills having newer progestin component were introduced. They were less androgenic and had fewer adverse effects on cardiovascular system and metabolic activities. Later, regulatory authorities raised a high alert i.e. “pill scare” in 1995 wherein these pills were associated with increased risk of VTE. Followed by this alert, large number of women discontinued OCs and an abrupt rise in births and abortions were noted[14].

Increased risk of VTE has been directly associated with doses of estrogen[15]. Thus, oral contraceptives with lesser doses of estrogen and progestogen have been introduced in the market, which also impose a reduced risk of cardiovascular diseases. Few studies compare risk of VTE development amongst women taking new generation OCs which contain drospirenone compared to those consuming third generation OCs, however the results are not conclusive[10]. Both these studies showed no association between OCs containing drospirenone and VTE compared to other OCs. On the contrary, Lidegaard and co-workers reported a relative risk of 1.6 (95 per cent CI 1.3-2.1) comparing OCs containing drospirenone with OCs containing levonorgestrel[16].

3.2 Ovarian Stimulation

Ovarian stimulation is generally done for treatment of infertility. Women undergoing such treatment are at increased risk of developing venous thrombo-embolism. Infertility treatment also involves the use of combined hormonal contraception (CHC) for down-regulation or estrogen for preparing the endometrium for pregnancy, both of which could contribute to increased risk of venous thrombosis in women[17]. Several studies have been conducted to evaluate the changes that occur in coagulation cascade during ovarian stimulation. It has been demonstrated that the physiological levels of estrogens directly affects hemostasis and is responsible for increase in coagulation factors such as VWF, factor VIII, and fibrinogen. Also, levels of anticoagulant factors such as protein C, protein S and antithrombin reduce with increase in estrogen levels[18]. Rova and co-workers studied risk of VTE development in Swedish women conceiving through IVF. They showed that VTE risk is ~10 folds higher in women conceiving through IVF during first trimester of pregnancy. Venous thrombosis risk is ~100 times higher in women conceiving through IVF and developing ovarian hyperstimulation syndrome (OHSS). In contrast to this, women who conceive through IVF using frozen embryos are not at enhanced risk of VTE[19]. Thus, substantial evidence is

available to conclude that ovarian stimulation increases the risk of venous thromboembolism.

3.3 Pregnancy

Incidences of venous thrombosis are more common in pregnant women compared to non-pregnant women of same age. Pregnancy associated increased risk of venous thrombosis has been reported previously[20]. The incidences of DVT are approx. 0.5 to 1.0 per 1000 live births during prepartum and peripartum[21]. Overall rate of venous thrombosis in women increase during reproductive years compared to men[4]. One of the major causes of maternal mortality in western countries is PE whereas pregnancy associated DVT is the main cause of maternal morbidity[22]. A study in Scotland showed 62 cases of venous thrombosis out of over 72,000 deliveries in Scotland. The risk of venous thrombosis is increased by at least 10 folds during delivery compared to nonpregnant women[23]. During pregnancy, DVT mostly occurs in left leg due to anatomic course of iliac vessels and is distributed equally in the three trimesters[24]. Pregnancy associated risk factors include immobilisation, chorioamnionitis, placental abruption, hypertension, preeclampsia, and fetal growth restriction[25]. Clinicians commonly use D-dimer test for the diagnosis of VTE as it has high sensitivity with moderate specificity and negative predictive values. During pregnancy, the D-dimer levels rise naturally with advancing gestation period and are highest during post natal period. Thus, diagnosis of VTE by D-dimer test during pregnancy is not reliable. Further investigations are needed to diagnose VTE during pregnancy.

3.4 Puerperium

Puerperium is the term given the period that starts from the completion of the third stage of labour upto six weeks after delivery. During this period, body tries to revert the anatomical and physiological changes in the body occurring during nine months of pregnancy. Risk of VTE is maximum in this period. Risk of developing DVT during the puerperium is significantly higher than antepartum[26]. If a pregnant mother suffers from DVT during pregnancy or puerperium, treatment is initiated using low molecular weight heparin (LMWH). This anticoagulant prevents the blood clot from getting bigger and does not harm the developing foetus as it cannot enter placenta. Moreover LMWH is safe for breast feeding mothers. However, the treatment usually lasts for entire pregnancy and puerperium. On the other hand, vitamin K antagonists such as warfarin can pass through placenta easily and thus can have adverse effects on pregnancy, such as miscarriage, premature delivery, low birth weight, developmental problem, neonatal bleeding and characteristic foetal embryopathy. Therefore, warfarin therapy is not recommended for VTE treatment during pregnancy[27] especially during first trimester when organogenesis is occurring as well as during puerperium.

3.5 Hormone Replacement Therapy

Antifibinolytic drugs, such as tranexamic acid, are used for treatment of heavy menstrual bleeding (referred as menorrhagia). These drugs reduce bleeding by inhibition of endometrial clot-dissolving enzymes. Such drugs may possess a risk of developing blood clots in leg and lungs[28] however results are contradictory[29]. Women suffering from menorrhagia are prescribed with tranexamic acid based drugs, which prevent the decomposition of fibrin in clotted blood leading to cessation of further bleeding. This inhibits dissolution of thrombi, thus making them more prone to thrombosis[30,31]. Menopause is marked as end of reproductive period. Postmenopausal hormone replacement therapy is prescribed for the treatment of menopausal symptoms. Estrogens form important part of hormone replacement therapy (HRT); however, their consistent and excessive use can increase risk of endometrial cancer. Therefore, it is often combined with progestin by clinicians. Risk of venous thrombosis is increased by 2 to 4 folds during hormone replacement therapy[32,33]. The risk is further increased in older and overweight women and also those with mutation in factor V Leiden and higher factor IX levels[34]. At the age of menopause, physiological aging occurs which itself is associated with increased plasma levels of blood coagulation factors, platelets and impairment of fibrinolytic mechanism[35]. The relative risk of thrombo-embolic events in women undergoing HRT also depends on dose and type of progestogen used. It has been observed that pregnane derivatives associated risks are higher than nor-testosterone derivatives[36]. In addition to dose, the route of administration affects the relative risk. Oral administration has been associated with higher risk compared to transdermal HRT[37].

3.6 VTE Risk at Menopausal Stage

No independent association between age at menopause and VTE risk has been reported so far. However, early and premature menopause reflects an adverse health status implying an accelerated aging process which involve premature cessation of ovarian activity[38,39]. This early aging process have been associated with increase in the incidences of age-related pathologies including arterial and venous disease[40].

4. RECURRENCE RATE OF VENOUS THROMBOSIS

Venous thrombosis is often fatal and majority of deaths occur amongst those suffering from PE. It has been estimated that around 20 per cent - 25 per cent of PE cases result in sudden death[41]. Venous thrombosis has high rates of recurrence and this is one of its most serious complications. Although men have higher rates of recurrent VTE than women but this sex difference remains unexplained. After completion of anticoagulant therapy following a VTE incidence, the risk of recurrence is highest during first year. Recurrence can occur even after 10 years of initial event and also remains throughout lives[42]. Women undergoing HRT confer a higher risk of recurrent venous thrombosis[43].

5. INCREASE IN VTE INCIDENCES AT HIGH ALTITUDES!

Environment at high altitude wherein the air is thinner and the environment is very cold is itself a stressful condition for the body. A person needs to acclimatise to decreased oxygen availability (hypoxic conditions) and decreased temperature to stay healthy. This process of acclimatisation involved various

physiological and biochemical adaptations to enhance oxygen uptake from oxygen depleted environment and improve tissue delivery. Several independent studies establish that relative risk of occurrence of DVT and PE increases significantly at high altitude[44,45]. Thus, there is substantial evidence in favour of direct relationship between high altitude exposure and a hypercoagulable state, however the mechanism is unclear. Although no reports are available on risk of women developing VTE at high altitudes, however, with limited available evidences, one can presume that women with gender specific risk factors could be at several times higher risk of developing VTE at high altitudes. Thus women using OC's, pregnant women and also those undergoing specific treatments such as ovarian stimulations or HRT should assess the risk before planning for high altitudes expeditions.

6. DVT DIAGNOSIS

Those presenting symptoms of DVT should undergo detailed assessment of risk factors with complete medical history as well as physical examination. The scores obtained after clinical probability algorithms help in categorising a person under low, intermediate or high risk zones[46]. This can further help in disease diagnosis and deciding treatment strategy. Usually clinicians opt for D-dimer test, compression ultrasound for lower extremities and venous ultrasound examination for VTE diagnosis. It is often difficult to diagnose DVT during pregnancy, as the symptoms such as leg swelling, dyspnea and chest pain are otherwise common during pregnancy period. Also, since the D-dimer concentrations increase with gestational age and are particularly raised during post partum period[47], hence this test may give false positive results if used for VTE diagnosis. In such cases, other non-invasive tests such as compression ultrasound examination could be more accurate.

7. SAFETY PRECAUTIONS

Being overweight and leading a sedentary lifestyle increases risk of thrombosis. VTE risk assessment tools should be applied by clinicians to all patients. Formation of unwanted blood clots can be prevented to some extent by taking some easy precautions. These include drinking lots of fluids which keeps the body hydrated and maintains fluidity of blood. Also, wearing loose clothing allows easy movement of body. Intermittent walking and stretching of limbs help keep blood flowing through the veins. Pregnancy safe exercises are highly recommended to avoid incidences of VTE and one should stay as active as possible to avoid incidences of VTE. Heparin and LMWHs are used to treat and prevent VTE during pregnancy. These drugs are considered safe because they do not cross placenta and thus do not enter circulation of the baby in the uterus. The use of Heparin and LMWHs does not cause any birth defects and bleeding problems in the babies[48].

Several reports cited in this review points that women at childbearing age, pregnancy, puerperium and lactation are at increased risk of VTE[49]. Women with a history of thrombosis should be extra precautions and may explore options of family planning. Traditional therapy methods like use of direct oral anticoagulants (DOACs) as well as vitamin K antagonists are often used to treat VTE because of limited advancements in this field. Since risk if VTE increases during HRT[50], bioidentical hormone therapy via the transdermal route has been reported as the safest opportunity for hormone replacement therapy[50,51]. Further studies and trials for more optimal and safer treatment technologies are awaited.

8. SUMMARY

Venous thrombo-embolism is a major health concern that affects millions of individuals every year. It has serious clinical consequences and is potentially fatal. Since, incidences of VTE can be silent and are mostly asymptomatic, public awareness pertaining to the prevention, causes and treatment is important. Women need to have valid information about the risks associated with the use of given oral contraceptives, ovarian stimulation, pregnancy and hormone replacement therapy. Systematic anticoagulation therapy can prevent progression of thrombus and PE.

More comprehensive data and experimental evidences are required to assess and establish the gender specific risks of VTE which could be helpful in its early and accurate diagnosis and treatment. Retrospective searching of large databases could be useful in establishing the links between occurrence of VTE with use of specific formulations of oral contraceptives and hormone replacement.

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