Pregnancy-associated venous thromboembolism

Part I - Deep vein thrombus diagnosis and treatment

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ABSTRACT

يعتبر التجلط الانسدادي الوريدي من الأسباب الرئيسية لوفيات الأمهات في العالم المتقدم. على مدى الـ20 عاماً الماضية كانت هناك زيادة في الإصابة بتجلط وريدي عميق بين النساء الحوامل، وهذه الزيادة يمكن تفسيرها بعدة عوامل بما فيها تقدم السن، الجراحة القيصرية، تاريخ تجلط وريدي، وجود thrombophilia. وللحد من حالات التجلط الوريدي العميق بين النساء الحوامل، وتحسين النتائج، نحتاج إلى فهم أوسع في عوامل الخطر، قدرة أفضل على تحديد النساء المعرضات للخطر من التخثر، وذلك لتوفير التشخيص الامثل وطرق فعالة وآمنة للعلاج. يعتبر التجلط الوريدي العميق والانسداد الرئوي مظهرين من مظاهر المرض نفسه، وغالبا ما يمكن الوقاية منه وعلاجه. وعلى الرغم من ذلك فان التجلط الانسدادي الوريدي لا يزال مشكلة كبيرة على الرغم من الانخفاض الكبير في معدل الوفيات المتعلقة بالحمل في البلدان الصناعية خلال القرن الماضي. وفي حين أن تشخيص التجلط الانسدادي الوريدي في الحمل يعتبر تحدي، والعديد من الاختبارات التشخيصية هي أقل دقة في الحوامل من غير الحوامل، والخيارات المتاحة هي ليست الامثل. يتكون هذا التقرير من جزأين، الجزء الأول: معالجة المسائل التالية في النساء الحوامل: وضع الإصابة بجلطات الأوردة العميقة، وكيفية تشخيص. الجزء الثاني: معالجة النساء الحوامل مع انسداد رئوي، التشخيص، وكيفية العلاج.

Venous thromboembolic (VTE) complications are leading causes of maternal mortality in the developed world. Over the past 20 years, there has been an increase in the incidence of deep venous thrombosis (DVT) in pregnant women, and this increase may be explained by the risk factors including older age, cesarean section, history of VTE, and presence of thrombophilia. To reduce the incidence of VTE in pregnancy and improve the outcomes, a wider understanding of the risk factors, and a better identification of women at risk of the thrombosis, with objective diagnosis and provide the optimal effective and safe treatment. Deep venous thrombosis and pulmonary embolism, considered manifestations of the same disease, are often preventable and usually treatable. Nevertheless, VTE remains a substantial problem despite the dramatic decline in pregnancy-related mortality in industrialized countries over the past century. While 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. This is a review in 2 parts, in part I, we address the following questions: In pregnant women, who developed DVT; how to diagnose, and the treatment once the diagnosis is confirmed. For each of these problems, the relevant background is briefly summarized, approaches recommended, and the suggested practical and relatively safe diagnostic management approaches. Part II, we address pregnant women with pulmonary embolism, how to diagnose and treat.

Saudi Med J 2009; Vol. 30 (1): 13-23

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Venous thromboembolic (VTE) remains the main direct cause of maternal deaths in the developed world,[1] and is also associated with long-term morbidity. Eighty percent of pregnant women with VTE continue to develop post-thrombotic syndrome (leg swelling, skin discoloration, ulcer near the ankles, and varicose vein), and the risk of developing chronic deep venous insufficiency in later life has been estimated to be as high as 65%.[2] Pregnancy and postpartum are well-established risk factors for venous thromboembolism, with estimates of the age-adjusted incidence of VTE

ranging from 4-50 times higher in pregnant versus non-pregnant women, with an absolute incidence rate of one in 500-2000 pregnancies (0.025-0.10%).[3-7] Venous thromboembolic is up 10 times more common in pregnant women than in non-pregnant woman of the same age,[8] and can occur at any stage of pregnancy, but the puerperium is the time of highest risk. Pregnant thrombophilic women are at an increase risk of developing VTE compared to non-thrombophilic women (3-15 fold higher risk).[9] In Saudi Arabia, a 20-year survey at a single institution of all maternal deaths that occurred among 56,422 total births, the second leading cause of death was pulmonary embolism (25%).[10]

Epidemiology of VTE during pregnancy. Venous thromboembolism complicates between one in 500, and one in 2000 pregnancies, and is more common postpartum than ante partum.[3,4,7,11-17] A population-based cohort study, using a 30 year data, detected an overall incidence of VTE of 200 per 100,000 woman per year.[7] 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. This was particularly evident with pulmonary embolism, which was 15 times more likely to occur in the postpartum period than during the pregnancy. Lower extremities deep venous thrombosis (DVT) during pregnancy occur at a rate of 0.13-0.61 per thousand pregnancies.[1,3,4,7] Despite its relatively low incidence, DVT may lead to pulmonary embolism, the most common cause of maternal deaths in the developed countries. In the past, rates of fatal pulmonary embolism were highest in the postpartum period, and the risk of thromboembolism was increased because of medical practices, such as operative (cesarean or instrumental) delivery, prolonged bed rest (most Saudi women still do so) after delivery, and use of estrogens to suppress lactation. Changes with health care practices have reduced the incidence of iatrogenic pulmonary embolism in the puerperium, but DVT still had the same incidence. Meta-analysis studies on DVT during pregnancy and the puerperium,[18] analyzing the period of risk and the leg of presentation, found that the DVT event rate during the first trimester was 21.9%, 33.7% during the second trimester, and 47.6 % for the third trimester. The overall estimated relative distribution of 100 deep vein thrombosis events during pregnancy and the puerperium would be 0.23 per day during pregnancy, and 0.82 per day in the postpartum period. The risk of DVT is approximately twice as high after cesarean delivery than vaginal birth.[14,15] In addition, DVT is more common in the left than the right leg. In one study of 60 pregnant women with a first episode of VTE, there were 58 isolated left lower extremity DVTs, 2 bilateral DVTs, and no isolated right lower extremity DVTs.[11] This striking distribution has been attributed to increased venous stasis in the left leg related to compression of the left iliac vein by the right iliac artery, coupled with compression of the inferior vena cava by the gravid uterus itself.[11,16,17] Pelvic vein DVT is felt to be more likely in pregnancy, perhaps making diagnosis more difficult. In an analysis of the DVT-free registry enrolling 5451 consecutive patients with ultrasound-confirmed DVT, only 1% of all patients had DVT confined to the pelvis, while 12% of pregnant and 11% of postpartum women had isolated pelvic DVT.[19]

Clinical conditions linked with thromboembolism. The postphlebitic syndrome is thought to be the long-term result of DVT in some patients, whether the DVT is symptomatic or asymptomatic, specialists now believe that this syndrome, which is characterized by varicose veins, edema, skin pigmentation, induration and ulceration, is often the result of venous valvular damage sustained during an episode of thrombosis.

The pathogenesis of VTE during pregnancy. Pregnancy and the postpartum period may be marked by the presence of all 3 components of Virchow's triad: venous stasis, endothelial injury, and a hypercoagulable state,[3] all 3 of which are normally present during pregnancy and the puerperium. Inherited or acquired thrombophilias unrelated to pregnancy increase thromboembolic risk.

Stasis. Venous stasis of the lower extremities occurs because of 2 factors: pregnancy-associated changes in venous capacitance, and compression of large veins by the gravid uterus. The lower extremity veins of pregnant patients appear 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, probably due to hormonally induced dilation of capacitance veins, which leads to venous pooling, and valvular incompetence.[20] These early changes are amplified by the inferior vena cava compression by the gravid uterus.[20,21] One study which assessed 24 pregnant women with monthly Doppler ultrasound examinations found progressive dilation of the deep veins of the legs during gestation. This corresponded to a decreased flow velocity in the left common femoral vein and inferior vena cava that was most severe in the supine position. Assuming the left lateral decubitus position significantly increased the velocity in both lower extremities.[21]

Endothelial injury. Delivery is associated with vascular injury and changes at the uteroplacental surface, which probably accounts for the frequency of VTE in

the immediate postpartum period. Forceps, vacuum extraction, or surgical delivery can exaggerate vascular intimal injury, and amplify this phenomenon.[4]

Hypercoagulability. Pregnancy is a hypercoagulable state associated with progressive increases in several coagulation factors, such as factors I, II, VII, VIII, IX, and X, (elevation of factors VII, X, VIII, fibrinogen and von Willebrand factor, which is maximal around term. This is associated with an increase in prothrombin fragments (PF1+2) and thrombin, antithrombin complexes.[22] There is a decrease in physiological anticoagulants manifest by significant reduction in protein S activity.[23,24] A progressive increase in resistance to activated protein C is normally observed in the second and third trimesters.[25] The overall fibrinolytic activity is impaired during pregnancy, but returns rapidly to normal following delivery.[25] This is largely due to placental derived plasminogen activator inhibitor type 2 (PAI-2), which is present in substantial quantities during pregnancy. D-dimer, a specific marker of fibrinolysis resulting from breakdown of cross-linked fibrin polymer by plasmin, increases as pregnancy progresses.[26] Overall, there is a 4-10 fold increased thrombotic risk throughout gestation and the post-partum period.

Ante- and postnatal risk factors of venous thrombosis. The incidence of VTE probably increases from 2-4-folds when a woman becomes pregnant, and is higher after a cesarean delivery than after a vaginal delivery.[27] In 2008, the Multiple Environmental and Genetic Assessment (MEGA) study, evaluated pregnancy, and the postpartum period as risk factors for venous thrombosis in 285 patients, and 857 control subjects. The risk of venous thrombosis was 5-fold increased during pregnancy and 60-fold increased during the first 3 months after delivery, compared with non-pregnant women. The risk of pregnancy-associated venous thrombosis was 52-fold increased in factor V Leiden carriers and 31-fold increased in carriers of the prothrombin 20210A mutation.

A 14-fold increased risk of deep venous thrombosis of the leg was found compared with a 6-fold increased of pulmonary embolism.[28] The risk of VTE in pregnancy is increased in woman with thrombophilic disorders such as the factor V Leiden mutation,[28] the prothrombin gene (20210G>A) mutation,[30] deficiencies of antithrombin, protein C, or protein S,[31-34] and the presence of antiphospholipid antibodies (APLA).[35] The risk factors for VTE during pregnancy and the puerperium have been explored, specifically including age >35 years,[36] multiple pregnancy,[36,37] personal or family history of VTE,[38] obesity, diabetes mellitus,[13,38] assisted reproduction technique (ART),[41] and smoking,[36,37] have been reported to be risk factors for antenatal VTE, whereas blood group A,[13,39] increasing age,[12,36,37] operative delivery[12,35,37] and hypertension,[12,37] premature delivery, or history of cardiac disease has been identified to be risk factors for postnatal venous

Table 1 - Risk factors for deep venous thrombosis

Risk factors
Patient's factors
Age >35 years
Obesity (body mass index >29 kg/m^2) in pregnancy
Thrombophilia
Past history of venous thromboembolic (especially if idiopathic or thrombophilia associated)
Gross varicose veins
Significant current medical problem (namely nephrotic syndrome)
Current infection or inflammatory process (namely active inflammatory bowel disease or tract infection)
Immobility namely bed rest or lower extremity trauma
Paraplegia
Recent long distance travel
Dehydration
Intravenous drug abuse
Recent surgery
Malignancy
Estrogen therapy, ovarian hyperstimulation
Postpartum
Stroke
Pregnancy/obstetric factors
Cesarean section particularly as an emergency in labor
Operative vaginal delivery
Major obstetric hemorrhage
Hyperemesis gravidarum, preeclampsia

thrombosis. The role of immobilization in pregnancy has not been settled,[40-43] although immobilization is a well documented risk factor in the non-pregnant state (Table 1). Until recently hospital-based case-control study found the ante partum immobilization is a risk factor for VT in the pregnancy for both ante-and postpartum VT.[44]

Clinical assessment of suspected DVT during pregnancy. Prompt diagnosis and treatment of DVT in pregnancy can greatly reduce the associated morbidity and mortality. At the same time, one must appreciate that the limited information from the literature of the validity of clinical assessment of suspected DVT in pregnancy, makes the initial evaluation and the diagnostic management of suspected DVT or established venous thrombosis in pregnancy is sparse, with emphasis upon clinical features surrounding the event and the indications for testing, will be discussed as follows: 1) Symptoms: classic symptoms of DVT include leg swelling, leg pain or discomfort (calf, thigh, or buttock), pitting edema, and discoloration (redness, or cyanosis) in the involved extremity, which is commonly found in normal pregnancy. These clinical features are usually not caused by thrombosis; but instead, reflect the physiological changes of pregnancy. It is not necessarily a correlation between the location of symptoms and the site of thrombosis instead symptoms in the calf alone are often the presenting manifestations of significant proximal vein involvement, while some patients with whole leg symptoms are found to have isolated calf vein DVT.

2) Physical examination. The general physical examination may reveal a palpable cord (reflecting a thrombosed vein), ipsilateral edema, warmth, and/or superficial venous dilation. There may be pain and tenderness in the thigh along the course of the major veins (painful deep vein syndrome). Several studies have shown the clinical diagnosis of DVT in pregnancy is unreliable.[45] since the symptoms and findings are often nonspecific. In nonpregnant individuals, DVT is confirmed by objective investigations in approximately 20-30% of suspected cases.[45] In symptomatic pregnant women, DVT appear to be less prevalent than in non-pregnant subjects due to leg symptoms, which is common during pregnancy. One cohort studies, one in pregnant women with suspected DVT[46] reported a prevalence of DVT of 8%.

Conditions can mimic DVT. Differential diagnosis in patients with suspected DVT include a variety of disorders, including musculoskeletal injury and venous insufficiency.[47] The range of disorders that can mimic DVT was illustrated in a study of 160 consecutive patients with suspected DVT who had negative venograms; the following causes of the leg pain were identified:[48] muscle strain, tear, or twisting injury to the leg (40%), leg swelling in a paralyzed limb (9%), lymphangitis or lymph obstruction (7%), venous insufficiency (7%), popliteal (Baker's) cyst (5%), cellulitis (3%), knee abnormality (2%), unknown (26%).

D-Dimer does it help in pregnant women with DVT? D-dimer is a degradation product of cross-linked fibrin blood clot, during pregnancy, D-dimer can be elevated because of the physiological changes in the coagulation system, and levels become abnormal at term and in the postnatal period in most healthy pregnant women.[49] Measuring D-dimer has been extensively studied for the diagnosis of DVT. D-dimer is detectable at levels greater than 500 ng/mL of fibrinogen equivalent units in nearly all patients with venous thromboembolism. However, the finding of elevated D-dimer concentrations alone is insufficient to establish the diagnosis of VTE, because elevated D-dimer levels are not specific for VTE (**Table 2**), and are commonly present in hospitalized patients, particularly the elderly, those with malignancy, recent surgery, and a myriad of other conditions, D-dimer levels increase with gestational age and during complicated pregnancies, such as those associated

Table 2 - Disorders associated with increased plasma levels of fibrin D dimer.

Disorders
Arterial thromboembolic disease
Myocardial infarction
Stroke
Acute limb ischemia
Arterial fibrillation
Intracardiac thrombus
Venous thromboembolic disease
Deep vein thrombosis
Pulmonary embolism
Disseminated intravascular coagulation
Pre-eclampsia and eclampsia
Abnormal fibrinolysis; use of thrombolytic agents
Cardiovascular disease, congestive failure
Severe infection/sepsis/inflammation
Systemic inflammatory response syndrome
Vasoocclusive episode of sickle cell disease
Severe liver disease (decreased clearance)
Malignancy
Renal disease
Nephrotic syndrome (namely renal vein thrombosis)
Acute renal failure
Chronic renal failure and underlying cardiovascular disease
Normal pregnancy

with preterm labor, abruptio placenta, or gestational hypertension.[49,50] These characteristics reduce the tests specificity and are likely to somewhat limit the use of D-dimer testing in pregnancy. D-dimer testing has assumed an increasingly prominent role in the exclusion of acute DVT in the non-pregnant population, but it has not yet been rigorously evaluated in pregnant patients. Therefore, D-dimer assay is in general, and more so in pregnancy, sensitive but non-specific markers for DVT. In summary, we suggest that pregnant women with suspected DVT on the basis of clinical assessment and D-dimer should undergo diagnostic imaging, because anticoagulant treatment of pregnant women with DVT is highly effective but carries significant risks (bleeding, osteoporosis, heparin-induced thrombocytopenia), whereas not treating patients with DVT can result in fatal and nonfatal PE. Therefore, when DVT is suspected, it is essential to diagnose the disease when it is present, and exclude the disease when it is not.

Radiologic investigation. Those with leg symptomatology suggestive of DVT, many objective tests that have been evaluated to confirm the diagnosis of DVT in non-pregnant individuals include contrast venography, compression ultrasonography (CUS), impedance plethysmography (IPG), and magnetic resonance venography (MRV).

1. Impedance plethysmography (IPG). The non-invasive test has been validated in pregnancy. Impedance plethysmography is accurate for the diagnosis of symptomatic occlusive proximal, but not calf DVT in non-pregnant patients. In patients with a normal initial test, serial testing is required (>7 to 14 days) to exclude clinically important, extending thrombi. In pregnant patients with suspected DVT, serial IPG is the only diagnostic approach that was carefully evaluated in a sizable (n=152) cohort study, which demonstrated the safety of withholding anticoagulants if the results were normal.[51] However, IPG has largely been abandoned because the test is less accurate than CUS in non-pregnant patients, and the machines are no longer being manufactured.

2. Compression ultrasonography (CUS). A more direct approach to the diagnosis of DVT involves use of compression ultrasonography. Compression ultrasonography is non-invasive, sensitive, and specific for the diagnosis of proximal DVT in symptomatic non-pregnant patients,[45,52,53] and test of choice in these patients, but insensitive for iliac vein and calf DVT, and not associated with exposure of fetus to radiation. The diagnosis of venous thrombosis using compression ultrasonography is made by the findings such as: abnormal compressibility of the vein abnormal Doppler color flow, the presence of an echogenic band, abnormal change in diameter during the valsalva maneuver.

Venograms are the "gold standard" test for the diagnosis of DVT of the lower extremities,[54] and an adequately performed normal test excludes, calf and proximal DVT.[48] Performance of venography during pregnancy is unpopular due to its painful (needle puncture of vein on the dorsum of the foot), invasive, associated with risk of anaphylaxis or renal failure from exposure to contrast dye, and there is absorption of ionizing radiation by the fetus. As a consequence, venography is not recommended as an initial screening in suspected DVT in pregnant women. However, non-invasive tests with nearly equivalent diagnostic accuracy for DVT have drastically reduced the need for venography. Venography is currently reserved for situations in which ultrasound or impedance plethysmography is not feasible, when non-invasive studies are equivocal, or when non-invasive studies are discordant with a strong clinical impression.

Magnetic resonance venography (MRV). Magnetic resonance venography of the lower extremities appears to be accurate for DVT,[55] MRV had a sensitivity of 100% and a specificity of 96%. Although the usefulness of this test may be limited by cost and lack of accessibility, it has the potential to be useful in pregnancy because it appears to be sensitive for all lower extremity DVT, including calf and ileofemoral DVT, and is not associated with radiation exposure to the fetus.

Adverse effects of radiation exposure in utero. During pregnancy the diagnosis of suspected DVT is problematic because of the fear of fetal exposure to radiation with diagnostic procedures, and the potential adverse effects of in utero radiation exposure on the fetus include oncogenicity and teratogenicity. Comprehensive review reporting the adverse effects after fetal radiation exposure of up to 0.05 Gy (5 rad).[56] Most of the larger studies that examined the association between radiaton exposure in utero and childhood cancer reported a slight increase in the relative risk (ranging from 1.2-2.4),[56] and the absolute risk is likely to be small because the incidence of cancer in the first 10 years of life in the general population is approximately 0.1% thus, doubling the incidence would increase it to approximately 0.2%.[58] The teratogenic potential after in utero radiation exposure had been reported no increase in pregnancy loss, growth retardation, or mental retardation.[56] Minor congenital eye abnormalities and a small increase in the proportion of male offspring have been associated with in utero radiation exposure.[56] The estimates of the doses of absorbed fetal radiation with the procedures used to diagnose DVT were reported (**Table 3**).[56] However, appropriate precautions should be taken, such as lead shielding of the fetus, minimizing fluoroscopy.

Table 3 - Estimated fetal radiation exposure with radiologic procedures.

Radiologic procedures	Estimated fetal radiation exposure, rad
Bilateral venography without abdominal shield	0.628
Unilateral venography without abdominal shield	0.314
Limited venography	<0.05
Pulmonary angiography via femoral route	0.221 – 0.374
Pulmonary angiography via brachial route	< 0.05
Perfusion lung scan using ^{99m}Tc-MAA	
3 mCi	0.018
1 to 2 mCi	0.006 – 0.012
Ventilation lung scan	
Using ^{133}Xe	0.004 – 0.019
Using ^{99m}Tc-DTPA	0.007 – 0.035
Using ^{99m}Tc-SC	0.001 – 0.005
Chest radiograph	< 0.001

Xe - xenon, DTPA - diethylenetriamine penta-acidic acid, Tc, technetium. Adapted from Ginsberg[56]

The best way to diagnose or exclude DVT during pregnancy. Bates and Ginsberg recommend the following steps in the diagnosis of venous thrombosis during pregnancy (**Figure 1**). The initial test for suspected DVT is CUS of the entire proximal venous system to the trifurcation in symptomatic pregnant women. If the initial test shows a clear-cut abnormality in the popliteal or femoral veins, a diagnosis of proximal DVT is made. A normal CUS does not exclude calf DVT, so the test should be repeated 1-2 days after referral (day 2 or 3) and, if normal, again one week later (days 6 to 8), to exclude the possibility of extending calf vein thrombosis. If the test becomes abnormal during repeated testing, acute proximal DVT is likely to be present, and if isolated iliac DVT is suspected (back pain, swelling of the entire leg), the options are available: (1) venography, (2) MRV, or (3) pulsed Doppler and/or direct visualization of the iliac vein. If Doppler is normal or equivocal (small area of non-compressibility in proximal veins or non-compressibility of calf veins), but the clinical suspicion of isolated iliac vein thrombosis is high, we

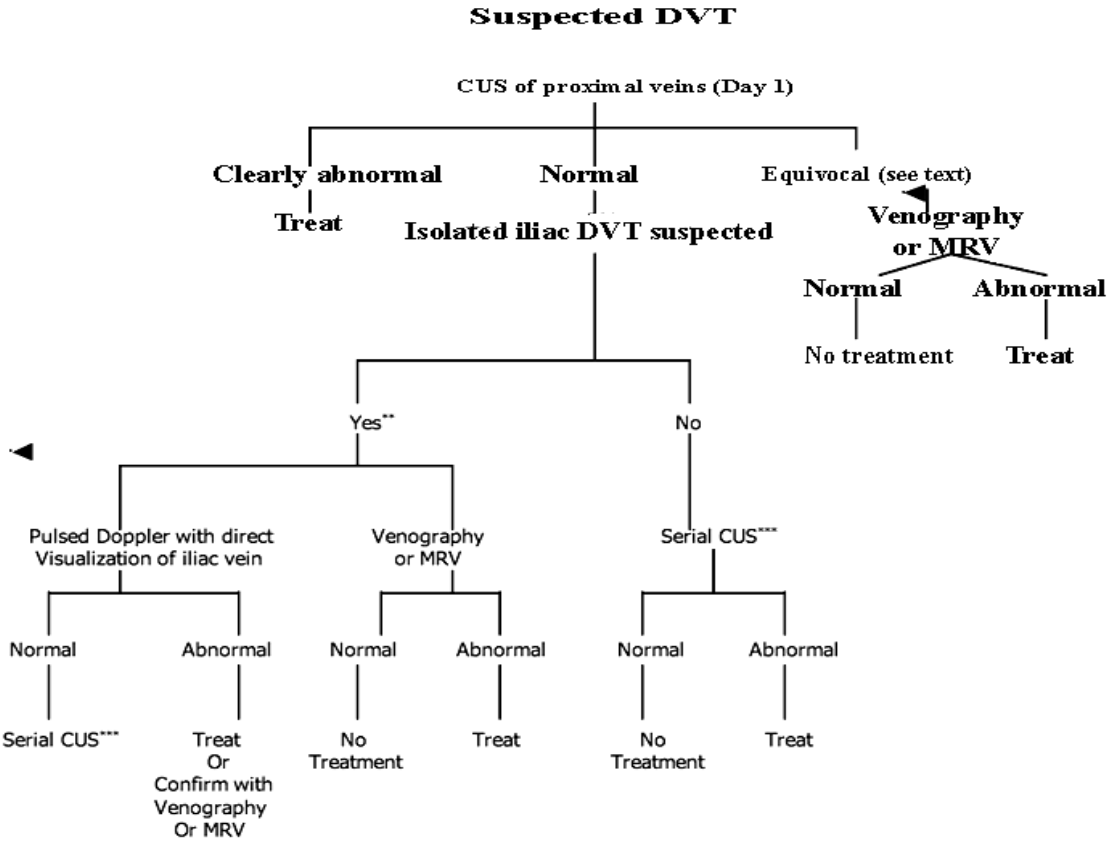

Figure 1 - Algorithm for the investigation of suspected deep venous thrombosis during pregnancy. CUS - compression ultrasonography; MRV - magnetic resonance imaging. *IPG is a suitable substitute for CUS. **D-dimer testing can be performed and, if normal, further testing withheld; if abnormal, investigate further. ***Repeat days 2 and 3 and 6 to 8; if highly suspicious MRV (adapted with permission from Ginsberg).[56]

recommend MRV or a complete venogram (the latter without a lead-lined apron) should be considered in order to make definitive diagnosis. It is highly likely that D-dimer testing will be complementary to venous ultrasonography for excluding DVT in pregnancy when both tests are normal. The safety of withholding anticoagulant therapy in pregnant patients whose serial IPG remains normal has been demonstrated in a cohort study,[51] and this test is a suitable alternative to CUS, but it is unavailable in most centers.

The appropriate initial therapy for DVT during pregnancy. Over the past 2 decades, there has been considerable changes in the management of venous thromboembolism in non-pregnant patients, while the therapeutic option in pregnancy are limited, the primary objective in the treatment of DVT is to prevent further clot extension, acute PE, recurrence of thrombosis, as well as, limiting the development of late complications, such as the post phlebitic syndrome, chronic thromboembolic pulmonary hypertension, and chronic venous insufficiency. In a clinically suspected DVT, treatment should be given until the diagnosis is excluded by objective testing, unless treatment is strongly contra-indicated.[59] Anticoagulant therapy is indicated for patients with symptomatic proximal lower extremity DVT, since pulmonary embolism will occur in approximately 50% of untreated individuals, most often within days or weeks of the event.[60,61] A mortality rate of <5% should be achieved with the use of anticoagulation therapy.

Baseline investigation. Before anticoagulant therapy is commenced, baseline investigation should be performed, blood sample should be taken for a full blood count, coagulation screen, urea and electrolytes and liver function tests.

Anti-coagulant therapy during pregnancy. Developing VTE during pregnancy require special attention, and should be referred to a specialize center. Safety is most important when treating pregnant women, and there are 2 therapeutic options, unfractional (UFH) and low molecular weight heparin (LMWH); they do not cross the placenta, and is not secreted into the breast milk, and can be safely given to nursing mothers.[62] Recently the American College of Chest Physicians Guidelines suggests alternative anticoagulants rather than pentasaccharides.[82] The risk of bleeding in the mother with UFH or LMWH is low and does not appear to be different from that reported in non-pregnant patients.[83]

Unfractionated heparin (UFH). The anticoagulant response to a standard dose of unfractionated heparin varies widely among patients, thus relation between the aPTT and the level of heparin differs in pregnant, compared non-pregnant patients. This makes it necessary to monitor the response, using either the activated partial thromboplastin time (aPTT) or heparin levels, and to titrate the dose to the individual patient.[63,64] During pregnancy, the aPTT response to heparin is often attenuated because of increased levels of factor VIII and fibrinogen.[84] Experimental studies and clinical trials have established that the efficacy of heparin therapy depends upon achieving a critical therapeutic level of heparin within the first 24 hours of treatment, usually via a continuous heparin infusion.[62-70] The critical therapeutic level of heparin, as measured by the aPTT, is 1.5 times the mean of the control value or the upper limit of the normal aPTT range, with a target range (aPTT ratio) of 1.5-2.5. For patients receiving UFH, ACCP Guidelines[82] suggests that platelet counts be obtained regularly, to monitor for the development of thrombocytopenia. The frequency and timing of such counts depends on the clinical situation. The heparin product should be stopped if any one of the following occurs, 50% in the platelet count, or a platelet count <100,000/microL.

Low molecular weight heparin. Low molecular weight heparin has been evaluated for the initial treatment of DVT by several clinical trials both in Europe and in North America.[71-78] Low molecular weight heparin is as effective and safe as UFH, and have a number of advantages over UFH.[79] (i) Greater bioavailability when given by subcutaneous injection. (ii) Duration of the anticoagulant effect is greater, permitting once or twice daily administration. (iii) Anticoagulant response (anti-Xa activity) is highly correlated with body weight, permitting administration of a fixed dose.

A meta-analysis of 11 randomized trials also has been published,[80] with a high degree of consistency, LMWH given in a fixed dose per kilogram subcutaneously either once or twice daily[81] was as effective as continuous intravenous UFH for the initial treatment of patients with proximal vein thrombosis.

Maternal complications of anticoagulant therapy during pregnancy. The maternal complications of anticoagulant therapy taking during pregnancy include hemorrahge, osteoporosis, thrombocytopenia, and allergy. With UFH, the rates of complication are more than LMWH. a) Major bleeding in pregnant patients is 2%;[86] bleeding complication appeared to be very uncommon with LMWH.[87] b) Heparin-induce osteoporosis is a significant problem with long-term UFH, through decreasing rates of bone formation and increased bone resorption.[88] In patients receiving long-term UFH, symptomatic vertebral fractures occur in about 2-3%, and significant reductions in bone density have been reported in up to 30%.[89,90] Low molecular weight heparin administered during pregnancy had no significant effect on bone mineral density, yet LMWH

has been reported to cause osteoporosis and vertebral fracture.[91] Heparin-induce thrombocytopenia (HIT) is approximately 3% of non-pregnant patient receiving UFH, which is frequently complicated by extension of preexisting venous thrombosis or the development of new arterial thrombosis. This should be differentiated from an early, transient, benign thrombocytopenia that can occur with initiation of UFH when used with LMWH, the incidence of HIT is much lower.[92] Heparin-induce thrombocytopenia should be suspected when the platelet count falls to less than 100x10 or to 50% of the baseline value 5-15 days after commencing heparin or sooner with recent exposure to heparin.[92]

The recommendations from the Eight ACCP Conference.[82] The treatment of VTE during pregnancy in women with acute VTE, either adjusted- dose LMWH throughout pregnancy or IV UFH (bolus followed by a continuous infusion to maintain the aPTT in the therapeutic range or subcutaneous therapy adjusted to maintain aPTT 6 hours after injection) for at least 5 days, followed by adjusted-dose UFH or LMWH for the remainder of the pregnancy into in therapeutic aPTT range) for at least 5 days (Grade 1a), followed by adjusted-dose UFH or LMWH for the remainder of the pregnancy (Grade 1b).

In women receiving adjusted-dose LMWH or UFH therapy, it is recommended to discontinue the heparin 24 h prior the elective induction of labor (Grade 1c).[82] Warfrain can be used after the delivery since it is safe for the breast-fed infant of a warfarin mother. Screening for underlying thrombophilia is also suggested.

Management during labor and delivery. In an attempt to minimize bleeding complications at the time of delivery (including epidural hematoma formation during neuraxial anesthesia), heparin therapy treatment should be discontinued, 24 hours prior to elective induction of labor, or delivery cesarean section. If spontaneous labor occurs, the woman should be advised that she should not inject any further heparin until she has been clinically assessed. If the woman is in labor and she has been administering UFH, then monitoring of the aPTT should be performed, and protamine sulphate may be given to reverse the heparin's anticoagulant effect, if required. A similar strategy has been proposed for the management of LMWH therapy during labor and caesarean section delivery, however, the anticoagulant effects of LMWH are not fully reversed with protamine sulphate.[94] Similarly, if the woman is deemed to have a very high risk of recurrent VTE women (namely women with recent VTE <4 weeks, a VTE diagnosed near term,) then IV UFH can be initiated and discontinued 4-6 hours anticipated time of delivery, [57] in order to limit the duration of time without therapeutic anticoagulation. Some clinicians have proposed that in this situation, consideration should be given to the insertion of a temporary IVC filter, and a planned induction of labor after reversal anticoagulation.[8,82] We as clinicians are hampered by lack of specific evidence to guide the management of suspected and confirmed the diagnosis of VTE in pregnancy. Further research and randomized control trials are required to validate all VTE treatment approaches as well as to make evidence-based recommendations in this area.

Practical points. a) In clinically suspected DVT treatment with LMWH or standard heparin should begin immediately until the diagnosis is excluded or confirmed by objective testing, unless treatment is strongly contraindicated. If timely diagnostic imaging is available, therapy can be withheld. b) In women with objectively diagnosis acute DVT, start either adjusted-dose LMWH throughout pregnancy or IV UFH (bolus followed by a continuous infusion to maintain the aPTT in the therapeutic range) for at least 5 days, followed by adjusted- dose UFH or LMWH for the remainder of the pregnancy. c) Warfarin should be avoided in pregnancy. d) Discontinuing LMWH or UFH therapy 24-hours prior to elective induction. e) In high risk women, namely women with recent VTE within 4 weeks, IV UFH therapeutic doses can be given and stopped 4-6 hours prior to the anticipated time of delivery. f) Anticoagulation should not be interrupted without IVC filter protection in the first 4 weeks after VTE diagnosis. g) When spontaneous labor occurs while the she is receiving adjusted- doses subcutaneous UFH, careful monitoring of the aPTT and if it is prolonged near delivery, protamine sulfate may be required to reduce the risk of bleeding. h) When spontaneous labor occurs while she is receiving LMWH, if there is a significant anticoagulant effect present or if anti-factor Xa level show an anticoagulant effect, several precautions should be taken: (i) epidural analgesia should be avoided for at least 24 hours after the last dose of LMWH, (ii) protamine sulfate should be considered, (iii) the obstetrician should be made aware of the potential for bleeding, (iv) inferior vena cava filters are indicated in woman who has a contraindication to anticoagulants, (v) anticoagulants should be administered for at least 6 weeks postpartum,[82] (vi) the epidural catheter should not be removed within 12 hours of the most recent injection,[59] (vii) LMWH should not be given for at least more than 4 hours after the epidural catheter has been removed, if safe to do so,[59] (viii) warfarin can be used after the delivery since it is safe for the breast-fed infant of a warfrain, (ix) post-partum warfarin should be avoided until at least the third day and no longer in

women at increased risk of post-partum hemorrhage. (x) Therapeutic anticoagulation therapy should be continued for the duration of the pregnancy and for at least 6 weeks postnatally, and until at least 3 months of treatment has been given in total and (xi) screening for underlying thrombophilia is also suggested.

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