Peripartum anesthetic management of parturient receiving anticoagulants

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Abstract

Classically, common therapies for thromboprophylaxis among pregnant females are heparin (either unfractionated and or low molecular weight heparin), vitamin K antagonists and antiplatelets. Recently, newer agents have been introduced into practice including danaporoids, direct thrombin inhibitors and fondaparinux. It should be noted that choice of antithrombotic agent during pregnancy is primarily based upon efficacy of antithrombotic agent to reduce maternal morbidity and mortality risks for associated condition with pregnancy and at the same time possess no or minimal inadvertent fetal and maternal complication. Unfractionated heparin has been used for decades for many indications during pregnancy. It is a large molecule, so it does not cross the placenta and thus, in contrast to the coumarin derivatives, does not cause teratogenesis or toxic fetal effects. Over the last 10 years LMWHs have become the preferred anticoagulants for treating and preventing thromboembolism in all patients. While comparative data are much less robust in pregnant patients, several series have confirmed the safety and efficacy of LMWHs in pregnancy.

Key word: VTE, APLAs, LMWHs, DVT, anticoagulants

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List of abbreviations

(ACCP)	American college of chest physicians
(APLAs)	Antiphospholipid antibodies
(ASRA)	American Society of Regional Anesthesia
(ATIII)	Anti-thrombin III
(BMI)	Body mass index
(CNB)	Centeral neuro axial block
(CrCl)	Creatinine clearance
(CS)	Cesarean section
(CVP)	Central venous pressure
(DVT)	Deep venous thrombosis
($ETCO_2$)	End tidal co_2
(GI)	Gastrointestinal
(HCII)	Heparin cofactor II
(HIT)	Heparin induced throbocytobenia
(INR)	International normalized ratio
(IUGR)	Intrauterine growth restriction
(IVC)	Inferior vena cava
(LMWH)	Low molecular weight heparin
(MRI)	Magnetic Resonance Imaging
(MTHFR)	Tetrahydrofolate reductase
(NIBP)	Non invasive blood pressure
(PAI-1)	Plasminogen activator inhibitor-1
(PCCs)	Prothrombin complex concentrates
(PE)	Pulmonary embolism
(PE)	Pulmonary embolism
(PTT)	Partial thromboplastin time
(SHE)	Spinal/epidural hematoma
(SPo_2)	Oxygen saturation
(SVD)	Structural valve deterioration
(TEE)	Transoesophageal echocardiography
(UFH)	Unfractionated heparin
(VKA)	Vitamin K antagonists
(VKH2)	Reduced form of vitamin K
(VTE)	Venous thromboembolism
(vWF)	Von wellibrand factor
(DIC)	Disseminated intravascular coagulation
(HELLP)	Haemolysis, elevated liver enzymes, low platelet count

Peripartum anesthetic management of parturient receiving anticoagulants

Advances in medical practice and proper understanding of several clinical conditions had led to increase in number of parturient receiving anticoagulation. Confirming the diagnosis or even suspicion in acute deep venous thrombosis (DVT) and or pulmonary embolism (PE) during pregnancy necessitates immediate therapeutic anticoagulation as pregnancy is a period of increased risk of thrombotic complications, owing to hypercoagulability, venous stasis, and vascular damage the three elements of Virchow's triad [1]. In addition to several other physiologic changes that further increase clotting risks including, high levels of fibrinogen and factors VII, VIII, IX, and X, Lower levels of protein S and increased resistance to activated protein C and finally Impaired fibrinolysis, due to inhibitors derived from the placenta [2]. More importantly venous thromboembolism (VTE) is among the leading causes of maternal death in developed countries [3]. All such factors had questioned whether routine prophylaxis against VTE should be considered in each single pregnancy? In fact such topic is of great controversy, however great agreement had evolved regarding the use of prophylactic anticoagulation in pregnant females with additional risks for VTE e.g. prior thromboembolic event [4], previous use of contraceptive pills) as risk of thromboembolic events are significantly increased among such group of patients[5].

Another clinical condition that requires anticoagulation is pregnant females with mechanical heart valve prosthesis (mitral or aortic valve replacement). The management of pregnant women with mechanical prosthetic valves is a challenge. Antithrombotic therapy is essential because the risk of valve thrombosis and death or systemic embolism is high if it is not given [6]. Vitamin K antagonists (VKA) by far are the most common anticoagulation therapy in such context outside the pregnancy period and there are no debate regarding its effectiveness in preventing thromboembolic manifestations. However, in a pregnant female the use of VKA carries risks of fetal abnormalities and even fetal death specially in early gestation, moreover intense debate regarding the safety and efficacy of unfractionated heparin and or low molecular weight heparin (LMWH) in prophylaxis against VTE over VKA in pregnancy [7].

Successful pregnancy outcome is dependent on trophoblast invasion into the uterine vasculature and on the development and maintenance of an adequate uteroplacental circulatory system. It is hypothesized that inadequate placentation and damage to the spiral arteries with impaired flow and prothrombotic changes lead to placental-mediated pregnancy complications[8]. The low-pressure uteroplacental system, much like the venous system, may be susceptible to thrombotic complications in hypercoagulable states. The most compelling data for a link between thrombophilia and pregnancy complications derives from studies in women with antiphospholipid antibodies (APLAs) [9] . In addition, there is convincing evidence from clinical studies that the presence of APLAs is associated with an increased risk of pregnancy loss [10]. Antithrombotic therapy with heparin and low dose aspirin has been shown to improve pregnancy outcome in these women with these antibodies . A number of studies have examined the relationship between hereditary thrombophilia and pregnancy related VTE. However, methodological limitations have made it difficult to obtain an accurate assessment for these risks[10]. In a systematic review of nine studies that assessed the risk of VTE in pregnant women with heritable thrombophilia, all congenital thrombophilia with the exception of homozygosity for the thermolabile methylene tetrahydrofolate reductase variant (MTHFR C677T) were found to be associated with a statistically significant increase in the risk of pregnancy-related VTE [11].

From all the aforementioned clinical conditions, there are sound intense rationale for various anticoagulation therapy among pregnant females, moreover anticoagulation for pregnant females with hereditary thrombophilia, whether associated with previous VTE are not only associated with decreased risks of VTE but also with decreased risks for miscarriage. However, anticoagulation during pregnancy carries numerous risks not only for the pregnant female but also for the fetus[11].

The antithrombotics currently available for the prevention and treatment of venous and arterial thromboembolism include heparin and heparin-like compounds (unfractionated heparin [UFH], LMWH, pentasaccharides, and heparinoids), coumarin derivatives, direct thrombin inhibitors, and antiplatelet agents. The corner stone in selection of any of above agent relies upon its efficacy, safety and finally when potential maternal benefits justify potential fetal risks. Maternal risks of anticoagulation are similar to those seen in nonpregnant patients and include bleeding (for all anticoagulants), as well as HIT [12], heparin-associated osteoporosis [13], and pain

at injection sites for heparin-related compounds . Teratogenicity [14, 15] and fetal hemorrhagic complications at time of delivery [16] due to antithrombotic therapy are of great concern and can play a major role in selecting antithrombotic regimen[17].

Finally, anticoagulated pregnant females presenting for elective and or emergency delivery, represent a great challenge for anesthesiologists, as perioperative management of such patients should be directed according to risks / benefits i.e. proper prophylaxis of VTE versus fetal and maternal hemorrhagic complication, bridging or stoppage of anticoagulation versus surgical and anesthetic techniques. Until the existence of the ideal antithrombotic agent, that provides optimum VTE prophylaxis and is devoid of any maternal and fetal complications, Peripartum anticoagulation therapy represents a crucial topic in obstetric anesthesia.

Indications for antithrombotic therapy among pregnant females.

Chronic Antithrombotic therapy indications are universal regardless of patient population studied, i.e. Prior venous thromboembolism (VTE), and patients with mechanical prosthetic valve represent the majority of patient population receiving antithrombotic therapy irrespective of clinical environment. Pregnancy related complications in women with antithrombin deficiency or antiphospholipid antibody syndrome (APLAs) and other VTE [18] can be added to the previous indications and represent the main indications for thromboprophylaxis among parturient[19].

I. Venous thromboembolism (VTE):

Classically VTE occurs primarily, due to the three components of Virchow's triad [1] (hypercoagulability, venous stasis and vascular damage). Pregnant females are at great risk to owe all components of Virchow's triad (Figure1) [20]. In addition; several changes in maternal coagulation system occurs during pregnancy (Figure 2) rendering pregnant female at increased risk of thromboembolic manifestations[2].

A. Prevalence and incidence of VTE among pregnant females:

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), remains a leading cause of maternal death in USA, causing 1.2 to 4.7 deaths per 100,000 pregnancies [21]. Symptomatic VTE is estimated to occur antepartum (from conception to delivery, or ~40 weeks) in 5 to 12 per 10,000 pregnancies, and postpartum (6 weeks) in 3 to 7 per 10,000 deliveries [22]. Compared with age-matched, nonpregnant controls, this translates risk that is increased 7- to 10-fold for antepartum VTE and 15- to 35-fold for postpartum VTE [23, 24]. The heightened clinical risk of VTE rapidly diminishes after delivery [23], returning to the antepartum level of risk by 3 weeks postpartum, and then returning to the nonpregnant level after 6 weeks [25, 26]

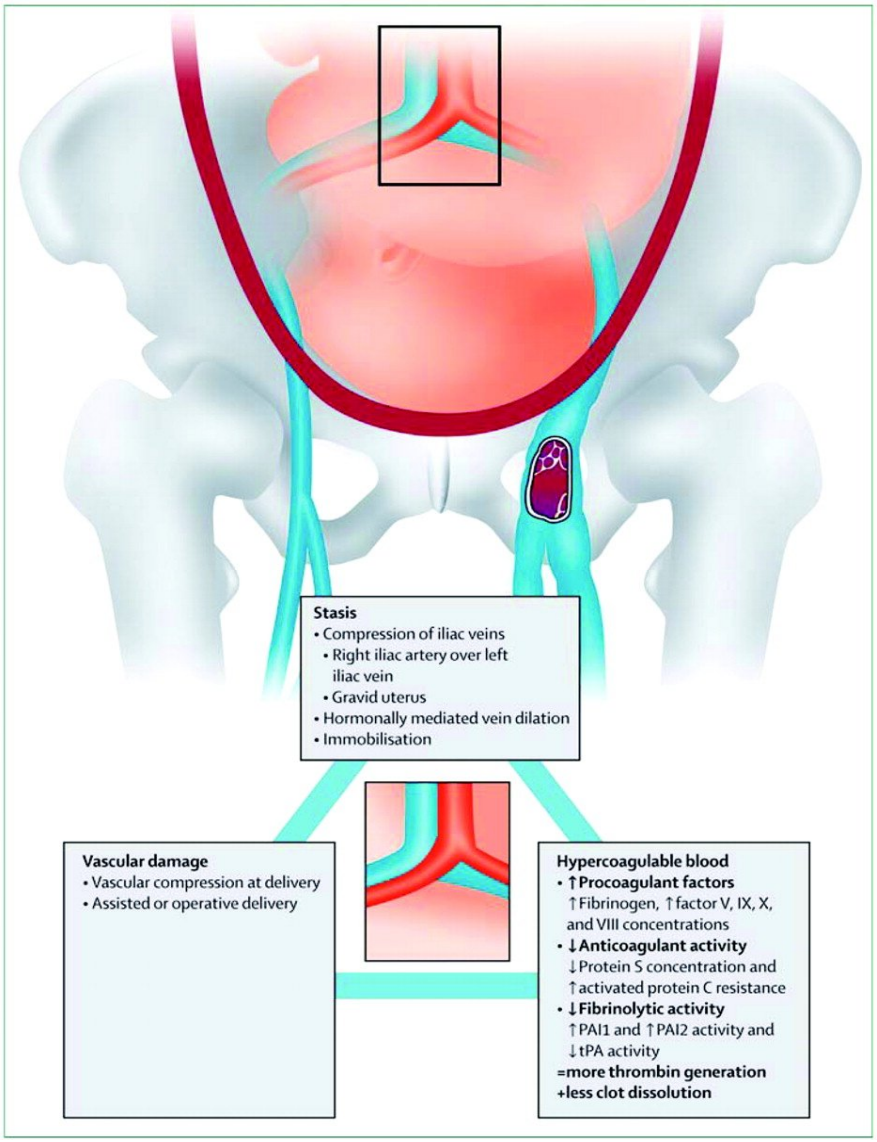

Figure 1: Components of Virchow's triad among pregnant females [20].

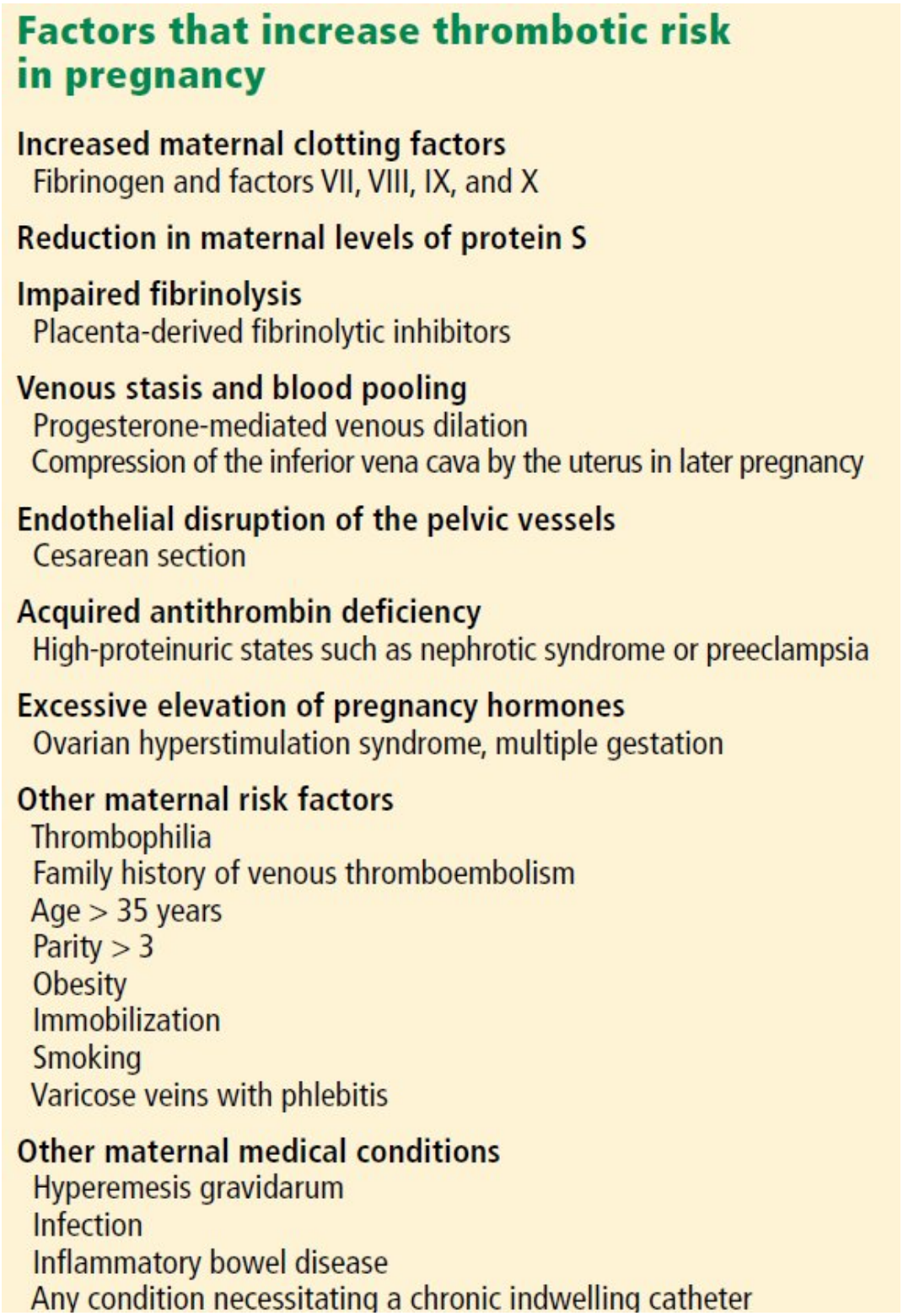

Figure 2: Factors that increase thrombotic risks in pregnancy [2].

B. Diagnosis of VTE in pregnancy:

Suspected DVT is common in pregnancy, given that leg swelling is a frequent complaint or finding. In addition, due to the fact that isolated iliac vein thrombosis occurs with increased frequency during pregnancy, patients may manifest with unusual presentations such as isolated buttock, groin, flank, or abdominal pain [27]. Dyspnea, chest pain, and unexplained tachycardia are common in pregnant women, so the diagnosis of PE is frequently considered. Bedside tests to exclude PE without diagnostic imaging have been developed and validated and have improved patient management in nonpregnant patients [28]. It should be noted that sensitivity and specificity of non invasive diagnostic tools in the field of DVT and PE are greatly lacking. Moreover, among pregnant females the fear from teratogenicity or long term fetal complications (e.g. malignancy) from diagnostic tools can render the use of such tools in limited situations. Figures 3 and 4 illustrates algorithm for diagnostic tools that can be used to confirm DVT and PE among pregnant females according to the best available evidence [29].

C. VTE prophylaxis:

Implementing routine low-molecular weight heparin (LMWH) thromboprophylaxis during pregnancy or peripartum is not feasible given the costs and potential side effects of prophylaxis and the low absolute event rate of postpartum VTE among all women (i.e., low- and high-risk) [22]. Prevention requires an optimal balancing of absolute increased bleeding risk from pharmacologic thromboprophylaxis and the absolute benefit of reduced VTE, which while serious, are relatively uncommon. The focus must remain on known high-risk groups with the understanding that recommendations for prophylaxis, even in high-risk groups, are based on a limited dataset. A recently updated Cochrane review addressed the effectiveness and safety of prophylaxis for VTE in pregnancy and the early postpartum period [30], The reviewers concluded that "there is insufficient evidence on which to base recommendations for thromboprophylaxis during pregnancy and the early postnatal period. Large scale randomized trials of currently-used interventions should be conducted[30]." Detailed insights and recommendations for VTE prophylaxis among high risk parturient and level of evidence will be discussed following.

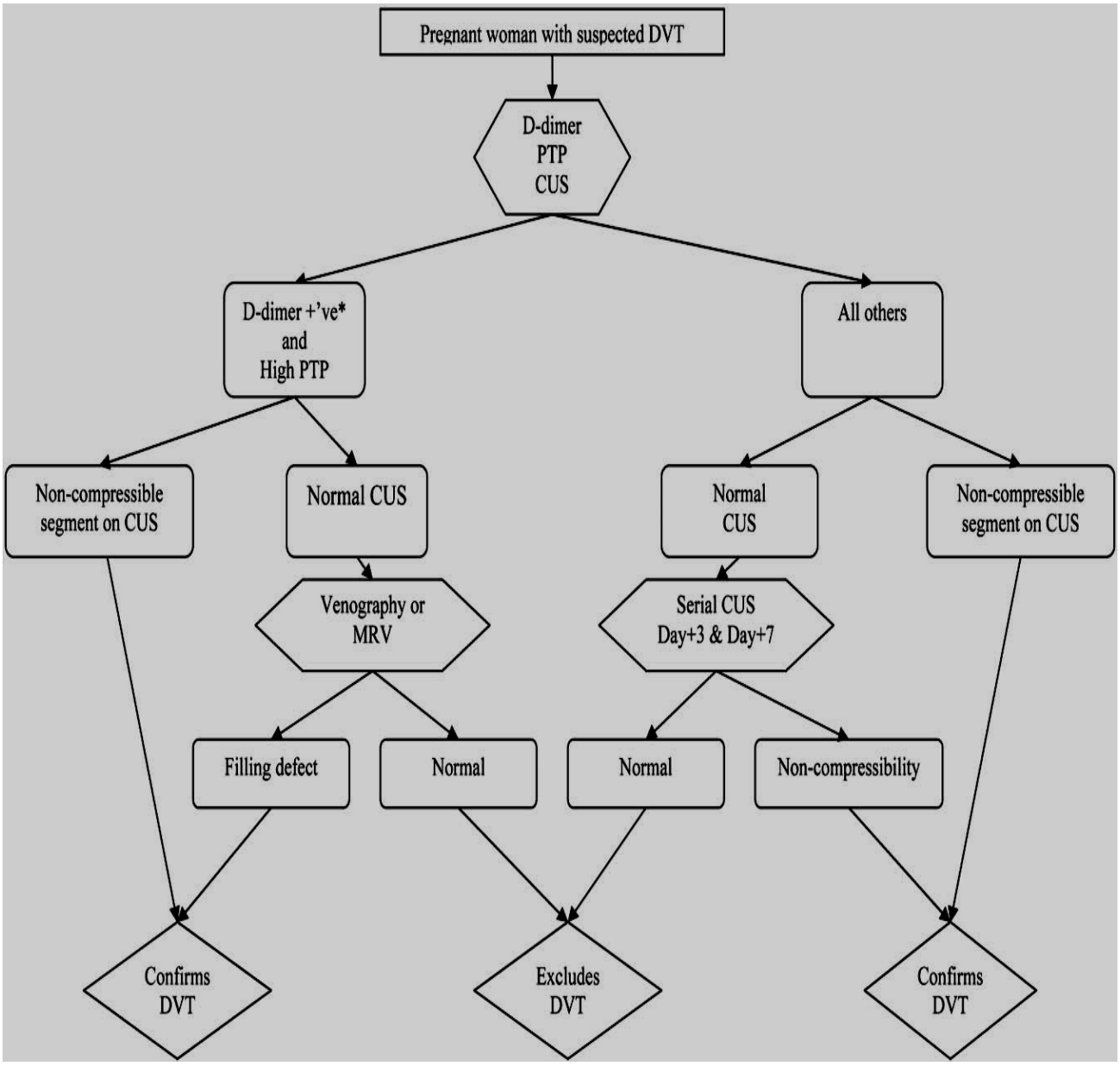

Figure 3: Algorithm for suspected DVT in pregnant women. *Using nonpregnant D-dimer cutoff (i.e., usual D-dimer cutoff in local practice). CUS=venous compression ultrasound imaging; PTP= pretest probability, MRV= Magnetic Resonance Venography [29].