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Thromboprophylaxis in Surgical Patients

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Abstract: This review has presented current information regarding thromboprophylaxis in surgery, including pregnancy. Where feasible, references have included current consensus conference recommendations and reliable review articles. Orthopedic surgical thromboprophylaxis has intentionally been deleted, as this topic is well covered in other articles in this issue (EurJ Med Res 9(3), March 2004).

Key words: Thromboprophylaxis; surgery

Introduction

Thrombosis is a common cause of death in the United States. Over two million individuals die each year from an arterial or venous thrombosis or the consequences thereof [1]. About an equal number suffer non-fatal thrombosis, for example deep vein thrombosis, non-fatal pulmonary embolus, non-fatal cerebrovascular thrombosis (CVT), transient cerebral ischemic attacks (40% of these will have a fatal or non-fatal CVT within one year) [2], non-fatal coronary artery thrombosis, retinal vascular thrombosis (RVT), and other non-fatal thrombotic events. These numbers emphasize the scope of the problem; by contrast about 550,000 will die this year in the USA from cancer; thus, fatal thrombosis is about four times as prevalent as fatality from malignancy [1]. Thrombosis, therefore accounts for extraordinary morbidity, mortality and cost of medical care [1]. Extraordinary numbers of deep vein thrombosis (DVT) and pulmonary embolus (PE) occur in association with surgery and almost all can be prevented by appropriate thromboprophylaxis [3]. To appreciate the scope of the problem, specific examples are: the incidence of DVT in the USA is about 159 per 100,000 or about 450,000 per year. The overall incidence of PE in the USA is about 139 per 100,000 or about 355,000 cases per year (clinical data); the incidence of fatal PE in the USA is 94 per 100,000 or about 240,000 deaths (autopsy data) [1, 3, 4, 5, 6].

Definition of Etiology

Surgical Prophylaxis of Venous Thromboembolism and Pulmonary Embolus

Numerous studies have provided evidence that patients who undergo surgery or trauma are at significant risk for developing venous thromboembolic complications, including pulmonary embolus (PE). Thus, an important task for the surgeon is to prevent deep vein thrombosis (DVT) and its complications and morbid sequellae (PE, chronic venous insufficiency, compartmental compression syndromes, other morbidity and mortality). Thus, it is important to define risk groups, by quantifying risk(s) when possible, where prophylaxis must be considered. Unfortunately, the attitudes and opinions, and occasionally "myths" regarding prophylaxis show immense regional variability [7]. Variations include the definition of risk groups, the numbers of patients receiving prophylaxis and the prophylactic modalities used. Because of this, various "consensus conference" groups have been formed in attempts to alleviate these problems. Formerly, there were at least three consensus conference groups, the American College of Chest Physicians (ACCP – begun in 1986) [8], the European Consensus Conference Groups (begun in 1991) and the Scandinavian Consensus Conference Group (begun in 1995) [9]. Since then, the International Consensus Conference group, derived from the European Group, has been formed and encompasses experts from the other groups [10, 11, 12, 13]. The primary purpose of consensus guidelines is to provide optimal direction to the practicing surgeon. If practice guidelines generated are successful and implemented clinicians are assisted in appropriate decision-making for individual patients, and provided protection against unjustified malpractice actions [14].

Unfortunately, many surgeons consider DVT to be "rare" or of "minor" significance. However the "rarity" is often due to the patient developing DVT / PE after discharge and the surgeon may never be informed of a subsequent admission or death; also, about 50% of DVT will progress to serious long-term sequelae including chronic venous insufficiency, stasis ulcers and venous claudication, all associated with significant long-term morbidity and requiring high costs of care [15]. About 30% to 50% of undetected, untreated DVT will progress to PE and about 40% - 50% with DVT will develop chronic venous insufficiency, with the chances increasing about 6-fold with each recurrent episode [1, 3, 15]. In addition, although many surgeons consider distal (calf) DVT to not be a significant problem, about 30% - 40% will extend proximately. Despite significant advances in prevention venous thromboembolism in surgery, recent studies reveals that despite innumerable

consensus conference meetings and resultant publications being widely disseminated, many surgeons in the USA are not yet offering appropriate thromboprophylaxis to appropriate patients and appropriate numbers of patients [16, 17, 18]. Incredibly, surveys of surgeons in the USA have revealed that many not only do not utilise appropriate thromboprophylaxis, but many are not even aware of guidelines which have been published and widely disseminated, including throughout the surgical literature, for over two decades by both the International and North American (ACCP) consensus conference groups [13, 17, 18, 19].

Surgical Prophylaxis

Without thromboprophylaxis, the frequency of fatal pulmonary embolism ranges from 0.1% to 0.8% in patients undergoing elective general surgery [3, 11, 13, 19, 20], 2% to 3% in patients undergoing elective hip replacement [13, 19] and 4% to 7% in patients undergoing surgery for a fractured hip [3, 13, 19]. The risk of post-operative deep vein thrombosis can be identified as low, moderate or high / highest, depending on the surgical procedure and the presence or absence of additional "predisposing" risk factors [1, 3, 7]. See Figures 1 and 2 for guidelines for assessing risk in

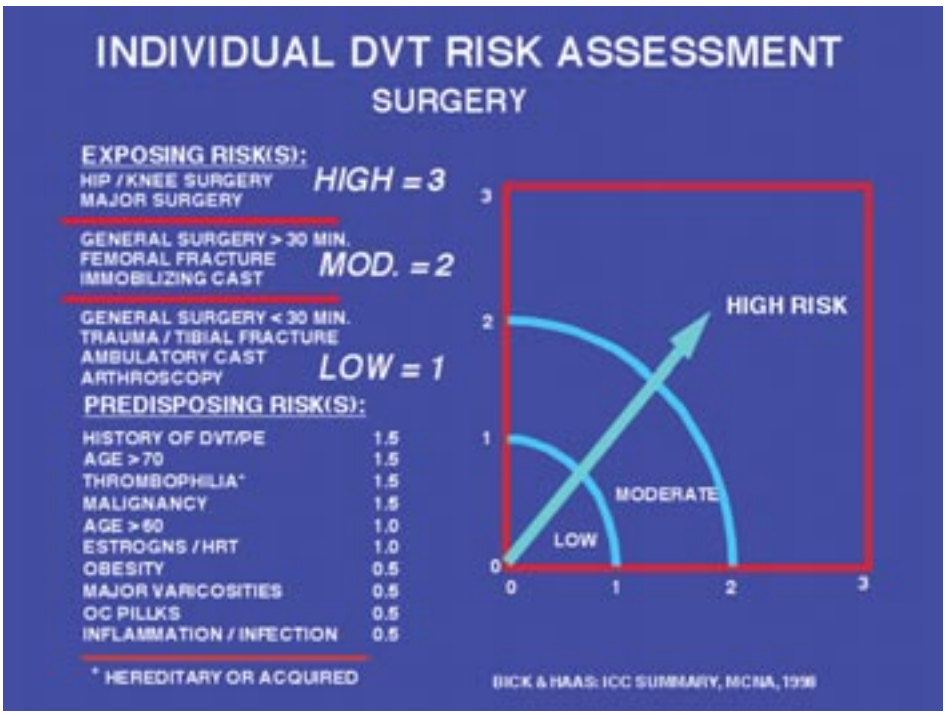

Fig. 1.

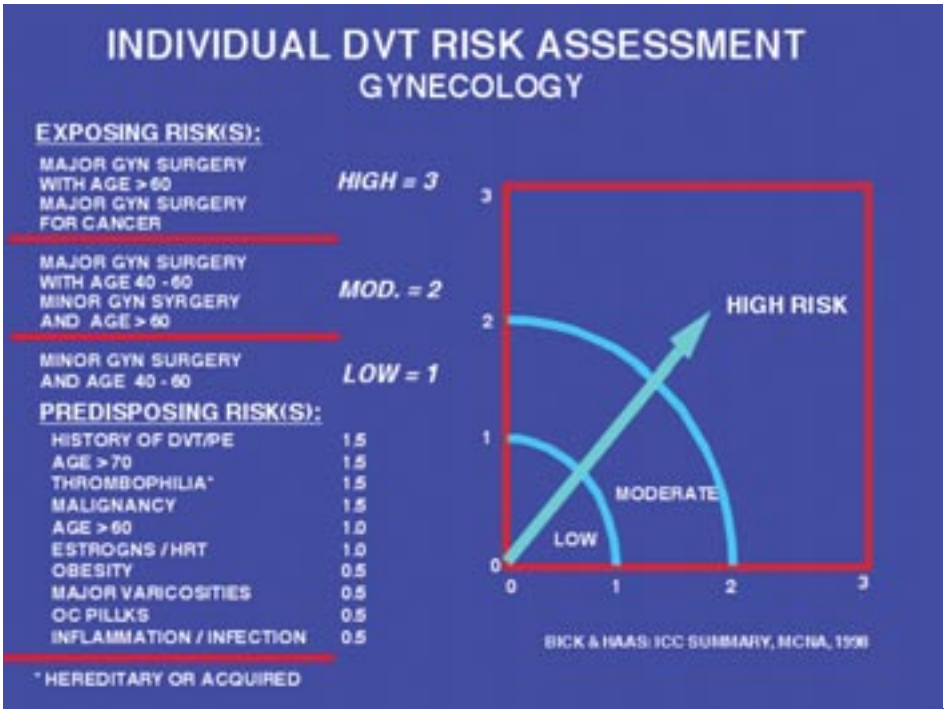

Fig. 2.

Table 1. Predisposing risks in surgical patients.

Increasing age
Immobility
Stroke
Prior DVT or PE
Malignancy
Trauma
Thrombophilia*
Obesity**
Major Varicosities
Cardiac failure
Hormone replacemant therapy
Oral Contraceptives
Pregnancy
Infection
Inflammation
Central venous catheters
Nephrotic syndrome

*Thrombophilia: Hereditary or acquired
**Obesity: Body mass index (BMI) > 30 kg/m^2

general, orthopedic and gynecological surgery patients [1, 3, 7].

Surgery for major trauma or orthopedic surgery, followed by abdominal surgery, is associated with a risk of up to 30% [21]. However, the degree of risk is increased by predisposing risk factors, including age, morbidity, malignancy, obesity, prior history of thromboembolism, immobility, varicose veins, recent operative procedures and hereditary or acquired thrombophilia, among others as shown in Table 1 [3, 7]. These factors are further modified by general care including duration and type of anesthesia, pre- and post-operative immobilization, level of hydration and the presence of infection or sepsis [3, 7]. Thus, the individual risk is determined by the type of surgery and an accumulation of predisposing factors, i.e. patients undergoing minor surgery but bearing several additional risk factors may also be at high risk for thromboembolic complications [3, 7, 11, 19]. Clearly, standards of care demand that all surgeons carefully assess each individual patient for risk factors, both "exposing" and "predisposing", and offering appropriate thromboprophylaxis for the procedure being performed.

Approaches to Thromboprophylaxis

The prophylactic measures most commonly used are low molecular weight heparin (LMWH), low-dose or adjusted dose unfractionated heparin (UFH), oral anticoagulants, intermittent pneumatic leg compression and graduated compression stockings, in probable descending order of efficacy. It should be noted that "foot-pumps" are not recommended surgical thromboprophylactic measures, nor is aspirin [3, 19]. Predisposing risks in surgical patients which must be considered in assessing overall risk for thromboprophylaxis decisions are depicted in Table 1. Exposing risks are evaluated slightly differently by the International Consensus Conference Group [13], which uses three risk stratification categories and the North American (ACCP) Consensus conference Committee which uses four stratification categories [19]. These two exposing risk stratification categories are summarized in Tables 2 and 3.

Table 2. Risk stratification categories of the International Consensus Conference Committee.

Category:	Calf vein thrombosis (%)	Proximal vein thrombosis (%)	Fatal pulmonary embolus (%)
High risk:	40 - 80	10 - 30	> 1
Moderste risk:	10 - 40	1 - 10	0.1 - 1.0
Low risk:	< 10	< 1	< 0.1

Table 3. Risk stratification categories of the North American Consensus Conference Committee.

Category:	Calf vein thrombosis (%)	Proximal vein thrombosis (%)	Clinical pulmonary embolus (%)	Fatal pulmonary embolus (%)
Highest risk:	40 - 80	10 - 20	0.2	0.002
High risk:	20 - 40	4 - 8	2 - 4	0.4 - 1.0
Moderste risk:	10 - 20	2 - 4	1 - 2	0.1 - 0.4
Low risk:	2	0.4		< 0.1

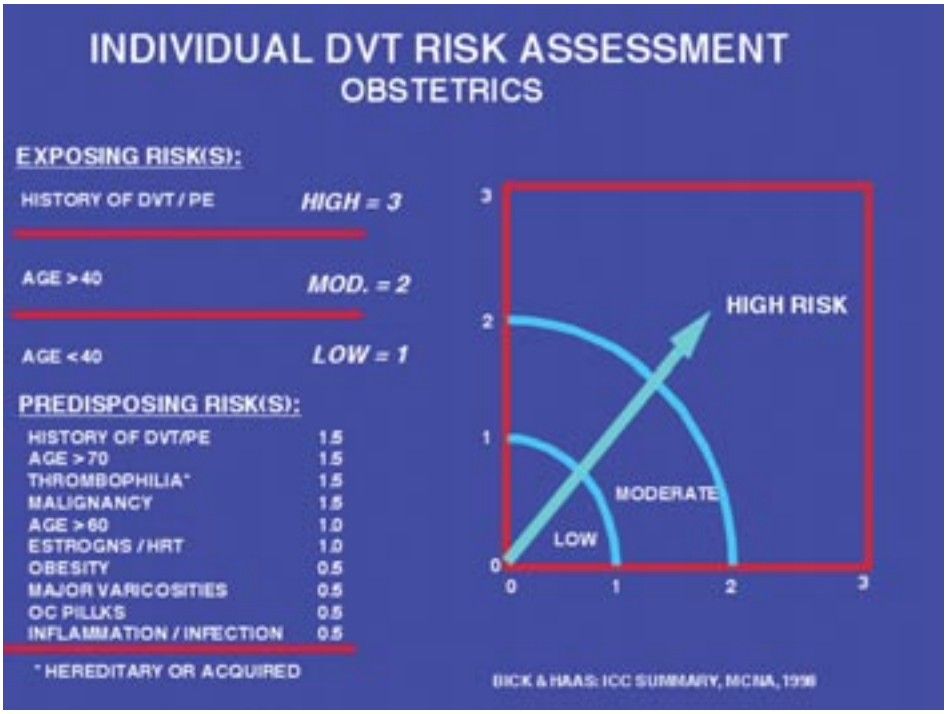

Fig. 3.

It has become standard practice to commence prophylaxis, for example, with low-dose heparin, prior to anesthesia in patients undergoing thoracic or abdominal surgery, and in Europe, prophylaxis is started the night before surgery in patients undergoing total hip or total knee replacement surgery [3, 7]. In North America, because of the concern related to perioperative bleeding, prophylaxis for patients having total knee or total hip replacement has often been started post-operatively [3, 19, 22, 23]. This difference in the patterns of practice may account for the differences in the rates of post-operative venous thrombosis in Europe and North America [3, 7]. A recent randomized trial failed to note a significant difference in DVT or bleeding when LMWH was started preoperative or postoperatively [24].

Low-Dose Unfractionated Heparin (UFH)

The effectiveness of low-dose unfractionated heparin for preventing deep-vein thrombosis has been established by multiple randomised clinical trials [25, 26, 27, 28]. Low-dose subcutaneous heparin is usually given in a dose of 5,000 units 2 hours preoperatively, and then postoperatively every 8 or 12 hours, or more commonly started post-operatively in North America. The incidence of major bleeding complications is not increased by low-dose heparin, but there is an increase in minor wound hematomas. The platelet count should be monitored every other day in all patients on low-dose heparin to detect heparin-induced thrombocytopenia [29]. Low-dose UFH is relatively inexpensive, easily administered, and does not require monitoring, except mandatory platelet counts.

Low-Molecular-Weight Heparin (LMWH)

A number of low-molecular-weight heparin fractions have been evaluated by randomised clinical trials in general surgical patients [30]. In randomised clinical trials comparing low-molecular-weight heparin with unfractionated heparin, low-molecular-weight heparins given once or twice daily are as effective or more effective in preventing thrombosis [30]. The incidence of bleeding is significantly lower in patients receiving LMWH versus UFH by noting a reduction in wound hematomas, severe bleeding, and the number of patients requiring repeat surgery for bleeding [31]. Like unfractionated heparin, although the incidence of heparin induced thrombocytopenia is less than UFH, every other day platelet counts should be performed [29].

Recent studies have shown that low-molecular-weight heparin is superior to LD-UFH in patients suffering multiple trauma [32].

Oral Anticoagulants

Warfarins can be started preoperatively, at the time of surgery, or in the early postoperative period; however, if started at the time of surgery or in the early postoperative period they may not prevent small venous thrombi from forming during surgery, or after surgery, as an antithrombotic effect is not achieved until the third or fourth postoperative day [3, 7, 21]. However, oral anticoagulants may be effective in inhibiting the extension of thrombi and potentially prevent otherwise clinically significant venous thromboembolism [3, 7, 21].

Intermittent Pneumonic Leg Compression (IPC)

Intermittent pneumatic leg compression is effective for preventing DVT in moderate-risk general surgical patients [33] in patients undergoing neurosurgery [34] and cardiac surgery.

Graduated Compression Stockings (GCS)

Graduated compression stocks (GCS) are a simple, safe and moderate effective form of thromboprophylaxis. GCS are recommended in low risk patients and only as an adjunct in those with medium and high risk [3, 7]. The only major contraindication is peripheral vascular disease. However, there is no conclusive evidence that GCS are effective in reducing the incidence of fatal or nonfatal PE [3, 7].

Specific Recommendations for Thromboprophylactic Modalities in Various Surgical Patients [3, 7, 13, 19]

Low risk general surgical patients (e.g. minor surgery without any risk factors): Low risk general surgery patients are those who are undergoing minor surgical procedures, are less than 40 years of age and have no additional risk factors. In general, no specific thromboprophylaxis is recommended other than early ambulation and adequate hydration.

Moderate risk general surgical patients (e.g. major surgery, age over 40 years, or surgery > 30 minutes without any additional risk factors). These are patients undergoing minor surgical procedures but have additional prothrombotic risk factors (Table 1), including those having non-major surgery and are between ages 40 and 60 years without additional risk factors or those undergoing major surgery who are younger than age 40 with no additional risk factors. These patients should be offered thromboprophylaxis with low-dose UFH, LMWH, IPC or GCS. The use of LMWH or low-dose UFH appear more effective than IPC or GCS alone.

High risk general surgical patients (e.g. major surgery, age over 60 years or presence of additional risk factors). These are patients having non-major surgery who are > age 60, or with additional prothrombotic risk factors or patients undergoing major surgery or with additional risk factors (Table 1). These patients should be treated with LMWH, low-dose UFH or IPC. If a patient in this group has a significant bleeding risk, IPC or GCS may be substituted, but this may be less efficacious. In addition to single modalities such as LMWH or low-dose UFH, combined modalities of pharmacological (LMWH or UFH) and mechanical methods IPC or GCS should be considered as they may be more effective.

Highest risk general surgical patients (e.g. major surgery in patients >40 with a prior history of thromboembolic disease, malignancy, thrombophilia, hip or knee arthroplasty, hip fracture, major trauma or spinal cord injury). These highest risk patients should be offered thromboprophylaxis with LMWH or low-dose UFH in conjunction with IPC or GCS; in those of highest risk, continued post-discharge thromboprophylaxis with LMWH or perioperative warfarin is recommended.

Guidelines for scoring risk assessment in general and orthopedic surgical patients are summarized in Figure 1 [3, 7].

Neurosurgery

Neurosurgery patients should be considered for mechanical methods of prophylaxis. The recommended thromboprophylactic measures are IPC with or without GCS; LMWH or low-dose UFH are alternatives but there are concerns about intracranial hemorrhage. In the highest risk neurosurgery patients, a combination of mechanical prophylaxis (IPC or GCS) with LMWH or low-dose UFH may be more effective than either modality used alone. In three randomized controlled studies involving a total of 422 patients the incidence of DVT was reduced from 21.3% in controls to 6.0% in the prophylactic groups using pneumatic compression (Relative risk 0.28; 95% CI: 0.16 to 0.51) [3, 17, 19].

Trauma

Multiple Trauma

Multiple trauma patients are at high risk for thrombosis and low molecular weight heparin represents the prophylaxis of choice [13, 19]. Intermittent pneumatic compression may be used when feasible, as this is unassociated with any bleeding risk. Other alternatives include low-dose UFH or warfarin based on extrapolation from other high-risk situations such as hip fracture and hip replacement surgery. Insertion of an inferior vena cava filter may be considered for very high-risk situations where anticoagulants may be absolutely contraindicated. However, recent randomized trials have questioned the efficacy of caval filters and suggest that in some individuals these devices may increase the incidence of DVT while not protecting against PE [35, 36].

Acute Spinal Cord Injury Associated with Paralysis

Low-molecular-weight heparin is the most effective prophylaxis [3, 13, 19]. Low-dose heparin, intermittent pneumatic compression, and GCS do not appear effective. Combining intermittent pneumatic compression with low-molecular-weight heparin or adjusted-dose heparin may provide additional benefit, but this is not yet supported by adequate data.

Gynecological Surgery

Low risk patients:
Patients undergoing minor procedures for benign disease and absence of additional risk factors need only early amputation and adequate hydration.

Moderate risk patients:
Low dose UFH (5000 units every 12 hours) or LMWH are effective prophylaxis in moderate risk gynecological surgery [3, 13, 19]. By extrapolation from other types of surgery. Intermittent pneumatic compression, continued for several days after surgery may also be considered since it is effective in higher risk patients.

High risk patients: (e.g. patients undergoing extensive surgery for malignant disease):
Low dose UFH (5000 units every 8 hours) or LMWH; either of these may be combined with mechanical modalities of IPC or GCS [3, 13, 19].

Guidelines DVT/PE risk assessment for gynecologic surgical patients is summarized in Figure 2.

Pregnancy
A common problem in pregnancy is the women with a prior history of DVT. If a prior history of only one DVT associated with a prior transient risk factor and no present risk factor, careful surveillance and postpartum anticoagulant therapy, either warfarin or LMWH (Dalteparin: 5,000 units subcutaneously every 24 hours) is recommended. If there is a single prior DVT associated with no definable risk factor, LMWH (5,000 units subcutaneously every 24 hours) during pregnancy and post-partum is recommended. In those women with a prior history of DVT and a thrombophilic disorder, surveillance is acceptable, however, LMWH at 5,000 units s.c. every 24 hours appears more effective. In patients with no history of DVT, but known to harbor thrombophilia, surveillance, LMWH during pregnancy or low-dose UFH are acceptable and post-partum (5,000 units subcutaneously every 24 hours) is acceptable. If the patient harbors antithrombin deficiency, the indications for thromboprophylaxis are stronger. In those with more than two prior episodes of DVT or PE with LMWH throughout pregnancy (5,000 units subcutaneously every 24 hours), and for the post-partum period is recommended; this should be followed by long-term appropriate thromboprophylaxis (LMWH or warfarin). Less common is the patient who develops DVT or PE during pregnancy; for these patients thrombotherapeutic regimens of dose adjusted LMWH should be used: dalteparin at 200 U / Kg / 24 hours or enoxaparin at 1.0 mg / Kg / 12 hours are acceptable [3, 7]. If considering using enoxaparin one should heed the recent U.S. FDA MedWatch adverse reaction reports associated with enoxaparin (Lovenox / Clexane) in pregnancy released by the FDA in January 9, 2002 [37]. This preliminary report suggests an association between enoxaparin and excessive fetal or maternal hemorrhage and death and fetal teratogenicity; clinicians are strongly encouraged to be thoroughly familiar with this FDA report [37]. In women who achieve unplanned pregnancy while on warfarin therapy for prior venous thromboembolic disease, warfarin should be discontinued immediately and LMWH (5,000 units subcutaneously every 24 hours) should be promptly instituted, used throughout pregnancy and used for 6 weeks post-partum If at all possible, in the patient on warfarin therapy, LMWH ((5,000 units subcutaneously every 24 hours) should be instituted before pregnancy is achieved to minimize chances of teratogenicity.

Pregnancy and Mechanical Heart Valves:

Pregnancy patients with mechanical heart valves present a major challenge. These patients should have warfarin stopped prior to conception and dose adjusted LMWH (Dalteparin) at 200 U / Kg every 24 hours started and used throughout pregnancy. For those concerned about epidural bleeds, therapeutic doses of UFH may be substituted for the two weeks prior to delivery. LMWH at therapeutic levels should be reinstituted for two – weeks postpartum, and then the patient is changed back to the preconception dose of warfarin. The reader is strongly cautioned regarding recent U.S. FDA MedWatch adverse reaction reports regarding the use of enoxaparin (Lovenox / Clexane) in any patient with mechanical heart valves; any clinician considering the use of enoxaparin in this group of patients should be thoroughly familiar with this adverse reaction report released January 9, 2002 [37].

Patients with Infertility or Recurrent Miscarriage Syndrome

Women with two or more unexplained miscarriages who have been evaluated for anatomical

Table 4. Thrombophilia defects associated with recurrent miscarriage and infertility (Descending order of prevalence).

Amtiphospholipid syndrome
Sticky platelet syndrome
PAI-1 polymorphisms
Elevated PAI-1
MTHFR mutations
Factor V Leiden
TPA deficiency
Prothrombin G20210A
Protein S defects
Protein C defects
Antithrombin defects
Hyperhomocysteinemia
Immune vasculitis
Heparin cofactor II defects

and hormonal defects are likely to harbor a thrombophilic defect, most commonly antiphospholipid syndrome [38, 39] (see Table 4 for prevalence of thrombophilias associated with recurrent miscarriage) [38]. These patients should be treated with preconception aspirin at a dose of 81 mg / day and immediately post-conception, dalteparin at 5,000 units per day should be added and both drugs used to term. If the thrombophilic defect is or includes one of the MTHFR mutations (C677T or A1298C), folic acid at 5 mg / day plus pyridoxine at 50 mg / day should be added to the ASA + dalteparin regimen. This is most conveniently given as Foltx at two tablets / day. It is thought this will not only blunt the prothrombotic tendency, premature cerebrovascular or cardiovascular risk tendency but will also significantly blunt the chances for neural tube defects associated with MTHFR mutations.

Urological Surgery

Low Risk Patients:
In patients undergoing minor urological procedures, like transurethral or other low risk procedures, who have no additional risk factors, early ambulation and adequate hydration is adequate thromboprophylaxis.

Medium Risk patients:
In patients undergoing major open urologic procedures, routine thromboprophylaxis with LMWH, UFH, IPC or GCS should be routinely used.

High Risk Patients:
For high risk patients, undergoing urologic surgery for malignant disease or those with other risk factors, LMWH or UFH should be used in combination with mechanical prophylaxis of IPC with or without GCS.

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