SOGC CLINICAL PRACTICE GUIDELINES

No. 95, September 2000

Prevention and Treatment of Venous Thromboembolism (VTE) in Obstetrics

These guidelines have been reviewed and approved by the Maternal Fetal Medicine Committee and were approved by the Council of the SOGC

PRINCIPAL AUTHOR

Nancy Kent, MD, FRCSC, Vancouver, BC

MATERNAL FETAL MEDICINE COMMITTEE

Line Leduc (Chair), MD, FRCSC, Montréal, QC
Joan Crane, MD, FRCSC, St-John's, NF
Dan Farine, MD, FRCSC, Toronto, ON
Susan Hodges, RN, Ottawa, ON
Nancy Kent, MD, FRCSC, Vancouver, BC
Gregory J. Reid, MD, FRCSC, Winnipeg, MB
John Van Aerde, MD, FRCSC, Edmonton, AB

Abstract

Objective: to identify risk factors for venous thromboembolism (VTE) in the peripartum period and to provide guidelines for risk assessment and thromboprophylactic measures for VTE in pregnant women. Guidelines for diagnostic testing and for acute and long term treatment of VTE are also provided.

Options: specific subgroups of pregnant women are defined and appropriate prophylactic measures are outlined.

Outcomes: venous thromboembolism remains a major cause of morbidity and mortality in pregnancy and the postpartum period. Identification of risk and adequate prophylaxis can decrease the incidence of VTE.

Evidence: evidence was gathered using Medline (National Library of Medicine) to identify relevant studies and from bibliographies of articles thus identified.

Recommendations: although evidence is lacking to date from Grade I studies (properly controlled randomized studies) in pregnant patients, there is good evidence to support the role of prophylaxis in reducing the incidence of VTE in patients identified to be at risk in the non-pregnant population (II B). Based on risk assessment more patients should be considered for thromboprophylaxis, including women with a past history of a VTE and a known thrombophilia on long-term anticoagulation, women with a past history of a VTE, women with a known thrombophilia who have never experienced a VTE and potentially considered in women at the time of Caesarean section (II B; III C). The occurrence of VTE is effectively reduced by the use of low dose unfractionated heparin. Experience with low molecular weight heparin and pregnancy is building, but is limited at present. Unfractionated heparin remains the standard for the treatment of VTE in pregnancy at the present time. Following initial heparinization for the treatment of VTE, patients should be continued on anticoagulation throughout pregnancy and for six to 12 weeks postpartum or a total of three months of anticoagulation (II A).

INTRODUCTION

Venous thromboembolism (VTE) is a major cause of maternal morbidity and mortality. The incidence has been reported to range from 0.5-3/1,000 pregnancies[1] occurring with approximately equal frequency in all three trimesters and postpartum.[2] Several risk factors predispose the pregnant patient to the development of VTE. Once VTE has occurred, prompt and adequate treatment must be initiated in order to reduce the morbidity and mortality associated with pulmonary embolism (PE), to reduce the extension of a deep vein thrombosis (DVT), and to reduce the morbidity associated with post-thrombotic leg syndrome.[3]

In a woman with a previous history of VTE the recurrence risk can be as high as 12 percent.[4] Thromboprophylaxis is more effective than treatment of established disease in decreasing the

associated morbidity and mortality.[5] The purpose of this paper is to provide guidelines for risk assessment, prophylaxis, diagnosis and treatment of VTE in pregnancy.

RISK FACTORS

A number of risk factors for the development of thromboembolic disease in pregnancy have been identified. Risk factors associated with uncomplicated pregnancy are summarized in Table I.

Risk factors that may be present in addition to those inherent in the pregnant state are listed in Table II. Thrombophilia is the term used to describe familial (congenital) or acquired abnormalities of hemostasis that could predispose an individual to venous thromboembolism. The main congenital thrombophilias are listed in Table II. It is possible for a woman to have more than one thrombophilia, as congenital thrombophilia may be a multigene disorder.[6] Increased thrombosis is also associated with acquired thrombophilias, such as the antiphospholipid antibody syndrome (APA).[7]

Congenital and acquired factors are often present concurrently. The risk of VTE increases with multiple factors.

It should be noted that women with APA syndrome and hyperhomocysteinemia are at increased risk of both venous and arterial thrombosis, hence management in these women should include daily low dose aspirin.

Most women with thrombophilias remain asymptomatic. However, thrombophilia screening should be offered to any woman with a personal or family history of a VTE, especially if the VTE occurred in the absence of other recognized risk factors or outside the pelvis and lower limbs in the context of a pregnancy. There is growing evidence to suggest that the incidence of thrombophilias is also increased in women with pregnancy complications, including late fetal loss, gestational hypertension, and intrauterine growth restriction. It is reasonable to consider thrombophilia screening in women with a history of one or more of the above poor outcomes.[8]

Although factors have been identified which increase the risk of VTE in pregnancy, it should be noted that most such events occur in the absence of such features. The prudent physician should have high suspicion for thromboembolic disease when suggestive symptoms and signs are present, and investigate the possibility thoroughly regardless of whether risk factors are present.

THROMBOPROPHYLAXIS IN OBSTETRICS

The issue of thromboprophylaxis is controversial. Expert opinion varies as to when, in whom, and how to use prophylaxis against VTE. The degree of anticoagulation depends on the particular thrombophilia involved and the specific risk factors present in any given case.

TABLE I **PREDISPOSING RISK FACTORS ASSOCIATED WITH PREGNANCY**

HYPERCOAGULABILITY	STASIS	ENDOTHELIAL
Increased factors; II, V, VII, VIII, IX, X, XII and fibrinogen	Increased venous distensibility, decreased venous tone	Vascular damage at delivery (Caesarean section or spontaneous vaginal delivery)
Increased platelet aggregation	50% decrease in venous flow in lower extremity by third trimester	
Decreased protein S, tissue plasminogen activator, factors XI, XIII	Uterus is mechanical impediment to venous return	
Increased resistance to activated protein C		
Antithrombin can be normal or reduced		

TABLE II **ADDITIONAL RISK FACTORS**

Previous VTE	Thrombophilias*	
Age > 35	Congenital –	protein C & protein S deficiencies
Obesity		resistance to activated protein C
Infection		(Factor V Leiden)
Bedrest/physical immobility		antithrombin deficiency
Shock/dehydration		hyperhomocysteinemia
Caesarean section		prothrombin gene variant
Operative vaginal delivery		plasminogen deficiency
Uterine instrumentation	Acquired –	antiphospholipid antibody syndrome
Pelvic surgery in the peripartum period		nephrotic syndrome (decreased antithrombin levels)

* The field of thrombophilias is in evolution. Additional thrombophilias are being discovered.

a) Women with a past history of VTE and known thrombophilia, on long-term anticoagulation

Full therapeutic anticoagulation is recommended throughout pregnancy and for 6-12 weeks postpartum, after which the previous anticoagulation regimen is resumed. For suggested regimens see below in "Treatment of VTE Occurring in Pregnancy: Long-term Treatment." Management may be modified based on the specific thrombophilia involved.[1] (III B)

b) Women with a past history of VTE

The recurrence risk may be as high as 12 percent. Yet there remains disagreement as to whether thromboprophylaxis in these cases is necessary or not. There is a lack of prospective trials on the effect of prophylaxis to prevent the recurrence of VTE in pregnancy.[9] However, based upon trials in the non-pregnant population, the recommendation is to use one of the following regimens in a patient with a previous VTE and institute anticoagulation postpartum for six weeks. (II B)

Prophylactic regimens:

- Unfractionated heparin 5,000 units sc every 12 hours throughout pregnancy.[9]
- Unfractionated heparin 5,000 units sc every 12 hours in the first trimester, 7,500 units every 12 hours in the second trimester, and 10,000 units every 12 hours in the third trimester.[4]

The second regimen is recommended based on the higher heparin dosages needed to achieve adequate heparin levels as pregnancy advances.

- Low molecular weight heparin (LMWH)

  Dalteparin (Fragmin©) – 2,500 IU sc if < 50 kg, 5,000 IU sc if 50-70 kg, 7,500 IU sc if > 71 kg once a day

  Enoxaparin – 40 mg sc once a day

There is insufficient evidence in pregnancy with respect to the use of LMWH to recommend its use routinely at present.

In cases where the previous VTE was unrelated to pregnancy or exogenous hormonal use, one further option remains to monitor with clinical surveillance throughout pregnancy and institute anticoagulation postpartum for six weeks.

c) Women with a known thrombophilia who have never experienced a VTE

The management in these cases is even more controversial. There is a lack of any prospective evidence to demonstrate that these women benefit from thromboprophylaxis.[4] In addition, management needs to be determined by the thrombophilia involved, as the risk of a VTE varies with the specific condition.[1] For example, the significant risk of VTE with a known antithrombin deficiency (50-70%) is present throughout pregnancy. Anticoagulant prophylaxis should be instituted once the pregnancy is confirmed and continued postpartum. Similar management is recommended with cases in which there are multiple thrombophilias, as the risk for DVT is considered to be higher.[6] However, with protein C and S deficiencies the risk of VTE is greatest in the postpartum period (18-20%). Hence, it may be acceptable to delay anticoagulant prophylaxis until labour and delivery and continue it for 12 weeks postpartum. (III C)

Current prophylaxis regimens for acquired thrombophilias, such as APA syndrome, include the use of low dose aspirin in conjunction with prophylactic heparin.[7]

Women in this category should be referred to a centre familiar with these disorders for individualized management.

Recommendation for thromboprophylaxis or full therapeutic treatment is based on Grade III C evidence.[1]

d) Consideration of postpartum thromboprophylaxis following Caesarean section

No prospective studies exist to evaluate the effectiveness of thromboprophylaxis following a Caesarean section to prevent VTE. The Royal College of Obstetricians and Gynaecologists in Britain has issued a report recommending the use of postpartum thromboprophylaxis in women who have moderate to high risk for VTE in association with a Caesarean section.[10] Prophylaxis needs to be considered in the presence of risk factors such as a previous VTE, a known thrombophilia (II B), a history of prolonged immobility or obesity. (III C) It is recommended to start treatment following delivery of the neonate at the time of the Caesarean section:[10]

- Unfractionated heparin 5,000 units sc every 12 hours until fully mobile
- LMWH sc once a day for five days, such as Enoxaparin 20 mg sc od

SIDE EFFECTS AND COMPLICATIONS OF HEPARIN THERAPY

Heparin-induced thrombocytopenia (HIT), caused by heparin-dependent IgG antibodies, is an uncommon (3%) but serious complication typically occurring six to 12 days after initiation of therapy.[11] If a patient has previously had heparin therapy the thrombocytopenia may occur more rapidly. The risk of major bleeding episodes is low (2-10%), however minor to moderate bleeding is increased slightly with unfractionated heparin.[12] Bruising at injection sites is common and can be decreased by instruction in appropriate injection technique. Osteoporosis is a dose dependent complication related to the duration of therapy.[13]

Allergies are uncommon to unfractionated heparin. Anticoagulation for a woman unable to take heparin, for whatever reason, should be managed by a haematologist.

LOW MOLECULAR WEIGHT HEPARIN

Experience with low molecular weight heparin (LMWH) in obstetrics is limited. LMWH may be administered once or twice a day. Dosage is based on maternal weight and requires less

monitoring as it has a predictable anticoagulant effect. LMWH does not cross the placenta[14] and does not appear to have teratogenic effects in animal studies.[15] Bleeding appears to be less with LMWH[16] although this remains to be confirmed in large trials. The risk of thrombocytopenia is less than with unfractionated heparin[17] and the risk of osteoporosis may also be less.[13] Cost remains a concern, as low molecular weight heparin is expensive at present. Large clinical trials using LMWH in pregnancy remain to be done. However, research is in progress.

At the present time unfractionated heparin remains the standard of care for anticoagulation in pregnancy in North America. There is insufficient evidence to date to suggest that LMWH is superior to unfractionated heparin in the prophylaxis and treatment of VTE in obstetrics.

WARFARIN

Warfarin is contraindicated during pregnancy due to its potential fetal effects. In the first trimester there is a risk of warfarin embryopathy (nasal hypoplasia, stippled epiphyses, eye anomalies, and developmental delay). Central nervous system abnormalities can occur at any stage in pregnancy. In addition there is a risk of fetal and neonatal hemorrhage with warfarin usage, especially near term.

DIAGNOSIS OF VTE

DIAGNOSIS OF A DVT

A high index of suspicion for DVT should be maintained. Most occur in the iliofemoral or calf veins with a predilection for the left leg (90%). Clinical and objective diagnosis is mandatory. Non-invasive diagnosis is recommended whenever feasible.

For DVT, venography is the gold standard. This invasive test involves radiation to both mother and fetus. A limited venogram, using lead apron shielding over the maternal abdomen and pelvis, decreases the radiation exposure to the fetus to < 0.05 rads but visualization of the iliac veins is compromised. A limited venogram is sufficient if possible.[18]

Serial impedance plethysmography (IPG) measures the changes in electrical impedance as the result of changes in blood volume within the limb. It can rule out a DVT when performed serially, but sensitivity and specificity are compromised late in pregnancy due to compression of the iliac veins.[19]

In the non-pregnant patient Duplex Doppler sonography has a 95 percent correlation with venography for popliteal and femoral vein thromboses. The thrombus itself can be seen in the occluded segment of the vessel, enhanced by the use of external compression. Internal compression by the gravid uterus, however, limits its sensitivity and specificity in pregnancy.[20]

Prospective studies looking at the sensitivity and specificity of Duplex Doppler to detect a DVT in pregnancy, along with those assessing the safety of withholding anticoagulants in pregnant patients with serial negative Duplex Doppler studies, are lacking.[20] However, it is a simple non-invasive test and in many centres is the initial test in a pregnant women with a suspected DVT.

Both Duplex Doppler and IPG have poor sensitivity to detect a calf vein DVT. It is necessary to repeat testing in those with a negative scan and a high clinical suspicion. Therapy may be safely withheld if serial studies are negative.[18] Venography should be performed if noninvasive studies are equivocal or unavailable.

Radioactive iodine labeled fibrinogen scanning is contraindicated in pregnancy. A single noninvasive study showing thrombosis or a positive venogram justifies treatment with anticoagulation.

DIAGNOSIS OF A PE

The symptoms and signs of a PE, as in the non-pregnant patient, are non-specific. In view of the frequently vague clinical presentation and the potentially life-saving benefit of anticoagulation, early recourse to diagnostic testing is warranted whenever the diagnosis of a PE is entertained. Pulmonary angiography is the gold standard for the diagnosis of a PE but it is invasive and carries significant morbidity.[21]

A chest Xray and ventilation-perfusion scan (V/Q scan) are the primary tools for diagnosis. Radiation to the fetus with a V/Q scan is minimal. A PE can be ruled out in patients with a low clinical suspicion and a normal or low probability V/Q scan. The diagnosis of a PE can be made in patients with a high clinical suspicion and a high probability scan. The limitation of the test is in those patients with a suspected PE and an intermediate scan.[22] It is reasonable to perform a Duplex Doppler or IPG to rule out a DVT in these cases. If these tests are normal, but the diagnosis is still a possibility, a pulmonary angiogram should be considered.

Given the significant implications of long-term treatment with anticoagulation and the impact on the use of hormonal therapy in the future, a suspicion of a VTE should be aggressively investigated with definitive studies unless contraindicated.

TREATMENT OF VTE OCCURRING IN PREGNANCY

The recommendation for treatment of a VTE in pregnancy is based on Grade II A evidence.

INITIAL TREATMENT

Before initiating treatment obtain a baseline CBC, including platelets (PT), and activated partial thromboplastin time (aPTT).

Unfractionated heparin:

Initial bolus of 5,000 IU followed by an infusion of approximately 30,000 IU/24 hours.

- Measure the aPTT six hours after the bolus.
- Adjust to keep the aPTT at the therapeutic level for the local centre (1.5 to 2.5 the control value).
- Repeat every 24 hours once therapeutic.

- Or measure the serum heparin level. Maintain serum heparin at 0.2-0.4 IU/ml (an aPTT of 60-85 sec).[23]

An example of a protocol for the adjustment of intravenous unfractionated heparin is listed in Table III.

LONG-TERM TREATMENT

1) Unfractionated heparin:

Adjust to keep aPTT at therapeutic levels six hours after the injection[23] (1.5 to 2.5 times the control or a heparin level of 0.1-0.2 IU/ml).

2) Low molecular weight heparin:

For example, for a 50-70 kg woman:

- Tinzaparin – 175 IU/kg sc once per day
- Dalteparin – 200 IU/kg sc once per day

Dose chosen to achieve an antiXa heparin level of 0.3-0.75 four hours post-injection.

No regular monitoring is necessary, but a single antiXa level done in the third trimester will ensure that the dose administered is within the therapeutic range. Administration twice a day during pregnancy, especially in the third trimester, appears to achieve better therapeutic levels.

Therapy should be continued throughout pregnancy and for six to 12 weeks postpartum or for a total of three months of anticoagulation.[5]

INTRAPARTUM MANAGEMENT

If thromboprophylaxis is being used, the patient should be instructed to discontinue administration of sc heparin at the onset of regular uterine contractions or on the morning of a booked induction. If an elective Caesarean section is planned and thromboprophylaxis is being used, the last dose of heparin should be given 6 - 8 hours before the Caesarean section is to be performed.

Evidence is lacking to suggest the appropriate timing of the administration of LMWH close to delivery. Some centres decrease the dose of LMWH back to the first trimester levels at 38 weeks gestation.[24] The half-life of LMWH is about four hours;[25] hence each centre utilizing LMWH must decide their own protocol for administration close to delivery. If the patient is on a prophylactic regimen utilizing LMWH, it must be discontinued 24 hours before the day of induction of labour. If therapeutic regimen is required, the patient should be switched to subcutaneous heparin in the weeks before delivery as per the centre's own protocol. The use of regional anesthesia must be individualized. The risk of a subdural haematoma should be low in the presence of normal coagulation studies or a heparin level < 0.4 IU/ml.[23]

If therapeutic heparin is required throughout labour, the patient should be switched to intravenous heparin and the dose adjusted to a therapeutic aPTT. There is a slight increase in the incidence of haematomas in a vaginal tear or episiotomy, but postpartum haemorrhage is not increased. Regional anaesthesia is contraindicated with therapeutic heparin.[26]

If the aPTT is greater than the therapeutic level, protamine sulphate may be used to neutralize the heparin. One mg of protamine sulphate neutralizes 100 units of heparin. Do not give more than 50 mg over any 15 minute period intravenously.

POSTPARTUM MANAGEMENT

Heparin can be resumed 4-12 hours postpartum if required. The clinical picture, presence of risk factors, and the mode of delivery will modify management.

If ongoing anticoagulation is required, oral warfarin can be instituted after appropriate initial intravenous therapy with heparin, or sc heparin can be resumed.

The decision to continue with heparin or switch to oral warfarin postpartum is based on individual patient and physician preference. Both are safe for breast-feeding.

Warfarin may be started the day following delivery. It can be given as 7.5 mg/day po on day one and two. Adjust to keep the International Normalized Ratio (INR) in the therapeutic range of 2 - 3. Warfarin therapy should overlap with intravenous heparin for 4 - 5 days until the initial INR is greater than two on two consecutive days.

Experience with LMWH in the lactating woman is limited.

Thrombophilic screening should be offered to all women who experience a VTE during pregnancy in the absence of a known risk factor. This should be done at least 12

TABLE III **TITRATION OF INTRAVENOUS UNFRACTIONATED HEPARIN[23] (INFUSION OF 40 IU/ML OF HEPARIN)**

aPTT (seconds)	Dosage change	Additional action
< 50	Repeat bolus ↑2,880 IU/24 hours iv	Repeat aPTT in 6 hours
50-59	↑2,880 IU/24 hours iv	Repeat aPTT in 6 hours
60-85	Don't alter	Repeat aPTT the next morning
86-95	↓1,920 IU/24 hours iv	Repeat aPTT the next morning
96-120	Stop infusion for 30 minutes ↓1,920 IU/24 hours iv	Repeat aPTT in 6 hours
> 120	Stop infusion for 60 minutes ↓3,840 IU/24 hours iv	Repeat aPTT in 6 hours

It is essential to adequately anticoagulate the patient in the first 24 hours. Initial intravenous treatment should be maintained for 5-7days.

TABLE IV[27]

QUALITY OF EVIDENCE ASSESSMENT	CLASSIFICATION OF RECOMMENDATIONS
The quality of evidence reported in these guidelines has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam.[27] I: Evidence obtained from at least one properly randomized controlled trial. II-1: Evidence from well-designed controlled trials without randomization. II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group. II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940's) could also be included in this category. III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.	Recommendations included in these guidelines have been adapted from the ranking method described in the Classification of Recommendations found in the Report of the Canadian Task Force on the Periodic Health Exam.[27] A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination. B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination. C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination, but recommendations may be made on other grounds. D. There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination. E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

weeks postpartum. Molecular screening for thrombophilias can be done during the pregnancy. However, functional tests, such as those required for antithrombin and protein C and S deficiencies, can be modified by the pregnant state. Hence, they should be repeated past the puerperium.

The long-term management of a woman with a confirmed thrombophilia should be referred to a centre with expertise in the management of these disorders.

NON-MEDICAL MANAGEMENT

- Compression stockings
  Reduce leg edema by raising legs and using graduated compression stockings (prescribe two; one to wash and one to wear). The stockings decrease the risk of post-thrombotic leg syndrome.[3] There are no controlled trials of the use of compression stockings in pregnancy or postpartum. (III B)
- Avoidance of prolonged sitting.
  Poor evidence to support a recommendation for or against its use. (III C)

ACKNOWLEDGEMENTS

The Maternal Fetal Medicine Committee of the SOGC wishes to acknowledge the contributions of:

- Dr. Michele David, consultant haematologist at Hôpital Sainte Justine, Montreal, QC
- Dr. Kuljit Grewal, consultant haematologist at Grace General Hospital, St. John's, NF
- Dr. Peter Tsang, consultant haematologist at Children & Women's Health Centre, Vancouver, BC

J Soc Obstet Gynaecol Can 2000;22(9):736-42

REFERENCES

1. Walker MC, Garner PR, Keely EJ. Thrombosis in pregnancy: A review. J Soc Obstet Gynaecol Can 1998;20(10):943-52.
2. Toglia MR, Nolan TE. Venous thromboembolism during pregnancy: A current review of diagnosis and management. Obstet Gynecol Survey 1996;52(1):60-72.
3. Lowe GDO. Treatment of venous thromboembolism. Balliere's Clin Obstet Gynaecol 1997;11(3):511-21.
4. Barbour LA, Pickard J. Controversies in thromboembolic disease during pregnancy: A critical review. Obstet Gynecol 1995;86:621-33.
5. Pineo GF, Hull RD. Prevention and treatment of venous thromboembolism. Drugs 1996;52(1):71-92.
6. Walker ID. Congenital thrombophilia. Balliere's Clin Obstet Gynaecol 1997;11(3):431-45.
7. Ballem P. Acquired thrombophilia in pregnancy. Seminars in Thrombosis and Hemostasis 1998;24 Supp 1:41-7.
8. Kupferminc MJ, Eldor A, Steinman N, et al. Increased frequency of genetic thrombophilia in women with complications of pregnancy. N Eng J Med 1999;340:9-13.
9. Ginsberg J, Hirsh J. Use of antithrombotic agents during pregnancy. Chest 1992;102(4):385S-390S.
10. Report on the R.C.O.G. Working Party on Prophylaxis Against Thromboembolism in Gynaecology and Obstetrics. London: Royal College of Obstetricians and Gynaecologists 1995.
11. King D, Kelton J. Heparin-associated thrombocytopenia. Ann Intern Med 1984;100:536-40.
12. Ginsberg J, Kowalchuk G, Hirsh J, Brill-Edwards P, Burrows R. Heparin therapy during pregnancy: Risks to the fetus and mother. Arch Intern Med 1989;149:2233-6.
13. Barbour L, Kick S, Steiner J, et al. A prospective study of heparin-induced osteoporosis in pregnancy using bone densitometry. Am J Obstet Gynecol 1994;170:862-9.
14. Melissari E, Parker C, Wilson N, Monte G, Kanthon C, Pemberton K, et al. The use of low molecular weight heparin in pregnancy. Thromb Haemost 1992;68:652-6.

15. Bertoli D, Borelli G. Toxic and mutagenic effects of low molecular weight heparin in rats. Drug Res 1986; 36: 1256-60.
16. Kakkar V, Cohen A, Edmonston R, et al. Low molecular weight heparin versus standard heparin for the prevention of venous thromboembolism after major abdominal surgery. Lancet 1993; 341:259-65.
17. Grace R. Thromboprophylaxis. Br J Hosp Med 1993;49:720-6.
18. Ginsberg JS, Hirch J, Rainbow A, Coats G. Risks to the fetus of radiologic procedures used in the diagnosis of maternal venous thromboembolic disease. Thromb Haemost 1989;61:189-96.
19. Hull R, Raskob G, Carter C. Serial impedance plethysmography in pregnant patients with clinically suspected deep vein thrombosis. Ann Intern Med 1990;112:663-7.
20. Macklon, N. Diagnosis of deep venous thrombosis and pulmonary embolism. Balliere's Clin Obstet Gynaecol 1997;11(3):463-77.
21. Greenspan R. Pulmonary angiography and the diagnosis of pulmonary embolism. Prog Cardiovasc Dis 1994;37:93-105.
22. The PIOPED Investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism: Results of the prospective investigation of pulmonary embolism diagnosis (PIOPIED). JAMA 1990;273:2753-9.
23. Toglia MR, Weg JG. Venous thromboembolism during pregnancy. N Eng J Med 1996;335:108-14.
24. Stephenson MD, Ensom MHH. The emerging use of low-molecular-weight heparis in pregnancy. J Soc Obstet Gynaecol Can 2000;22(2): 120-7.
25. Fejgin MD, Lourwood DL. Low molecular weight heparins and their use in obstetrics and gynecology. Obstet Gynecol Survey 1994; 49(6):424-30.
26. ACOG Educational Bulletin. Thromboembolism in pregnancy. March 1997;234:1-9.
27. Woolf SH, Battista RN, Angerson GM, Logan AG, EEL W. Canadian Task Force on the Periodic Health Exam. Ottawa: Canada Communication Group, 1994:xxxvii.

OTHER REFERENCES

The Thrombosis Interest Group. www.thrombosis interest group.

Supplement of the Journal SOGC,
September 2000, Volume 22, Number 9,
Rogers Media,
777 Bay Street, 5th Floor
Toronto, Ontario M5W 1A7
Tel: (416) 596-5038
Fax: (416) 596-5023

September 2000