

Venous thrombo-embolism in pregnancy



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Venous thrombo-embolism (VTE) represents a major cause of morbidity and mortality during pregnancy, complicating 0.5 to three of every 1000 pregnancies. While VTE is the leading single cause of maternal mortality in many countries (approximately one death per 100,000 maternities), most VTE events during pregnancy are not fatal. The risk of VTE during pregnancy is about eight times that of a non-pregnant woman of the same age range. The risk of VTE in the puerperium is further increased about 25 times; ie three to five times more deep venous thrombosis (DVTs) occur postpartum than antepartum and this risk is three to 16 times greater after caesarean section than with vaginal delivery. The increased pregnancy-related risk of VTE is due to the fact that pregnancy itself is a hypercoagulable state, to the increase venous stasis during pregnancy and delivery, and to the risk of damage to pelvic vessels at delivery.

Older studies indicated that antepartum VTE risk is lowest during the first two trimesters and highest during the third trimester. More recent data on large series have shown that the diagnosis of DVT was made before 15 weeks in over 50 per cent of antepartum VTE cases.

Table 1 represents a list of common major VTE risks. An interesting laboratory finding has been the evidence that individuals with blood group O have a decreased risk of VTE. The mean relative risk is one half that of the population. The biological explanation for this is unclear.

Table 2 presents a three-tiered risk stratification for VTE in pregnancy, that may be of use in determining the prophylactic antithrombotic measures in individual women.

With respect to recurrence rates, an important study has been reported by the McMaster group. These investigators followed a cohort of pregnant women with a single previous episode of VTE, withholding thrombo-prophylaxis until after delivery unless there was a clear documented recurrence of VTE and blinding information as to underlying thrombophilia. Three out of the 125 women in the study had such a recurrence (2.4 per cent). Importantly, there were no recurrences in the 44 women without a known thrombophilia and whose previous VTE episode was associated with a temporary risk factor. Three of the 51 women with a test indicating acquired or genetic thrombophilia or a previous VTE episode that was idiopathic had an antepartum recurrence of VTE (5.9 per cent).

The issue of thrombophilia may often seem of perplexing complexity for the non-specialist. It is important to emphasise that the list of acquired and genetic thrombophilias continuous to grow rapidly. What we currently define as 'negative thrombophilia screen' is typically based on a mostly very incomplete

Table 1: Risk Factors for VTE in Pregnancy

Clinical Risk Factors	
<ul style="list-style-type: none"> • Age > 35 years • Obesity • Prolonged immobilisation • Surgery during pregnancy • Multiple pregnancy • Malignancy • Ovarian hyperstimulation syndrome (thrombosis often on atypical locations) 	<ul style="list-style-type: none"> • Multiparity • Personal/family history VTE • Pelvic trauma • Caesarean section • Preeclampsia • Nephrotic syndrome
Hereditary Thrombophilias	
<ul style="list-style-type: none"> • Activated protein resistance/ factor V Leiden • Prothrombin gene mutation • Antithrombin, protein C, protein S deficiency • Others 	
Acquired Thrombophilias	
<ul style="list-style-type: none"> • Antiphospholipid antibodies • Elevated factors • Elevated PAI-1 and PAI-2 • Hyperhomocysteinemia • Others 	

Table 2:
Risk Stratification for VTE in pregnancy

Low Risk
<ul style="list-style-type: none"> • Age < 35 years, • Uncomplicated pregnancy • Vaginal delivery or elective caesarean section
Moderate Risk
<ul style="list-style-type: none"> • Age > 35 years • Obesity • Gross varicose veins • Recurrent infections • Immobility > 4 days before delivery • Preeclampsia • Emergency caesarean section
High Risk
<ul style="list-style-type: none"> • Three or more moderate factors • Hereditary or acquired thrombophilia • Personal or family history VTE • Caesarean section hysterectomy

thrombophilia screen, usually only consisting of factor V Leiden, prothrombin gene, the inhibitor deficiencies (antithrombin, protein c and S) and the results of antiphospholipid screening. Many more other genetic thrombophilias have already been identified. Testing for these thrombophilias has not yet been introduced in the clinical arena, often for budgetary reasons. Many more thrombophilias will be identified by research in the years to come. The important implication of this rapid increase in knowledge is that a patient screened for thrombophilias in the mid 1990s clearly needs to be screened again, that is, if the outcome of that test would be relevant to the clinician.

Table 3 is adapted from a review by McLintock et al (2001) attempts to give an overview of the pregnancy associated VTE risks in women with some of the common hereditary thrombophilias.

The classical diagnosis of DVT consists of calf pain, oedema (particularly unilateral) and pain with dorsiflexion of the foot (Homan's sign). It should be emphasised that this description has long fallen by the wayside, since careful non-invasive studies have shown that only 30 per cent of pregnant patients with DVT express this triad and many consider the Homan's sign not only unreliable, but also potentially dangerous. A common presentation in pregnancy is with the complaint of low back or flank pain, calf discomfort or the clinical recognition of tenderness when the patient is examined. The presence of unilateral oedema, especially if associated with some tenderness, is particularly important since the actual clinical presentation is often quite subtle. The clinical diagnosis of small pulmonary embolism is notoriously difficult. Important clinical markers include: unexpected dyspnea, chest pain, unexpected cough, tachypnoea, tachycardia, and anxiety.

The utility of clinical laboratory testing in diagnosing VTE is greatly reduced due to the intrinsic prothrombotic state inherent in pregnancy. The D-dimer assay elevates and becomes progressively more positive during the second and third trimester. The high-risk postpartum period is also a time of elevated D-dimers, regardless of the presence of VTE. It is clear that in both pregnant and non-pregnant individuals, clinical and/or laboratory criteria alone are not adequate to establish the diagnosis of DVT or pulmonary embolism.

The imaging reference standards for diagnosis are ascending contrast venography for DVT and pulmonary angiography for pulmonary embolism. The primary modality for DVT diagnosis is compression ultrasound (CUS) with or without colour flow Doppler. CUS is the imaging modality of choice for proximal DVT; the sensitivity for calf thrombi is low. CUS is limited by the inaccuracy in detecting pelvic DVT and particularly in pregnancy, diagnosis may be challenging. Repeated CUS, after an initial negative, may be indicated in symptomatic patients, especially in the setting of high clinical probability.

Owing to the limitations of CUS in pregnancy, MRI has emerged as a particularly useful technique for the diagnosis of pelvic and iliofemoral thrombosis and more recently, also for calf thrombosis.

Table 3: Estimated pregnancy-related risk of VTE in women with hereditary thrombophilia (McLintock et al 2001)

	AT (very rare)	C (rare)	S (rare)	FVL or PGM homozygous (uncommon)	FVL or PGM heterozygous (common)
Personal history of VTE independent of family history	>30 per cent	10-20 per cent	10-20 per cent	10-20 per cent	2-10 per cent
Family history of VTE in one or more first degree relatives	10-30 per cent	10-20 per cent	10-20 per cent	10-20 per cent	2-10 per cent
Family history of VTE in a distant relative	10-30 per cent	10-20 per cent	2-10 per cent	2-10 per cent	<2 per cent
No personal or family history of VTE	10-30 per cent	10-20 per cent	<2 per cent	<2 per cent	<2 per cent

AT = antithrombin deficiency; C = Protein C deficiency; S = Protein S deficiency; FVL = G1691A mutation in the factor V gene (Factor V Leiden) causing activated protein C resistance; PGM = G20210A mutation in the prothrombin (factor II) gene

While Ventilation/Perfusion (V/Q) scans have been the primary modality for the diagnosis of pulmonary embolism, spiral CT imaging has supplanted the V/Q scan in many institutions. A full V/Q scan gives an exposure of about 50 mRads, well below the commonly used safety 'benchmark' of 4000 mRads.

The whole rapidly evolving field of anticoagulation in pregnancy and the puerperium is too big to discuss in the context of this short overview. A series of dot points (based on the Obstetric Medicine Consensus Report, MJA 2001; 175: 258) summarises the key issues for non-specialists.

- For the management of acute VTE events in pregnancy, therapeutic doses of low-molecular weight heparins (LMWH) may be used, unless the shorter half life of intravenous unfractionated heparin (UH) and predictable reversibility by protamine are important. Treatment should be continued up until delivery and into the puerperium.
- Pregnant women who have had an acute VTE event should be delivered by a specialist team.
- In the case of recent thrombosis, delivery should be planned and the time during which anticoagulation therapy is ceased around the time of delivery should be minimised.
- Therapeutic doses of LMWH contraindicate the use of regional anaesthesia and a switch to intravenous UH before delivery may allow greater flexibility in this regard.
- Prophylactic doses of LMWH can be used to reduce the risk of (recurrent) VTE events in pregnancy. The regimen used will depend on the previous history, the family history and

the presence of risk factors, including the genetic and acquired thrombophilias. The risk of antepartum LMWH in prophylactic doses appears to be very low. LMWH, similar to UH do not cross the placenta. LMWH induced HIT (heparin-induced thrombocytopenia) virtually does not exist and the risk of osteoporosis appears to be very low.

- The use of Warfarin in the postpartum period is not a contraindication for breastfeeding.
- All 'at risk' women should be monitored for signs and symptoms of VTE during the first week postpartum.
- Intra- and postpartum hydration should be maintained and early mobilisation encouraged.
- Graduated compression stockings with or without calf stimulation should be used during and after caesarean section in women at moderate and high risk.
- In women at high risk, LMWH or UH should be used and continued for at least five days.

My! How O and G has changed!

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Compounding this, when valid surgical interventions are performed, obesity increases all parameters of adverse outcomes. Obstetrically, obesity adds its complement of woes, whilst the long-term complications on cardiovascular and skeletal systems inevitably will occur. It is to be recalled that cardiovascular disease is still the main cause of death of women in this country.

On a totally different tack, it has been heartening to see how the Integrated Training Program run by the College has been a quantum leap in the basic training of young O and G professionals. Paradoxically, despite the continued spectre of medico-legal litigation, there has been a reassuring response in the last two years in the number and quality of applicants for the College training program.

The resurgence in interest bodes well for the future of O and G. This pragmatic optimism is based on the knowledge that our primary purpose is the best care for our women. The art lies in the ability to harness technology to effectively and efficiently achieve our goals.

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