Ultrasound Studies of the Deep Venous System of the Leg in Pregnancy

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Declaration

I declare that this thesis has been composed by me and that the work is my own. I further declare that this thesis has not been submitted for any other degree, diploma or professional qualification.

Nicholas S Macklon

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Publications

The following papers derived from the work presented in this thesis have been submitted for publication.

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Abbreviations

The following abbreviations are used throughout this thesis:

APC	Activated Protein C
APTT	Activated Partial Thromboplastin Time
AT	Antithrombin
CFA	Common Femoral Artery
CFV	Common Femoral Vein
CNS	Central Nervous System
CS	Caesarean Section
CW	Continuous Wave
dB	Decibel
DVT	Deep Venous Thrombosis
ECG	Electrocardiograph
FDA	Food and Drug Administration (of the United States)
FDP	Fibrinogen Degradation Product
F max	Maximum Frequency Shift
F min	Minimum Frequency Shift
IV	Intravenous
IVC	Inferior Vena Cava
LMWH	Low Molecular Weight Heparin
MHz	Megahertz
mW	millewatt
PAI	Plasminogen Activator Inhibitor
PI	Pulsatility Index
POP	Popliteal Vein
PRF	Pulse Repetition Frequency
PSNT	Protamine Sulphate Neutralisation Test
PTE	Pulmonary Thromboembolism
RCOG	Royal College of Obstetricians and Gynaecologists
RI	Resistance Index
SA	Spatial Average
SC	Subcutaneous
SE	Standard Error
SFV	Superficail Femoral Vein
SMR	Scottish Morbidity Returns

SP	Spatial Peak
SPTA	Spacial Peak Temporal Average
TAMV	Time Averaged Maximum Velocity
TAV	Time Averaged Velocity
t-PA	Tissue Plasminogen Activator
VVI	Venous Variation Index

Aims of Thesis and Abstract

Aims of Thesis

The continuing importance of thromboembolic disease as a cause of maternal mortality and morbidity despite changes in obstetric clinical practice designed to prevent thromboembolism in pregnancy, indicates a need for more information on who is at particular risk, the best means and technique of diagnosing deep venous thrombosis in pregnancy and appropriate strategies for prevention.

Ultrasound now offers a reproducible, accurate and non-invasive means of examining vascular anatomy and function. In the field of obstetrics interest in ultrasound has until recently been limited to examination of the fetus. However, with ultrasound becoming established as the first line-investigation for suspected DVT in pregnancy , and showing promise as a screening tool, obstetricians are becoming aware of its important role in maternal medicine. Interpretation of any test requires a knowledge of what constitutes normality. Despite its place as the new 'Gold Standard' for DVT in pregnancy, the effect of pregnancy itself on interpretation has been uncertain. Ultrasound offers the means of quantifying the changes which occur in deep venous anatomy and blood flow velocity in pregnancy, and enables the effect of interventions on these parameters to be determined.

The three principal aims of the work presented in this thesis were:

1. To determine the incidence of venous thromboembolic disease in pregnancy in Scotland, to assess how certain risk factors impact on this population and to determine whether women considered to be at low to moderate risk may be sustaining undetected subclinical DVT with implications for long-term morbidity.

2. To assess how pregnancy alters the anatomy and blood flow velocity within the proximal deep veins of the leg, so that the normal appearances at different gestational stages could be described, and thus aiding the ultrasound diagnosis of DVT in pregnancy.

3. To investigate the impact of increasing gestation, alteration in posture, mode of delivery and mechanical means of thromboprophylaxis on vessel size and dilatation and flow velocity pattern ; factors which may influence the risk of thrombogenesis.

Abstract

The thesis begins with a review of thromboembolic disease in pregnancy. The physiological changes which render blood more prone to clot in pregnancy are reviewed, and an overview of prevention, diagnosis and treatment of thromboembolic disease in the pregnant woman is presented. The following chapter considers the evidence for the role of venous stasis and vessel dilatation in initiating thrombogenesis and examines how pregnancy may provide the haemodynamic, anatomic and rheological conditions for thrombogenesis to occur.. There then follows a discussion of duplex Doppler ultrasound as a means of quantifying changes in venous anatomy and blood flow velocity and validity of the techniques employed are considered. A reproducibility study carried out by the author and a colleague is then presented, demonstrating good inter and intra-observer agreement for the techniques employed.

In order to determine the incidence of recorded thromboembolic complications in Scottish obstetric practice, a retrospective study of DVT and PE complicating obstetrics in Scotland from 1982 to 1992 was conducted. Analysis of data concerning over 700,000 maternities extracted from the SMR 2 database held by the Common Services Agency for the National Health Service showed that age over 35 years and emergency caesarean delivery were important risk factors for obstetric DVT and PTE. The incidence of antenatal DVT and PTE was 0.615/1000 and 0.108/1000 maternities respectively in those under 35 years of age and 1.216/1000 and 0.405/1000 maternities respectively in those over 35 years. Postnatal DVT occurred with an incidence of 0.424/1000 after caesarean section and 0.173/1000 after vaginal delivery. A prospective ultrasound screening study for asymptomatic DVT in the early puerperium was performed in 140 women at low-moderate risk of DVT. No DVT were detected. This suggests that puerperal DVT is rare in women at low to moderate risk, and that undetected subclinical DVT are unlikely to be causing significant long-term morbidity.

The effect of increasing gestation and posture on vessel diameter, flow velocity and respiratory fluctuation in flow. In the supine position, vessel diameter increased and flow velocity decreased with advancing gestation. These changes were most marked in the common femoral vein. No significant gestational changes in respiratory flow fluctuation were observed. Flow velocity was significantly slower in the left compared to the right common femoral and popliteal veins, in keeping with the

observed increased incidence of left ileofemoral DVT in pregnancy. Adoption of the left lateral position increased flow velocity in both legs throughout pregnancy and postnatally. The deep venous system of the leg was studied with duplex Doppler ultrasound in the early and late puerperium. Flow velocity was reduced in the left leg and changes in vessel diameter and flow velocity were observed between the 4th and 42nd postnatal day. Although flow velocity was reduced in the common femoral vein after caesarean section compared to vaginal delivery, no other differences were observed.

The physiology of venous flow in the proximal deep veins of the leg was studied. A pulsed Doppler ultrasound study of flow phasicity showed respiratory phasicity to be present in 95% of subjects. In the supine position during pregnancy and the puerperium, venous flow velocity was maximal on inspiration but on standing upright it was maximal during expiration indicating that intra-abdominal pressure may influence venous return.

Duplex Doppler ultrasound was used to study the effects of three types of stocking on venous diameter, flow velocity and respiratory fluctuation in the supine, left lateral and upright positions in non-pregnant women. Graduated stockings reduced vessel diameter at the popliteal vein, but no other effects were observed. In contrast, adoption of the left lateral position caused a significant reduction in vessel diameter and increase in flow velocity.

In addition to providing novel information on the epidemiology of thromboembolic disease in pregnancy, the data here presented address the effects of pregnancy, postural changes and a common therapeutic intervention on deep venous flow and may contribute to our understanding of the clinical pattern and pathophysiology of DVT in pregnancy, its diagnosis and prevention.

Chapter 1

Pulmonary thromboembolic disease and pregnancy

Summary

Pulmonary thromboembolism remains a major cause of maternal mortality. The increased risk associated with pregnancy is, in part, imposed by physiological alterations in the coagulation and fibrinolysis systems, and these changes and their impact are outlined in this chapter, which discusses the clinical context surrounding the work presented later in this thesis. Risk factors for DVT are also considered and the importance of appropriate thromboprophylaxis is emphasised. A clinical approach to prevention and treatment of DVT is described, with reference to the particular problems associated with pregnancy. In critically reviewing methods of DVT diagnosis, ultrasound is shown to provide an appropriate methods for the symptomatic pregnant patient. The diagnosis of pulmonary embolism is also addressed.

1.1 Introduction

Pulmonary thromboembolism, along with pre-eclampsia, has remained a major cause of maternal mortality over the last forty years (Department of Health, et al 1996). It has persisted as a major cause of maternal mortality despite modern trends in obstetric practice which have led to reduced periods of immobilisation, outpatient management of pregnancy complications previously considered to require admission and earlier discharge after delivery. The clinical diagnosis of deep venous thrombosis is unreliable (Genton & Turpie 1980), and the physiological changes which take place in pregnancy, such as peripheral oedema and venodilatation may make the early recognition of DVT more difficult. In the most recent Confidential Enquiries into Maternal Deaths (Department of Health et al 1994), 70% of those who had suffered a fatal PTE had no documented clinical evidence of DVT. Similarly, the recently published Report of the National Confidential Enquiry into Perioperative deaths (DHSS 1993) found that in most of the 20% of perioperative deaths attributed to PTE, the preceding DVT had not been diagnosed. (DHSS 1993). Given the difficulties in detection of DVT, particularly in pregnancy, effective diagnostic strategies are required. Identification of those at increased risk and the provision of appropriate thromboprophylaxis may enable obstetricians and gynaecologists to reduce the mortality and morbidity associated with thromboembolic disease.

1.2 Physiological adaptation of the coagulation system in pregnancy

Normal pregnancy is associated with major changes in the coagulation and fibrinolytic systems. These have traditionally been thought to represent an adaptive and preparatory mechanism for the haemostatic challenge of delivery and also to maintain the placento-uterine interface during pregnancy. The overall effect from these changes is an increased thrombotic potential which is most marked around term and the immediate post-partum period.

Factor XIII, high molecular weight kininogen and prekallikrein increase in pregnancy although reports on the latter have not been entirely consistent with some authors reporting no change in prekallikrein levels (Hellgren & Blomback 1981, Sayama et al 1981, Adam et al 1985). Factor XI levels fall gradually through pregnancy reaching their nadir at term (Hellgren & Blomback 1981). Factor IX remains static or increases slightly (Beller & Ebert 1982). Both factor VIII coagulant activity and von Willebrands factor antigen increase progressively as pregnancy advances (Hellgren & Blomback 1981, Stirling et al 1984, Sorensen et al 1995). These increases in the two components of the factor VIII complex appear to occur in parallel in the first half of pregnancy, but then diverge due to a greater increase in von Willebrands factor antigen. This increases by around twofold the ratio of von Willebrands factor antigen: factor VIII coagulant activity (Hellgren and Blomback 1981, Inglis et al 1982, Stirling et al 1984). Factor VII also increases in pregnancy (Stirling et al 1984, Beller and Ebert 1982). Factor X increases while Factors II and V show do not change (Stirling et al 1984, Hellgren & Blomback 1981). Fibrinogen increases substantially and progressively with gestation and a significant change is evident from the first trimester and an almost twofold increase over non-pregnant levels by term (Stirling et al 1984, Hellgren & Blomback 1981). Factor XIII shows an initial increase but then falls to normal non-pregnant values in late pregnancy (Persson et al 1980)

The endogenous inhibitor of coagulation antithrombin III was initially thought to decrease in pregnancy; however, more recent studies show that levels do not appear to change in pregnancy (Stirling et al 1984, Hellgren and Blomback 1981, Weiner & Brandt 1982, Francalanci et al 1995). Although antithrombin III may increase following delivery (Hellgren & Blomback 1981), this has not been a consistent finding (Weenink et al 1982, Bremme et al 1992). Protein C levels remain constant or increase slightly (Mannucci et al 1984, Malm et al 1988, Bremme et al 1992). Protein S normally exists in plasma in two forms; the functionally active free protein

S and protein S complexed with C4b-binding protein which is functionally inactive. Normally an equilibrium exists in plasma between these two forms. In normal pregnancy there is a reduction in protein S activity and this appears to be due to a reduction in total protein S as measured antigenically rather than a change in C4b-binding protein (Comp et al 1986).

Fibrinolytic activity is impaired during pregnancy, but returns rapidly to normal following delivery (Bonnar et al 1969,1970, Stirling et al 1984). This is due to placentally derived plasminogen activator inhibitor type 2 (PAI-2) which is present in substantial quantities during pregnancy (Booth et al 1988, Lecander & Astedt 1986, Nilsson et al 1986). The endothelial derived inhibitors of plasminogen activator (PAI-1 and PAI-2) increase in pregnancy (Bremme et al 1992, Ishii et al 1994, Halligan et al 1994, Sorensen et al 1995). Increased levels of t-PA Ag have also been reported (Kruithof et al 1987, Sorensen et al 1995, Ishii et al 1994). However, in early pregnancy, t-PA activity has been shown to be close to the standard range seen in non-pregnant women and to gradually decrease during later pregnancy, before recovering to the normal range 48 hours after delivery (Ishii et al 1994). Plasminogen increases during pregnancy (Bonnar et al 1969, Hellgren & Blomback 1981, Beller & Ebert 1982) as does antiplasmin. Despite the reduction in fibrinolytic activity, fibrinolysis cannot be completely shut down as FDPs remain present in the plasma with several studies showing that FDPs increase as pregnancy progresses (Stirling et al 1984, Thorburn et al 1982, Bonnar et al 1969, Woodfield et al 1968).

The activity of the fibrinolytic system in response to stimulation of fibrinolysis by venous occlusion has been assessed in pregnancy. Total t-PA release is significantly reduced in pregnancy with free t-PA remaining below the limit of detection of the assay following occlusion (Ballegeer et al 1987). This is in contrast to the non-pregnant situation where both total and free t-PA increases significantly following venous occlusion. These data suggest that t-PA release is impaired in pregnancy and that free t-PA is rapidly inhibited, in keeping with the high levels of plasminogen activator inhibitors noted in pregnancy *(vide supra).* Despite this impairment in the response to venous occlusion, D-dimer fragment of cross-linked fibrin is substantially increased in the first, second and third trimesters as compared to non-pregnant women (Ballageer et al 1987, Bremme et al 1992, Francalanci et al 1995). This indicates that fibrinolysis is still occurring and clearly is not impaired to the extent suggested by the reduced levels of t-PA and increased PAI-1 and PAI-2.

Impaired fibrinolysis can be found in some patients with a history of deep venous thrombosis (Isacson & Nilsson 1972) and the physiological impairment of fibrinolysis seen in pregnancy may contribute to the increased thrombotic risk associated with pregnancy. Overall, the data discussed in relation to changes in the coagulation and fibrinolytic systems in pregnancy suggest that activation of both systems is occurring with deposition of fibrin and subsequent fibrinolysis with increased levels of FDP's. These changes are compatible with a compensated state of low grade disseminated intravascular coagulation. This is supported by other studies where increased fibrinopeptide A, FDP's and platelet release products have been found in normal pregnancies indicating coagulation, fibrinolysis and in-vivo platelet activation respectively (Gerbasi et al 1990), in keeping with compensated low grade disseminated intravascular coagulation.

Platelet count does not change significantly during pregnancy (Stirling et al 1984, Hellgren & Blomback 1981, Beller & Ebert 1982), although there may be a slight fall towards the end of the third trimester (Fay et al 1983) in keeping with reports of a trend towards a reduction in platelet lifespan (Rakoczi et al 1979, Wallenburg and van Kessel 1978). The increase in mean platelet volume and volume distribution width (Fay et al 1983, Sill et al 1985, Tygart et al 1986, Singer et al 1986) also suggests that a compensated state of progressive platelet destruction occurs during the third trimester. This may be supported by the enhanced platelet reactivity reported by some studies in normal pregnancy (Morrison et al 1985, Burgess-Wilson et al 1986), although others have reported that platelet reactivity is unchanged (Whigham et al 1978, Greer et al 1988). O'Brien et al (1986) have shown that circulating platelet aggregates are increased in normal pregnancy, in keeping with enhanced reactivity in-vivo, while ex-vivo platelet reactivity was simultaneously reduced. This may reflect a degree of platelet exhaustion secondary to enhanced activation *in-vivo*. *In-vivo* activation in late pregnancy is also supported by increased plasma levels of ß-thromboglobulin in the second and third trimester compared to the first trimester and non-pregnant levels (Douglas et al 1982). Thus, normal pregnancy is associated with a degree of enhanced platelet destruction which is compensated for by increased production. Following the haemostatic challange of delivery, platelet count has been thought to increase (Hellgren & Blomback 1981). However, more recent studies suggest that the platelet count remains unchanged after uncomplicated vaginal delivery and may be slightly reduced after normal and uncomplicated caesarean section (Dahlstrom &Nesheim 1994).

The majority of the pregnancy related changes in the haemostatic systems revert to normal following separation of the placenta. There is evidence of contact system activation and platelet consumption immediately following delivery, then an increase in fibrinogen, factor VIII:C and platelet count a few days later (Bonnar 1970, Hellgren & Blomback 1981). The fibrinolytic system rapidly returns to normal in keeping with the loss of the placental source of PAI-2 (Wiman et al 1984). The normal non-pregnant state is regained by around 4 weeks after delivery.

1.3 Incidence of DVT and PTE

Difficulties in diagnosing DVT in pregnancy have resulted in variations in the reported incidence of deep venous thrombosis (DVT) and non-fatal PTE associated with pregnancy. Clinical diagnosis has estimated the incidence of DVT in pregnancy between 0.05% and 1.8% (Hiilesmaa 1960, Aaro & Juergens 1971, Coon et al 1973), increasing to between 0.08 -1.2% following a vaginal delivery (Daniel et al 1967, Husni et al 1967, Aaro & Juergens 1971, Flessa et al 1974), and to 2.2-3.0% (Husni et al 1967, Hiilesmaa 1960) following caesarean section. A Swedish study which confirmed the clinical diagnosis by objective means (plethysmography, thermography, and venography) found an incidence of 0.07% during pregnancy (Bergqvist et al 1983). The same group, using plethysmography, screened 169 women following caesarean section and found an incidence of DVT of 1.8% (Bergqvist et al 1979). A retrospective review of 35,000 pregnancies at Queen Charlottes Hospital, London, found an overall incidence of DVT and PTE of 0.09% (Letsky & de Swiet, 1984). Further studies based on objective screening techniques are required to clarify the true incidence of DVT in pregnancy .

The young age of pregnant women renders chronic venous insufficiency arising from DVT in pregnancy a significant cause of long-term morbidity. Studies of the frequency of objectively diagnosed deep venous insufficiency in women with a history of proven DVT in pregnancy have shown the prevalence of deep venous insufficiency in the previously thrombosed leg to be 65% compared to 22% in the healthy leg, the latter acting as a control (Lindhagen et al 1986). This frequency of 65% is significantly greater (Bergqvist et al 1992) than that found after postoperative DVT diagnosed by radio-labelled fibrinogen uptake testing (32%) or after clinically suspected acute DVT confirmed by venography (49%) (Lindhagen et al 1984, 1985).

1.4 Risk Factors for DVT

The risk of fatal PTE following caesarean section is greater than after vaginal delivery and risk appears greater after an emergency procedure. This may be due to reduced mobility, and trauma to pelvic veins at the time of operation. It is also likely that there is an increased risk following forceps deliveries since one study has shown that 25% of cases of thromboembolism occurred in complicated pregnancies which included difficult forceps deliveries and prolonged labour (Aaro & Juergens 1974).

The Confidential Enquiries into Maternal Deaths for England and Wales show that age and parity are important, with risk increasing more sharply with age, especially in those over 35 years old, than with increasing parity. The risk of fatal PTE in a 40 year old para 4 being 263.6 per million maternities compared to 11.3 per million maternities in a 20-24 year old para 4 (Department of Health 1989).

Restricted activity, often associated with hospitalisation and bed rest for complications of pregnancy such as hypertension, is also an important risk factor especially when the patient may have an increased likelihood of other risk factors such as operative delivery. Obesity is undoubtedly an important risk factor for DVT/PTE as such patients have impaired fibrinolytic activity, poor mobility and an increased likelihood of venous stasis. The venous tone appears to be reduced in pregnancy resulting in diminished flow prior to physical obstruction by the gravid uterus, although physical obstruction of the inferior vena cava also occurs later in pregnancy due to uterine size and may exacerbated by engagement of the fetal head (Flessa et al 1974, Wright et al 1950).

If a surgical procedure is carried out during pregnancy or the puerperium, such as post-partum sterilisation, then there is an increased risk of thrombotic problems. Other risk factors include a hypertensive problem in pregnancy, excessive blood loss (Department of Health 1989), sickle cell anaemia (Thomas et al 1982, Van Dinh et al 1982), dehydration and to have a blood group other than O (Jick et al 1969, Bergqvist et al 1983). Hereditary thrombotic problems such as ATIII or protein C deficiency, and acquired thrombotic problems such as lupus anticoagulant also place the patient at increase risk and these are discussed below.

A previous history of a DVT during pregnancy increases the risk of a future thrombosis both within and outwith pregnancy. The risk of recurrence during pregnancy and the puerperium has been reported to be 15% and the risk of DVT not

pregnancy and the puerperium has been reported to be 15% and the risk of DVT not associated with pregnancy, over a median follow up of over 10 years, reported to be 33% (Bergqvist et al 1992). These data are similar to those obtained from a retrospective review of the literature (Bergqvist et al 1992) and other retrospective studies (Tengborn et al 1989). However, de Swiet's group have reported 59 pregnancies in women with a history of thrombosis who received no anticoagulant therapy antenatally (although intra-partum and post-partum prophylaxis was given). None of these women had any thromboembolic complication (de Swiet et al 1987). These figures suggest that the risk of recurrence during pregnancy in those not receiving prophylaxis may be less than 5%.

1.5 Thromboprophylaxis

1.5.1 Heparin

The most commonly used mode of thromboprophylaxis in pregnancy is subcutaneous heparin (Greer & de Swiet 1993). Since neither unfractionated standard heparin nor low-molecular weight heparins cross the placenta (Flessa 1965, Forestier et al 1984, 1987, Andrew et al 1985, Omri et al 1989) or the breast, it is particularly suited in these respects for use in pregnancy. While it might increase the risk of haemorrhage in the mother and utero-placental bed, there is no risk of fetal haemorrhage *per se* or of any teratogenic effect. There are, however, other risks associated with the use of heparin in pregnancy, the most worrying of which is heparin induced osteoporosis. Heparin induced osteoporosis has been reported in patients on long term heparin therapy during pregnancy with resultant problems such as vertebral collapse (Hirsh 1991). This was initially thought to be an idiosyncratic phenomenon and it may be that only a subgroup of patients are susceptible to the effect of heparin on bone mineralisation (Ginsberg et al 1990). However, de Swiet et al (1983) have shown objectively that the effects appear to be dose and duration related and that significant bone demineralisation occurs in women taking subcutaneous heparin 20,000 i.u. daily in pregnancy and 16,000 i.u. daily after delivery for greater than 22 weeks compared to women on short term therapy (<7 weeks). In addition, an intermediate effect may be seen in patients on therapy for 10-22 weeks (de Swiet et al 1983). There was no correlation between loss of bone mass and symptoms which might be attributable to this (de Swiet et al 1983). A recent prospective consecutive cohort study using bone-densitometry to evaluate subclinical heparin-induced osteoporosis demonstrated a significant decrease in mean femur bone density among those taking longterm

subcutaneous heparin prophylaxis (Barbour et al 1994). However, no dose-response relationship could be demonstrated. Among 184 women receiving subcutaneous heparin in the range of 13,000 to 40,000 i.u. over a mean duration of 25 weeks, Dahlman (1993) demonstrated a 2.2% incidence of osteoporotic fractures. In this study a dose relationship was evident, with those sustaining fractures receiving a mean of 24,500 iu heparin/24 hours compared with an average of 19,100i.u. heparin for the whole group. However, a vertebral fracture was sustained by one woman who had received low dose prophylaxis (15,000 i.u. / 24 hours) for 7 weeks.

It is not known if low molecular weight (LMW) heparins will confer any benefit in this regard. In animal studies, chronic dosing with unfractionated and low molecular weight heparin given in comparable doses both resulted in osteoporosis of a similar degree (Matzsch et al 1987). However, bone density scans performed after delivery of 11 patients who had received low molecular weight heparin thromboprophylaxis throughout pregnancy and for at least 12 weeks postpartum showed normal mineral mass (Melissari et al 1992).

Whether or not the osteoporosis induced by longterm heparin is reversible remains unclear. Zimran et al (1986) suggested the effect may be reversible. However, osteopenic effects could still be demonstrated up to two years after cessation of treatment in de Swiet's study (de Swiet et al 1983) and a significant reduction in femur bone densitometry was present six months after ceasing heparin prophylaxis in Barbour's study (Barbour 1994).

Heparin can also cause thrombocytopaenia, allergic reactions and alopecia, but these appear to be uncommon. The incidence of heparin induced thrombocytopaenia has been estimated at between 0-30% (King & Kelton 1984). However, most recent studies have reported an incidence of between 1 and 5%. Should this complication develop heparin should be stopped and within several days the platelet count will usually return to normal. An alternative anticoagulant may be required especially if a thrombotic problem has developed. As these thrombotic problems are related to platelet activation, anti-platelet therapy with aspirin may be of benefit (King & Kelton 1984). There have also been reports of LMW heparins being used successfully in pregnancies complicated by heparin allergy and thrombocytopaenia (Harenberg et al 1987, Henny et al 1986) although it appears that severe heparin induced thrombocytopaenia may also occur with heparinoids (van Besien et al 1991). In our own practice we have successfully used enoxaparin for therapeutic anticoagulation in

a patient with severe thrombosis and heparin induced thrombocytopenia (Macklon et al 1995).

Previous studies suggested that heparin might be associated with an adverse fetal outcome in up to one third of pregnancies associated with its use (Hall et al 1980). This is surprising as heparin does not cross the placenta and bleeding complications are not common enough to explain it. However, a recent literature review of 186 studies which reported 1325 pregnancies associated with anticoagulant therapy and which took into account factors such as maternal co-morbid conditions, found that heparin therapy was not associated with any adverse fetal or infant outcome (Ginsberg et al 1989, Ginsberg 1991).

1.5.2 Warfarin

Warfarin also requires special consideration in pregnancy as it readily crosses the placenta and is a known teratogen. It produces a specific warfarin embryopathy which may occur following exposure to the drug in the first trimester, with the period between 6 and 9 weeks gestation (Hall et al 1980) being the most vulnerable stage. It is difficult to estimate the incidence of warfarin embryopathy as most studies have been retrospective, however, an extensive recent literature review has placed the incidence at 4.6% (45 of 970 pregnancies associated with oral anticoagulant therapy) (Ginsberg et al 1989, Ginsberg 1991). The only prospective study of coumarin anticoagulation in pregnancy was performed in patients with valvular heart disease (Iturbe-Alessio et al 1986). This study showed an incidence of fetal abnormality of almost 30% in infants exposed to a coumarin between 6 and 12 weeks gestation. Furthermore, when heparin was substituted for warfarin between the 6th and 12th weeks, none of the infants were found to have warfarin embryopathy. Thus, warfarin embryopathy appears to be a significant but potentially preventable problem for mothers requiring anticoagulation in pregnancy.

The warfarin embryopathy takes the form of abnormal bone and cartilage formation termed chondrodysplasia punctata which is characterised by nasal and midface hypoplasia, frontal bossing, short stature and stippled chondral calcification. Other abnormalities have also been documented in association with warfarin therapy, including microcephaly, central nervous system abnormalities, optic atrophy, cardiac defects and the asplenia syndrome (Stevenson et al 1980, Cox et al 1977, Hall et al 1980, Ginsberg 1991). It should be noted, however, that central nervous system abnormalities may occur with warfarin exposure at any stage of pregnancy (Hall et al

1980, Ginsberg 1991). The mechanism behind central nervous system abnormalities is thought to be related to small intracerebral bleeds and subsequent scarring in-utero. As the fetal liver enzyme systems are immature, the levels of vitamin K dependent coagulation factors are low. Consequently, warfarin therapy maintained in the therapeutic range in the mother poses the risk of excessive anticoagulation and subsequent bleeding in the fetus. The incidence of CNS abnormalities has been estimated at around 3% from retrospective studies (Hall et al 1980, Ginsberg 1991) based on literature reviews. Among a group of 22 infants whose mothers took warfarin during the second and third trimesters, no intellectual or developmental difference was demonstrated when compared to matched controls (Chong et al 1984). Chen et al (1982) found no developmental problems in infants exposed to warfarin in the second and third trimester except in one infant with congenital hydrocephalus. These latter two studies suggest that the incidence of CNS abnormalities may be much lower than previously thought. The outcome of affected infants is variable due to varying severity of the warfarin embryopathy syndrome. However, around 50% of survivors with the embryopathy appear to do well while those with haemorrhages or CNS abnormalities do poorly (Hall et al 1980).

The use of warfarin also places both mother and fetus at increased risk of haemorrhagic complications in later pregnancy, during delivery and in the early post partum period (de Swiet et al 1977). Early reports found a high incidence of fetal intracerebral haemorrhage in late pregnancy (Villa Santa 1965). There is a substantial risk of major haemorrhagic complications for both mother and fetus during delivery, especially if this is carried out by operative means, even with optimal anticoagulant control. As warfarin has such a long duration of action it will take several hours for any reversal of anticoagulation to occur following parenteral vitamin K administration, and fresh frozen plasma will be required to correct the haemostatic defect in an emergency situation.

Warfarin has also been associated with an increase in spontaneous abortion rates when administered in the first trimester, ranging from 28-44% (Salazar et al 1984, Lutz et al 1978, Chen et al 1982). There is some evidence to suggest that if heparin is substituted for coumarin derivatives the spontaneous abortion rate may be lessened.

1.5.3 Low molecular weight heparins

Low molecular weight heparins may offer advantages over unfractionated heparins. A recent multicentre, randomised, double blind study comparing a once daily subcutaneous injection of 2500i.u. LMWH (Fragmin, Kabi Pharmacia) with twice daily 5000i.u. subcutaneous unfractionated heparin in 3809 patients undergoing major elective abdominal surgery found no difference in their thromboprophylactic efficacy. However, the incidence of wound haematoma and severe bleeding was less frequent in the group given the LMWH. Additionally, Leizorovicz et al (1992) have shown the low molecular weight-heparin, enoxaparin (Rhone-Poulenc-Rorer, UK) to have a bioavailability of 90% (compared to 10% for unfractionated heparin) in non-pregnant women and a longer elimination half-life than unfractionated heparin, allowing once daily administration. With regard to osteoporosis, it is not known if low molecular weight (LMW) heparins will confer any benefit. In animal studies, chronic dosing with unfractionated and low molecular weight heparin given in comparable doses both resulted in osteoporosis of a similar degree (Matzsch et al 1987). However, bone density scans performed after delivery of 11 patients who had received low molecular weight heparin thromboprophylaxis antenatally showed normal mineral mass (Melissari et al 1992).

The role of low molecular weight heparins (LMWH) in thromboprophylaxis in pregnancy has yet to be established. Anecdotal reports of the successful use of these compounds in pregnancy (Priollet et al 1986, Many et al 1992) have been followed by larger studies. Sturridge et al (1994) reported a series of sixteen women treated with enoxaparin. The 20mg dose failed to increase the anti-Xa levels to the recommended level of 0.2 units/ml, and the higher dose of 40mg once daily was recommended. Additionally, anti Xa activity was noted to fall in the second half of pregnancy. In our own practice we have found that the low molecular weight-heparin, enoxaparin (Rhone-Poulenc-Rorer, UK), has better bioavailability than unfractionated heparin as determined by anti-Xa levels (unpublished data) and may be satisfactory on a once daily dose. However, in the light of data currently available we would recommend, at least until more experience is gained, that anti-Xa levels are monitored and dosage adjusted to achieve satisfactory anti-Xa levels. In the puerperium once daily administration is likely to provide adequate thromboprophylaxis.

1.5.4 Dextran

Dextran may also be considered for intra-partum or intra-operative prophylaxis although its efficacy is perhaps uncertain, at least in non-pregnant surgical patients (Turpie 1992). Its precise mode of action is not certain but may be due to haemodilution and improved flow as well as its effects on the haemostatic system which include anti-platelet effects, a fall in factor VIII and possibly enhanced plasminogen activators (Bergqvist 1983). Its disadvantage is the small risk of anaphalactoid reaction, but this can be markedly reduced by pre-treatment with the low molecular weight hapten dextran (Bergqvist 1983), although widely used in Europe it is not available in the UK. There is also evidence to suggest that heparin and dextran may be associated with haemorrhagic problems if used together (Bergqvist 1983).

1.5.5 Physical methods

Physical methods of prophylaxis such as intermittent calf compression or graduated compression stockings are also of value intraoperatively and postoperatively especially in the low risk situation or if combined with other thromboprophylactic techniques (Turpie 1992). There is good evidence for their efficacy among ambulant post-operative surgical patients (Scurr et al 1987). Their efficacy in providing effective long-term thromboprophylaxis in pregnancy has not been evaluated. Further, their mode of action remains uncertain.

1.5.6 The approach to thromboprophylaxis

Until recently, long term administration of anticoagulants was employed in the antenatal period as the established prophylactic therapy for women with a past history of thromboembolism occurring within or outwith pregnancy. However, the risk of antenatal thromboembolism in these women is much lower than previously thought. When this is balanced against the hazards of anticoagulation, prophylactic therapy is questionable and perhaps is best reserved for those with recurrent severe problems, congenital or acquired thrombophilia or those with post-phlebitic insufficiency. Additionally, pregnancy is not contraindicated in women with such a history (Lowe et al 1992). Some authorities, however, still advise prophylactic anticoagulant therapy if the previous problem occurred in pregnancy, starting four to six weeks before the gestation when the previous thromboembolic problem occurred (Hathaway & Bonnar 1987, Rutherford & Phelen 1986). A recent survey has shown that 52% of UK obstetricians would still use prophylaxis ante-natally in women with a previous DVT outwith pregnancy, rising to 81% if the previous DVT had occurred during pregnancy

and 97% if the patient had recurrent problems (Greer & de Swiet 1993). These figures for those patients with a single episode of DVT reflect the controversy over the need for prophylactic heparin in this group of patients. If subcutaneous heparin prophylaxis is employed, then it should be used in a similar manner as chronic therapy following a thromboembolic problem (see below). As thromboembolism is a potentially fatal condition and prophylaxis is not without hazard, the various risks of these problems should be discussed pre-pregnancy, or at least in early pregnancy, with the patient, no matter which prophylactic philosophy is taken. All authorities do agree, however, on postnatal prophylactic therapy in patients with a past history of thromboembolism with 5,000 i.u. of heparin subcutaneously 8 hourly (or 7,500 i.u 12 hourly) switching to warfarin within 7-10 of delivery and continuing therapy for at least 6 weeks (Lowe et al 1992, RCOG 1995). As previously stated, breast feeding is not contraindicated with either heparin or warfarin.

Increasingly, short term prophylactic heparin is being used postpartum in patients with significant risk factors such as operative delivery, obesity, age over 35 years old, high parity and restricted activity prior to delivery (Lowe et al 1992). Such prophylaxis must be encouraged if we wish to impact upon the morbidity and mortality associated with DVT and PTE in the puerperium.

A further group of patients meriting special consideration with regards to thromboprophylaxis in pregnancy are those with congenital or acquired thrombophilia. The main congenital thrombophilias are deficiencies of the endogenous inhibitors of coagulation ATIII, Protein C and Protein S although abnormalities of fibrinolysis, hereditary dysfibrinogenaemias, and homocystinuria may also be responsible for recurrent thromboembolism (Winter & Douglas 1991). In recent years a further congenital thrombophilia, activated protein C (APC) resistance has been identified. A point mutation at a cleavage site in factor Va makes the altered form, known as factor V Leiden, inaccessible to activated protein C. The prevalence of this condition among non-pregnant patients with DVT has been found to be between 20% and 33% compared with a prevalence of around 5% in the general population (Rosendaal et al 1994, Koster et al 1993, Svensson and Dhalback 1994). APC resistance is therefore a major risk factor for venous thrombosis. Since it is far more prevalent in the general population than the other known hereditary thrombophilias, it is likely to be a significant factor underlying venous thrombosis in pregnancy. While case reports of APC resistance in pregnancy have recently been published (Cook et al 1994), insufficient information currently exists to enable the formulation of guidelines on the management of affected women. In view of the

pregnancy associated changes in the coagulation system, pregnancy may act to unmask thrombophilia in young women and an assessment of the need for thromboprophylaxis in pregnancy and the puerperium should be made.

Prophylactic treatment, usually with subcutaneous heparin, appears to reduce the incidence of thrombosis in AT III deficiency (Douglas et al 1990). The dose of subcutaneous heparin should be adjusted to maintain the APTT 5-10 seconds above the normal value on a sample taken immediately prior to heparin administration. Monitoring of APTT and platelet count should be carried out at least fortnightly. When delivery is imminent, the heparin is reduced to 5000 i.u. twice daily and ATIII concentrate infused on alternate days to maintain the ATIII concentration greater than 80% of normal. Following delivery, ATIII infusions and heparin are continued for seven days, then warfarin can be employed as the risk of postpartum haemorrhage will have diminished by that time. Low molecular weight heparins have been successfully employed for prophylaxis in ATIII deficient women (Henny et al 1986, Manson et al 1991) and may be superior to unfractionated heparin (Manson et al 1991). However, further and more extensive evaluation of these compounds is required in this situation. Warfarin should continue for 3 months or indefinitely if there is a past history of thromboembolism. Oestrogen containing contraceptives should be avoided as they are associated with thrombosis, but the progesterone only pill appears suitable. Similarly, those women who carry the factor V Leiden mutation are at additional risk of venous thrombosis while taking the oestrogen containing contraceptive (Vandenbrouke et al 1994) and alternative contraceptive measures should be advised.

The risk of thrombosis with Protein C and Protein S deficiency appears to be much less than with ATIII deficiency, although superficial thrombophlebitis is more common. Conard et al (1990) have reported on 93 pregnancies in 36 patients with protein C deficiency and 44 pregnancies in 17 patients with protein S deficiency. In the absence of anticoagulant therapy the incidence of thrombosis during pregnancy was 7% and 0%, and during the puerperium 19% and 17% for protein C and protein S deficiency respectively. While there is a clear case for prophylaxis in the puerperium, the need for prophylaxis in pregnancy is less certain, especially in protein S deficiency. However, all these conditions should be considered and preferably evaluated prepregnancy in women with a previous history of thrombosis or pregnancy problems.

The major acquired thrombophilic problem seen in pregnancy is lupus anticoagulant or anticardiolipin antibody syndrome (Lubbe & Butler 1992). In obstetric medicine lupus anticoagulant is associated not only with thrombotic problems but also with recurrent fetal loss and intrauterine death (Nilsson et al, 1986), pre-eclampsia, growth retardation and chorea gravidarum (Branch et al, 1985; Lubbe et al, 1984; Lubbe & Walker, 1983). The aim of the 'traditional' treatment of lupus anticoagulant in pregnancy was to suppress autoantibody production with steroids and inhibit platelet function with aspirin. A coagulation test to assess lupus anticoagulant should be monitored and when this returns to normal steroids may be reduced to a maintenance dose. However, the use of steroids in this condition has recently come into question. A combination of heparin (10,000 i.u. twice daily) and low dose aspirin may be as effective as aspirin and steroids while avoiding the side effects of chronic steroid therapy (Cowchuk et al 1992). In addition, it may be that aspirin alone, in the absence of major maternal thromboembolic events, may be as good as combination therapy for fetal outcome. However, more information in this area is urgently required in order to guide treatment. Recently, the use of intravenous immunoglobulins and fish oil derivatives has been reported to improve outcome, but these studies were uncontrolled (Buckley 1994).

1.6 Treatment of DVT

The administration of anticoagulant therapy to prevent further thromboembolic complications and extension of any existing thrombus has been shown to reduce mortality from DVT from 13% to 0.7% (Villa Santa 1965). The acute therapy for DVT/PTE is heparin and this is no different in pregnancy. Most regimes employ intravenous administration of a bolus of 5,000-10,000 i.u. followed by a continuous infusion of 1,000-1,600 i.u. per hour for 5-10 days. Subcutaneous therapy may be a satisfactory alternative to continuous intravenous therapy as it is a more practicable treatment regime for patients and staff. The risk of haemorrhagic complications with subcutaneous therapy does not appear to be any greater than with continuous intravenous infusion (Andersson et al 1982, Hull et al 1986a) and the efficacy appears to be equally good in terms of recurrent thromboembolism (Andersson et al 1982).

A variety of tests are available for monitoring heparin therapy. These include the activated partial thromboplastin time (APTT), the heparin level measured by the protamine sulphate neutralisation test (PSNT), the thrombin clotting time and factor Xa inhibitory activity (anti-Xa). Perhaps the most commonly used of these is the

APTT. This should be maintained in the range 1.5-2 times the normal result since animal and clinical studies have shown an APTT of <1.5 times the normal level to be associated with thromboembolic recurrence while on therapy (Zucher & Cathay 1969, Basu et al 1972). The risk of haemorrhagic complications does not correlate well with APTT however (Pitney et al 1970, Hirsh 1986) and haemorrhagic complications appear to be related more to other factors such as heparin level or an underlying haemorrhagic tendency. The anti-platelet effects of unfractionated heparin may also contribute to the haemorrhagic effects of high heparin levels. In some patients with venous thrombosis, very high doses of heparin are required - in excess of 50000 i.u./day, to prolong the APTT by 1.5-2 times the normal mean. Such patients are often termed heparin resistant. It has been shown that the anticoagulant effect of heparin is markedly decreased in late pregnancy with approximately 1.5 times as much heparin being required in pregnancy to double the APTT compared to the non-pregnant situation (Whitfield et al 1983). This phenomenon may be related to high concentrations of procoagulant factors particularly factor VIII (Hirsh 1986) and the increased plasma volume (Bonnar 1976) found in late pregnancy. Because of these difficulties some workers suggest that the PSNT is more useful (Letsky and de Swiet 1984) as a monitoring test in pregnancy. This test calculates the heparin concentration from the amount of protamine sulphate required to neutralise the effect of heparin on the thrombin clotting time (therapeutic range 0.6-1.0 i.u./ml).

Following the acute phase of therapy, chronic anticoagulation is required. In view of the problems of warfarin in pregnancy (see above) heparin is preferable. This is given as 10,000 i.u. heparin twice daily subcutaneously and can be administered in a small volume if a concentrated heparin solution (50,000 i.u./ml) is employed. Monitoring is rarely necessary unless larger doses are being used or in special situations such as antithrombin III deficiency where it may be important to ensure that adequate heparin levels have been obtained. Since such low dose heparin does not affect the conventional coagulation tests, therapy is monitored by the anti-Xa activity method of Denson and Bonnar (1973), and levels should be maintained at less than 0.4 u/ml. At such levels, there appears to be no risk of bleeding in labour (Hathaway & Bonnar 1987) and blood loss during caesarean section performed following subcutaneous low dose heparin is no different from that following placebo (Hill et al 1988). In the puerperium, the heparin dosage can be reduced to 7500 i.u. twice daily subcutaneously as recommended by de Swiet (1985) or 5000 i.u. three time a day. In view of the risk of haemorrhage if warfarin is employed in the early puerperium, heparin should be continued for at least 7-10 days. After this time warfarin may safely be used. In the case of an antenatal thrombosis, treatment should be continued

throughout pregnancy and for at least six weeks following delivery as it takes some time for the "physiological coagulopathy" of pregnancy to disappear. Six weeks therapy seems satisfactory for a simple post partum DVT but a longer period of three months or more may be required in the case of a PTE or a very extensive DVT.

If warfarin is employed, it should be started approximately three days prior to stopping heparin, due to the time required for its maximal effect to occur. Various regimes exist for warfarin loading. A satisfactory one is 20 mg on the first day of warfarin therapy, 10 mg on the second day, then stop the heparin and maintain anticoagulation with a maintenance dose of warfarin which should be titrated against the prothrombin time which is the most satisfactory test for warfarin's anticoagulant effect. The heparin should not be stopped until the prothrombin time is in the therapeutic range (2.0-4.0 times the normal control plasma).

Should heparin therapy fail to prevent recurrent thromboembolism despite adequate anticoagulation, or if there is extension of clot into the common iliac veins or inferior vena cava itself, the insertion of a vena cava filter may be required to prevent PTE. These filters are inserted into the inferior vena cava via the femoral or jugular veins and lodged below the renal veins, although in pregnancy or in the presence of extensive thrombus reaching the region of the renal veins they may be sited between the renal veins and the intrahepatic section of the inferior vena cava. The Cardial filter has been used successfully in pregnancy (Narayan et al 1992) and is probably preferable to the Greenfield filter as it has a simple delivery system and requires a smaller catheter.

1.7 Diagnosis of DVT

1.7.1 Clinical diagnosis

The importance of accurate diagnosis of DVT in pregnancy cannot be overstressed as the presence of a DVT places the woman at substantial risk of PTE, while anticoagulant therapy without a firm diagnosis may subject the woman to unnecessary and potentially dangerous anticoagulant therapy. The most common clinical features are pain, tenderness, swelling, oedema, Homan's sign, a change in leg colour and temperature, and a palpable thrombosed vein. Over 80% of DVT in pregnancy are left sided (Lindhagen et al 1986). However, the clinical diagnosis of DVT is unreliable having both a low sensitivity and a low specificity with less than 50% of cases of DVT including those involving major proximal veins being recognisable

clinically, while venography substantiates the diagnosis in only about 40% of patients with clinical findings compatible with DVT (Genton & Turpie 1980, Ramsey 1983). It is also noteworthy that the majority of women dying from PTE had no clinical evidence of DVT yet thrombus was found in leg and pelvic veins at post-mortem (Department of Health et al 1991). Objective diagnosis is therefore essential. Despite this, a survey among general physicians in Scotland in 1982 showed that 47% were diagnosing (and presumably treating) DVT on clinical diagnosis alone (Prentice et al 1982) and obstetricians may have been no different. Ramsay (1983) has estimated, that by using clinical diagnostic criteria alone, that 2 patients out of every 3 would receive anticoagulants unnecessarily. The causes of "pseudothrombo-phlebitis" include ruptured Bakers cyst, muscular injury and cellulitis, although the presence of such diagnoses does not exclude DVT as a Bakers cyst and DVT not uncommonly coexist (Belch et al 1981).

In view of the low sensitivity and specificity of clinical diagnosis outlined above it is crucial that an objective assessment of DVT is performed particularly in the pregnant patient. Perhaps the biggest contribution the clinician can make is to be aware of the presence of risk factors and alert to the possibility of the diagnosis which should not depend on clinical examination alone to establish or refute the presence of thrombosis.

1.7.2 Venography

Venography remains the "gold standard" of the objective tests for DVT. It is an invasive technique but has the greatest degree of sensitivity and specificity of all the objective tests, and is the technique against which other techniques are compared. In the hands of a skilled radiologist it will probably detect up to 95% of peripheral thrombi (Browse, 1978). However, a number of studies have recently demonstrated considerable inter-observer variation in the evaluation of venograms in non-pregnant patients with suspected DVT (Lea Thomas et al 1991), in thromboprophylactic studies (Wille-Jorgansen et al 1992, Couson et al 1993) and in the evaluation of phlebographic changes produced by thrombolytic therapy (Bounameaux et al 1992). Furthermore, at least 10% of contrast venograms performed in non-pregnant subjects are inadequate for interpretation (Huisman et al 1986). There are also risks associated with venography. These include pain at the time of injection of contrast, hypersensitivity to the medium, or rarely extravasation of the medium resulting in damage to the skin of the foot. Thrombosis can occur secondary to venography due to the irritant effects of the hyperosmolar media on the venous endothelium and may be lessened by elevating the legs and flushing the legs with isotonic saline or by

giving a single dose of heparin after the examination, although studies have not confirmed the effectiveness of the latter option (Bettman & Paulin 1977, Cranley 1975). Lowering the osmolality of contrast media will reduce the irritant effects and subsequent DVT formation (Bettman & Paulin, 1977) although it will not be abolished. The use of a non-ionic low osmolality medium has been shown not be provoke thrombosis compared to an ionic hyperosmolar medium (Albrechtsson & Olsson 1979).

There has been a reluctance to employ venography in pregnancy because of the radiation hazard to the fetus. A 2.4-fold increase in the risk of childhood cancer has been associated with prenatal X-ray exposure (plain films of the abdomen or pelvimetry) during the third trimester (Harvey et al 1985). However, this problem can be alleviated by performing limited venography, where the uterus is be shielded so that the direct radiation dose to the fetus is small and less than with X-ray pelvimetry (Laros & Alger 1979). The risks of unwarranted anticoagulation must also be considered. Where clinically indicated, such in severe thrombotic problems, venography should still be employed if it is deemed necessary for optimal patient management.

1.7.3 Impedance plethysmography

Impedance plethysmography (IPG) is non-invasive, indirectly measuring changes in the volume of a limb by the change in electrical resistance across it. Following inflation of a thigh cuff the venous outflow of the limb is occluded. In the absence of any obstruction to venous flow, release of the cuff will result in a rapid outflow of blood and an associated change in electrical resistance as measured between 2 electrodes placed round the limb. In the presence of venous thrombosis the rate of emptying will be reduced. In the non-pregnant this technique has been shown to have a sensitivity ranging from 63% to 95% and a specificity of 83% to 96% in the detection of proximal occlusive venous thrombi (Ramchandani et al 1985, Hull et al, 1984, Anderson et al 1993). Up to 80% of false positive tests may be attributed to the presence of non-vascular space occupying lesions (such as Baker's cysts) which act to reduce the rate of venous drainage from the limb (Huisman et al, 1986) and cannot be differentiated by IPG. However, despite the physiological changes in venous flow in pregnancy due to reduced venous tone, and obstruction to flow by the gravid uterus, this technique can still be successfully employed in pregnancy provided the physiological changes are taken into account (Clarke-Pearson & Jolovsek, 1981). In view of the risk of false positives result from external compression, however, it would seem prudent to confirm the diagnosis by venography or ultrasound. The main

disadvantage of this technique is its very poor sensitivity in detecting calf vein thrombosis (Hull et al, 1976) and non occlusive thrombi. While this technique may still have a role in screening it has been largely superseded by the increased availability of ultrasound imaging.

1.7.4 ^{125}I-Fibrinogen scanning

This technique is now only of historical interest and has no place for screening or diagnosis in the pregnant or post-partum situation. In pregnancy, radio-iodine may cross the placenta and the breast and accumulate in the fetal or neonatal thyroid. In the non-lactating mother it has been used post-partum as employed by Friend & Kakkar (1970). The mother's thyroid can be protected by the concomitant administration of potassium iodide to prevent uptake of radioactive iodine. A recent review has shown many of the studies demonstrating the accuracy of this technique to be flawed (Lensing & Hirsh 1993); in many of the published studies on surgical and orthopaedic patients, interpretation of scan results was not carried out independently of venogram results, with which the technique was compared. In those studies where independent interpretation was documented, therefore minimising bias, a sensitivity of 55% was estimated. Lensing & Hirsh (1993) have therefore called into question the validity of the many studies which used ^{125}I- Fibrinogen scanning as the test of efficacy when evaluating thromboprophylactic agents. Concern over the true accuracy of the technique and the theoretical possibility of viral transmission has led to the test being withdrawn from clinical use.

1.7.5 Other diagnostic techniques

Liquid crystal contact thermography has also recently undergone evaluation as non-invasive screening methods for DVT after general surgery. However, the sensitivity and specificity of the technique is poor (Bounameaux et al 1992). The effect of pregnancy on the peripheral microvasculature further reduces the specificity of the technique and its use has not become established. Recently the measurement of D-Dimer in plasma has been found to aid the diagnosis of suspected DVT and PTE (Bounameaux et al 1989, 1992) and may provide a useful test to exclude the presence of DVT or PTE or aid the diagnosis where other investigations such as the ventilation/perfusion lung scan is equivocal. Although this technique has not be assessed in a pregnant population, it may still provide assistance with the diagnosis in this situation, at least in the absence of other complications, such as severe pre-eclampsia or major haemorrhage with disseminated intravascular coagulation. This technique is worthy of further evaluation in pregnancy.

Isotope venography using radiolabelled albumin platelets or red blood cells (Lisbona et al 1982) has been used in the non-pregnant however these techniques have not been fully evaluated and in view of the radiation hazards are unlikely to find any place in the diagnosis of DVT in pregnancy.

A technique with greater promise in pregnancy is that of light-reflection rheography which has been shown to be as accurate as other non-invasive tests in the diagnosis of deep venous thrombosis in non-pregnant patients (Thomas 1991, Mitrani 1989). This non-invasive method uses light emitting diodes and a sensor to measure light reflected from the skin surface. The intensity of the reflected light establishes a graphic pattern that indirectly quantifies parameters of venous function by measuring changes in the microcirculation. A recent study indicated the utility of the technique in pregnancy if the sitting position is adopted, as this prevents artefactual effects secondary to the presence of the gravid uterus (Allbert at al 1991). Further assessment of this technique in pregnancy and the puerperium is required.

1.7.6 Ultrasound techniques

In recent years, several ultrasound techniques have been applied as a quick non-invasive means of assessing venous thromboembolic disease and it has now become the first choice investigation for DVT in pregnancy.

Continuous wave Doppler ultrasound

Continuous wave Doppler imaging is the most basic technique and involves the use of a hand-held pencil-like device, the probe of which contains two transducers. One continuously sends sound waves while the other continuously receives a signal. It lacks any focusing ability, has no range resolution and does not permit interrogation of any particular vessel. However, the femoral and popliteal veins can be assessed by evaluating three Doppler parameters; (1) Spontaneous venous flow, which is easily detected in large vessels, (2) Phasic variation of venous flow occurring during the respiratory cycle, (3) Augmentation of flow which occurs when a more distal part of the leg is compressed. This indicates patency between the point of compression and the sampling site. Meaningful results are difficult to achieve with continuous-wave Doppler. Non-occlusive thrombosis may not alter blood flow sufficiently to affect the signal. The overall sensitivity and specificity in testing the symptomatic patient are inadequate to maintain widespread use of the technique when compared to real-time ultrasound (Nix et al, 1989, George et al 1990).

Duplex Doppler ultrasound

The combination of real-time imaging with pulsed Doppler (duplex scanning) enables visualisation and sampling of the Doppler characteristics of a specific vessel by placing the range gate within the vessel lumen. The physical principles underlying the application of Doppler ultrasound to blood flow assessment are discussed in Chapter 2 but in essence, this equipment pulses the Doppler signal, which controls the range or depth in tissue that is sampled by altering the length of time the system waits after sending a pulse to record the Doppler information. A completely absent signal or a continuous but non-variable signal is interpreted as abnormal, the latter indicating proximal obstruction or collateralisation of venous flow **(Plate 1.1)**.

Thrombus Visualisation.

Direct real-time visualisation of thrombus is possible (Sullivan et al. 1984, Aitken & Godden, 1987) **(Plate 1.2)** but of little clinical use. Clot echogenicity is variable, dependent on transducer frequency, age of clot and extent of the thrombolytic process. The echogenicity of a clot does not indicate whether it is acute nor does it permit assessment of the age of the clot (Murphy et al 1990). Additionally, slow flowing blood can appear sufficiently echogenic to mimic the appearance of the clot (Machi et al 1983).

Valsalva Manoeuvre

The normal physiological response of the femoral vein to the Valsalva manoeuvre is a 50-200% increase in vessel diameter. If thrombus is present the vessel demonstrates a limited or absent response. This finding is effective in the upper femoral region but the response rapidly diminishes in the more distal parts of the leg. Excellent patient co-operation is required for adequate performance of this technique (Effeney et al 1984). Although a normal increase in vein diameter excludes DVT, an abnormal response is not specific for thrombus and may be due to extrinsic causes of vessel compression or to congestive cardiac failure. The gravid uterus does not appear to prevent the valsalva response at the femoral vein and it has been described as a diagnostic method in pregnancy (Duddy & McHugo 1991).

Venous compression

The compression technique for venous clot continues to constitute the principal method of ultrasound assessment for DVT. The deep veins may be examined from the level of the inguinal ligament to the bifurcation of the popliteal vein as it extends into the tibial and peroneal veins (Aitken & Godden 1987). The femoral veins are best evaluated in the supine position while the popliteal veins may be examined in the

decubitus position, with the patient lying prone with the legs flexed 20°, or by elevating the foot and leg and scanning from below (Cronan 1993). The gain should be set so that normal vessels appear free of internal echoes. This can be achieved by determining that the accompanying artery is free of internal noise. The vessel should first be examined in the longitudinal axis to localise the vein but compression is best applied in the transverse axis since the transducer will not roll off the vessel. Compression should be applied sufficient only to dimple the overlying skin. If the artery is compressed, excessive pressure has been used. The lumen of a thrombus-free vein will completely collapse on compression **(Plate 1.3)**, while DVT will prevent co-aptation of the venous wall (Cronan et al 1987). In the symptomatic patient, clot usually extends over one or more venous segments (Markel et al 1992) so continuous compression assessment over every millimetre of the vessels length is unnecessary. The confirmation of normal compressibility at 2cm intervals may be interpreted as a thrombus free vessel (Cronan 1993). In the area of the inguinal ligament and in the adductor canal, complete compression of the vessel is difficult without applying additional, and possibly painful, compressive force. If uncertainty as to the compressibility of a deep vessel remains, the opposite leg can be examined as a control. Alternatively, patency can be determined using pulsed Doppler or colour Doppler techniques. Despite these limitations, compression ultrasound has been extensively validated against venography. If the results of a series of studies are pooled a sensitivity of 95% for detecting lower extremity DVT and a specificity of 98% can be demonstrated (Cronan et al 1987, Naidich et al 1988, Raghavendra et al 1984, Raghavendra et al 1986, Cronan et al 1988, Sullivan et al 1984, Duazat et al 1986, Vogel et al, 1987, Appelman et al 1987, Langsfield et al 1987, Aitken &Godden 1987, George et al 1987, Oliver 1988, O'Leary et al 1988, White et al 1989, Lensing et al 1989, Monreal et al 1989, Habscheid et al 1990, Mussarakis et al 1990). Assessing outcome after a negative compression ultrasound scan also demonstrates the reliability of the technique (Vaccaro et al 1990, Sarpa et al 1989). Recently, a large prospective randomised trial comparing serial compression ultrasonography with serial impedance plethysmography for the diagnosis of DVT using contrast venography as a reference has confirmed the positive predictive value of an abnormal ultrasound test to be 94% compared to 83% for impedance plethysmography. In non-pregnant patients with repeatedly normal results, the incidence of venous thromboembolism during the six-month follow-up period was 1.5% for compression ultrasound and 2.5% for serial impedance plethysmography (Heijboer et al 1993).

Although there are no comparative studies in the literature on the use of compression ultrasound in pregnancy, it is now being successfully employed for DVT diagnosis in

pregnancy (Greer et al, 1990, Polak & Wilkinson 1991). It can also be combined with pulsed Doppler ultrasound and Doppler colour flow mapping to facilitate the diagnosis of thrombus.

Colour Doppler ultrasound

Colour Doppler ultrasound uses computer processing to assess multiple gates simultaneously. The entire real-time image can be interrogated for Doppler shifts (Mitchell 1990). Moving blood produces a Doppler shift dependent on blood flow velocity and the angle subtended by the ultrasound beam (the Doppler angle). Flow is assigned a colour based on direction and a shade based on Doppler frequency shift. A normal vein should fill with colour whereas thrombus is represented as a filling defect **(Plate 1.4)**. If the colour gain is set to high, colour may appear outside the vessel wall, making detection of mural thrombus difficult. The value of complete colour filling of the vessel lumen to exclude thrombus appears to reside principally in the reduction in time required to assess the veins, and in the ability to identify and examine smaller veins for thrombus (Rose et al 1990, Mattos et al 1992).

1.7.7 Calf vein thrombus

The clinical importance of calf vein thrombi remains controversial. There is now a considerable body of evidence suggesting that significant emboli do not embolise from isolated calf veins (Meibers et al 1988, Cohen et al 1988, Philbrick & Becker 1988, Moser & Le Moine 1981). Venogram and duplex ultrasound studies have indicated that 10-20% of calf vein thromboses propagate proximally (Meibers et al 1988, Philbrick & Becker 1988). Thus calf vein DVT contribute only a small proportion of DVT causing PTE. However, if PTE is to be prevented then treatment of isolated calf vein thrombi should be considered (Havig 1977), particularly as the relationship between calf vein thrombi and postphlebitic syndrome remains uncertain (Lagerstedt et al 1985, Lohr et al 1991). In the pregnant patient, isolated calf vein thrombi appear uncommon as most clinically significant thrombi are found in the ileofemoral segment in pregnancy (Bergqvist & Hedner 1981). However, should calf symptoms persist after a negative proximal leg assessment, the possibility of proximal extension into the popliteal vein should be considered and the veins assessed 3-5 days later (Huisman et al 1986), although only 5% of those offered return for follow up examination (Cronan et al 1988). More recently, imaging of the calf veins with colour flow Doppler has been reported (Polak et al 1989). Blood flow is often very slow in the small veins of the calf and slow-flow Doppler capabilities are required.

Asking the patient to adopt a sitting position and the use of augmentation can aid vessel visualisation. Using these techniques, the sensitivity for detection of clot can approach 85% (Yucel 1991).

1.8 Diagnosis of pulmonary thromboembolism

The signs and symptoms of PTE depend on the number and size of the emboli and arise from mis-matching of ventilation and perfusion, reduced cardiac output due to arterial obstruction, and infarction or collapse of lung segments. Clinical features are non-specific and just as in the non-pregnant include dyspnoea, pleurisy, haemoptysis, chest pain, abdominal pain, hypertension, fever, collapse and sudden death. The differential diagnosis will include chest infection, pneumothorax, aspiration, amniotic fluid embolism and myocardial infarction. Like DVT, the bedside diagnosis of PTE is unreliable. The classic triad of dyspnoea, pleuritic pain and haemoptysis is present in only a fifth of patients with major PTE (Wenger et al, 1972) and pulmonary embolus is diagnosed in less than one third of episodes (Windebank, 1987). In view of these non-specific symptoms the clinician must remain vigilant to the possibility of PTE. Traditionally, initial investigations include ECG, chest X-ray and blood gases. However, these tests are of no diagnostic value for PTE (Robin, 1977). They may initially be normal and the ECG may show changes resulting from the effects of pregnancy itself on the heart in the absence of PTE. The main use of these tests is in helping to exclude other pathology. Chest X-rays, ECG and arterial blood gases not in keeping with the diagnosis of PTE were the principal reasons for treatment not being given in many of the cases in the Confidential Enquiries (Department of Health et al, 1991) yet symptoms or signs such as dyspnoea, chest pain, hyperventilation and cyanosis were present. A ventilation-perfusion isotope lung scan should be obtained if PTE is suspected. The radiation dose to the fetus is low. A ventilation perfusion mismatch is suggestive of PTE. A normal result effectively excludes the possibility of PTE. An abnormal result showing normal ventilation and a perfusion defect which is segmental or larger is size is diagnostic of PTE (Windebank, 1987). With smaller defects the diagnosis is far from certain (McBride et al, 1986; Hull et al, 1986b) as other conditions can cause sub-segmental mis-match. In addition matched defects do not always indicate a chest problem other than PTE, as one third of patients with matched defects have been shown to have PTE (Windebank, 1987). In patients in whom the ventilation-perfusion scan shows sub-segmental mismatching then ultrasound imaging of the deep veins or venography should be performed as this may

help reach a decision regarding treatment (Genton & Turpie, 1980). Although since one third of patients with PTE have no evidence of DVT (Hull et al 1986b), a negative bilateral lower limb compression ultrasound study cannot exclude PTE (Sciff 1987).

1.9 Ultrasound in assessing chronic venous disease

Old thrombus may mimic the appearance of acute thrombus when imaged with ultrasound. In most cases of acute thrombus, however, resolution of the of thrombus occurs during the first 6 months. After 6 months, approximately 48% of the veins have demonstrable abnormalities on ultrasound examination and 52% appear completely normal (Cronan & Leen 1989). The abnormalities described include a small proportion (14%) that appear completely occluded. A larger percentage of veins show partial recanalisation with a residual clot organised along the vessel wall (Sevitt et al 1973) which being thickened resists compression. When the vein is compressed, the residual lumen collapses, but the original vein walls remain separate, resulting in an appearance consistent with that of acute non-occlusive thrombus. Ultrasound assessment of venous diameter can aid in determining the age of thrombus. Whereas acute thrombus causes dilatation of the vessel often to twice the size of the adjacent artery (Murphy et al 1990), in the presence of old thrombus, the vein is of similar size to the adjacent artery. The presence of collateral vessels, while indicating chronic disease does not exclude acute on chronic disease. Colour Doppler may be of assistance in assessing the true thickness of the vessel wall when partial occlusion by an acute thrombus is suspected but in difficult cases serial ultrasound examinations to look for changes suggestive of acute DVT or venography may be required.

1.10 Interpretation of venous ultrasound in pregnancy

The assessment of ultrasound techniques in pregnancy has been limited. Little data exist on the normal changes in pregnancy and the puerperium and how they may alter the anatomy of the deep veins of the leg and the flow characteristics as detected by Doppler. Interpretation, particularly in late pregnancy may therefore be difficult. In view of its non-invasiveness, safety and high degree of sensitivity and specificity ultrasound is now the first choice, first line diagnostic technique for DVT in

pregnancy. A better understanding of the interpretation of deep venous ultrasound in pregnancy is therefore essential.

1.11 Conclusion

Thromboembolism contributes substantially to maternal mortality and morbidity but the true incidence in pregnancy and the puerperium is uncertain. The clinician must be aware of the risk factors for thromboembolism which are often present in patients who go on to develop DVT or PTE. The risk can be reduced by thromboprophylaxis with agents such as low dose heparin, and graduated compression stockings and the wider use of such prophylaxis in high and moderate risk situations associated with pregnancy should be encouraged. Furthermore, the clinician must be alert to the possible diagnosis of thromboembolism in pregnancy or the puerperium and utilise objective diagnostic investigations such as ultrasound examination.

Plate 1.1 Occlusive thrombus is present in the vessel shown. The Doppler flow signal from the sampled region is consistent with absent flow.

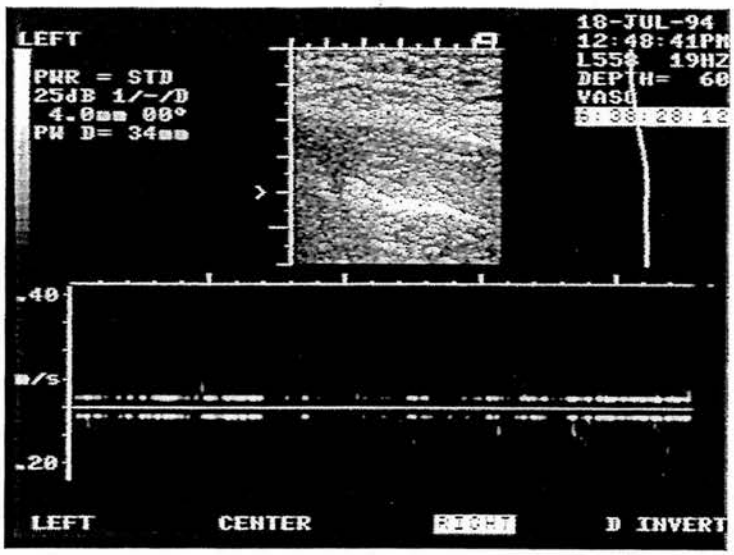


Plate 1.2 Echogenic thrombus is seen to distend the CFV, imaged in the transverse section.

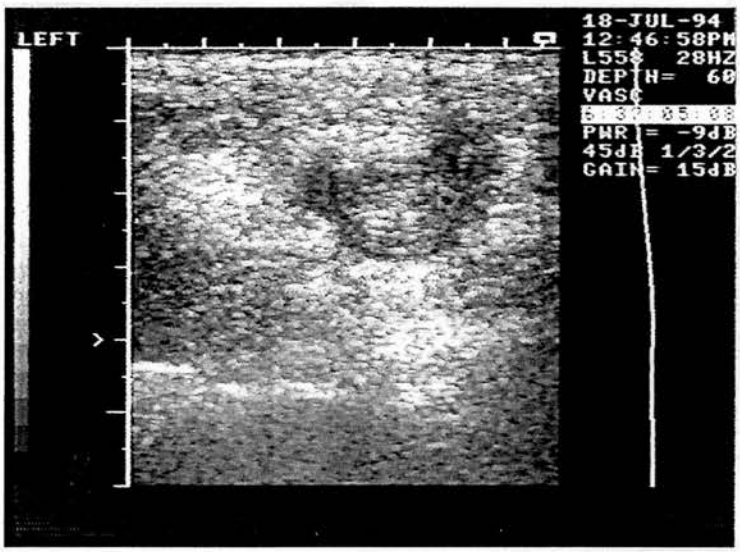
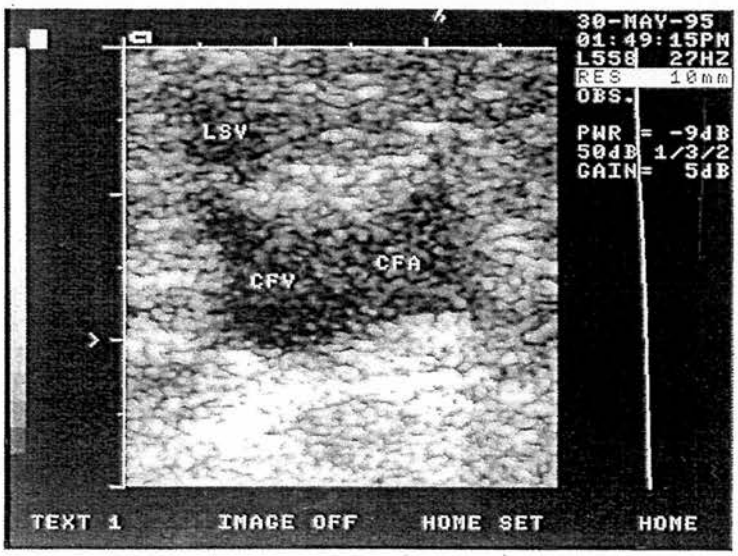


Plate 1.3 The lumen of the CFV, imaged in transverse section (a) has collapsed on application of compression, indicating a thrombus free segment (b).

(a)



(b)

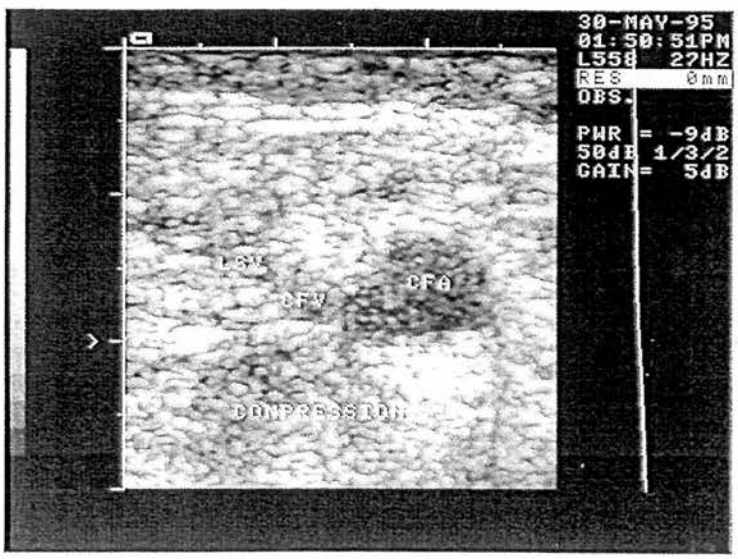
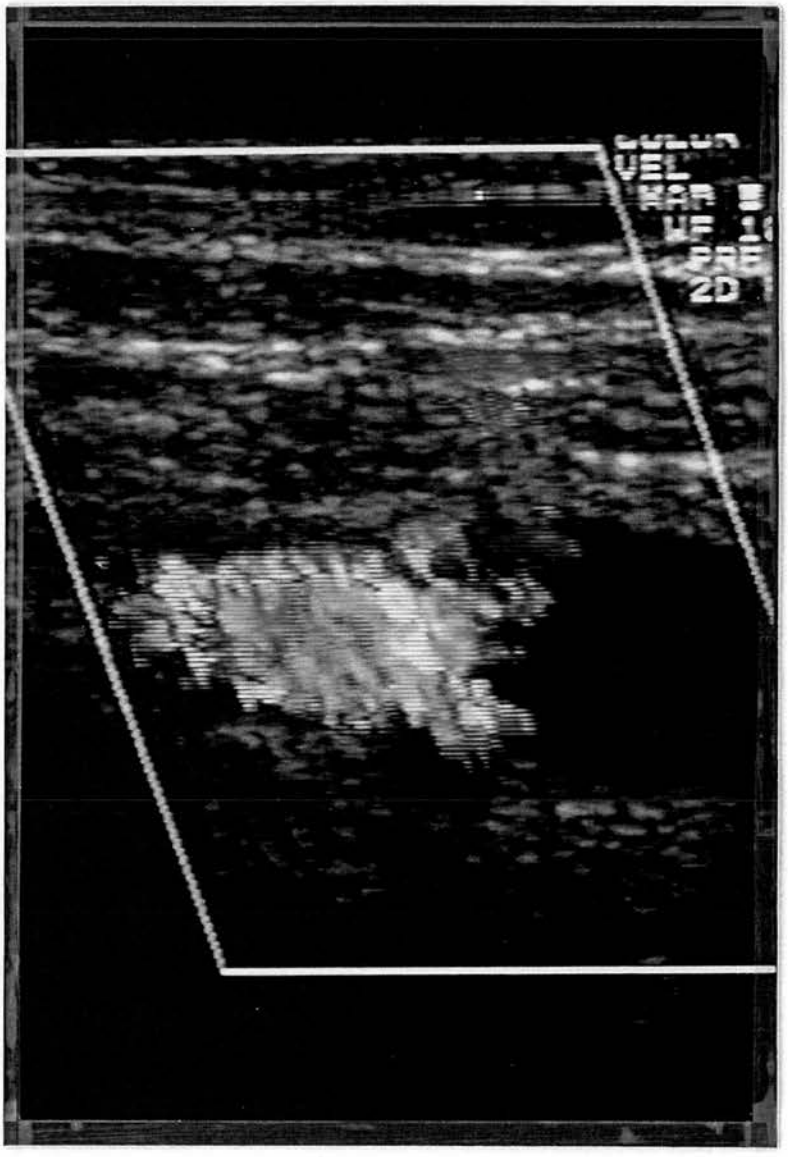


Plate 1.4 Colour flow is seen to fill the artery adjacent to the vein which demonstrates a filling defect consistent with occlusive thrombus.



Chapter 2

Venous haemodynamics in pregnancy; thrombogenesis and prophylaxis

Summary

Clinical and epidemiological evidence points to the role of venous stasis as an initiating factor in thrombogenesis. Mechanisms by which stasis may lead to thrombus formation include the accumulation of clotting factors, hypoxia leading to endothelial damage and altered shear forces. Venous dilatation may occur under the same conditions associated with stasis and can cause damage to the endothelium and basement membrane sufficient to expose thrombogenic tissues. The literature relating to the effects of pregnancy on deep venous anatomy and flow suggests that reduced venous flow velocity may result from increasing venous distension, both of which may predispose to thrombus formation. Little contemporary data quantifying these changes is available however. Pregnancy associated alterations in blood flow rheology may also play a role, although it is probably the combination of these physiological changes which act to increase the pregnant womans risk of thromboembolic disease. The efficacy of physical means of thromboprophylaxis further support the role of stasis and vessel dilatation in initiating thrombogenesis, although their precise means of action remains uncertain.

2.1 Introduction

In 1856 Virchow presented his classic triad, stating that changes in blood elements (hypercoagulable state), reduced flow velocity (stasis), and vein wall injury combined to create a setting that promotes thrombus formation. It has been known for over 200 years , however, that static blood left for many hours in isolated veins does not clot (Hewson 1771, Lister 1863) and contemporary studies have demonstrated that simple stasis alone is not associated with thrombus formation (Thomas et al 1985, Aronson & Thomas 1985). Yet the crucial role of stasis in enabling the initiation of thrombogenesis is borne out by clinical and epidemiological evidence. A study of 2 groups of spinal cord injury patients, one with paralysis and the other without demonstrated a 100% incidence of deep venous thrombosis in the paralysed group, but none in the non-paralysed patients (Myllynen et al 1985), and in a study of acute stroke patients, the paralysed limbs had a 63% rate of thrombosis as compared to only 7% in the non-paralysed limb (Warlow et al 1976). Autopsy studies show a relationship between bedrest and venous thrombosis (Sevitt & Gallagher 1961), and demonstrate the soleal sinuses to be the principal site of venous thrombogenesis (Gibbs, 1957). Additionally, post-operative patients have been shown to be at higher

risk during the period of immobility (Gallus 1976) while devices designed to reduce venous stasis have been demonstrated to be effective in preventing post-operative venous thrombosis (Caprini et al 1988).

2.2 Stasis and thrombogenesis

Several theories have been put forward to explain how stasis may lead to thrombogenesis. Mammen (1992) has postulated that stasis permits prolonged interaction between the prothrombotic coagulation proteins with a lack of dilution and clearance by free flowing blood of activated clotting factors, which may accumulate locally, while blood coagulation inhibitors are locally consumed. Autocatalytic activation of the coagulation may then occur, leading to further local hypercoagulation (Davie et al, 1979).

Alternatively, stasis may cause local hypoxaemia which itself results in endothelial damage. When flow is restored, the damage may attract phagocytic blood cells which become attached to the damaged endothelium (Malone 1977). However, Thomas (1983) found no evidence that the vessel wall changes, produced by venous stasis, led to platelet adhesion and aggregation or thrombus formation. Although Schaub (1984) was able to demonstrate that stasis of blood can lead to leukocyte adhesion, the resultant endothelial damage and exposure of subendothelial collagen previously described by Stewart et al (1974), only occurred after prolonged (>24 hours) stasis. Although leukocyte adhesion to and migration through the endothelium appears to be a rapid phenomenon, the resultant thrombosis is slow to develop. Leukocyte migration almost certainly occurs during venous thrombogenesis but is probably not causative.

The presence in venous valve pockets of nidi of aggregated platelets and leukocytes in postmortem specimens has been demonstrated (Sevitt 1974 &1978), and they are likely sites of thrombus initiation. Other workers have shown that blood within the valve pockets becomes rapidly hypoxic during induction of stasis (Hamer et al, 1981). Further evidence for the importance of the venous valve pockets was put forward by Karino and Motomiya (1984) who demonstrated the existence of a profoundly stagnant region in the deepest portion of the pockets, where a secondary vortex with low red cell concentration appears to occur. Finding that fluid circulated in these areas at extremely low velocities, with the creation of a very low shear field, they showed

the potential of the secondary vortex to act as an automatic trap for large cellular aggregates. These may then propagate with resultant thrombogenesis.

The shear forces acting in the presence of flowing blood also merit consideration in the context of thrombogenesis. Blood flow through large, straight venous segments has been shown to be parabolic. That is, the velocity is maximal at the centreline and decreases to zero at the vessel wall. In such conditions, platelets concentrate close to the vessel wall, while red blood cells are predominantly centrally located (Eckstein et al, 1988). The shear rate in this context describes the rate at which fluid velocity changes as one moves radially. This rate is taken to be zero at the centreline and maximal at the vessel wall (Eckstein et al 1988). The shear stress is the product of the shear rate and the blood viscosity, and reflects the force per unit area in a direction tangential to the vessel wall (Goldsmith & Turitto, 1986). However, at low shear rates, such as those present in large veins, blood behaves as a non-Newtonian fluid in that its viscosity is dependent on shear rate, being higher at lower rates. In general, low flow rates and low shear rates occur in the proximal leg veins. Low flow and shear rates will tend to increase viscosity, further exacerbating local stasis, and thus predisposing to the initiation of and propagation of venous thrombosis.

Other workers have thrown further light on how shear forces may influence thrombogenesis. While unstirred platelets do nor spontaneously aggregate, the application of shear stresses to platelet suspensions can induce aggregation without the addition of agonists (Peterson et al 1987). Shear stresses can also influence the nature of platelet surface agonist receptors (Ikeda et al, 1991). Recently Noris et al (1995) showed that the synthesis of the potent vasoactive mediator, nitric oxide (NO) by cultured endothelial cells, can be modulated by different flow conditions, with laminar shear stress being associated with an upregulation of NO synthase mRNA and NO production. Their findings suggest that constant release of NO by the vascular endothelium under laminar shear stress may have a physiological role in maintaining the non-thrombogenicity of the vascular wall. Further, it has been demonstrated that fluid shear stress can stimulate secretion of tissue plasminogen activator by cultured human endothelial cells, while plasminogen activator inhibitor type 1 secretion remains unstimulated (Diamond et al 1990).

Recent work on orthopaedic patients suggests that alterations in deep venous diameter may also play a role in bringing about the conditions in which thrombus formation might occur. Although direct injury to the vessel wall may occur locally in patients

undergoing orthopaedic procedures, the commonest sites for DVT are the more distant veins which are not directly damaged. Endothelial lesions distant to the operative site have been demonstrated in canine models (Stewart et al 1983, Schaub et al 1978). These endothelial lesions occurred as multiple microtears at the junction of tributaries with large veins, such as the femoral veins, and were found to be infiltrated with leukocytes and platelets, thus serving as potential initiation sites for thrombus. Anatomic studies have shown that these junction sites are areas of structural weakness and the possibility therefore arises that dilation of the vein wall may occur beyond the ability of the endothelium and basement membrane to maintain their integrity at these points, resulting in intimal rupture and collagen exposure. In 1987 Stewart et al showed that dilatation of the vessel beyond a critical point was associated with an increased incidence of venous lesions in a canine model of total hip replacement. Subsequently, Camerota et al (1987) demonstrated that intraoperative venodilatation occurred distant to the operative site in human subjects undergoing total hip replacement. Patients in whom postoperative DVT developed had a mean operative venodilatation in the contralateral cephalic vein of 28.9% ± 3.9% compared to 11.6% ± 1.6% in those in whom DVT did not develop. Further evidence for the importance of venous dilatation was provided by the finding that the administration of a venotonic agent resulted in less operative venodilatation and a lower incidence of DVT.

2.3 The Effects of Pregnancy

2.3.1 Venous blood flow and anatomy.

The effect of pregnancy on deep venous flow conditions has been a topic of research interest throughout this century. In 1924, Klee measured the blood flow during pregnancy using the flourescein method of Koch (1922). He found the circulation time to be prolonged in pregnancy with the greatest slowing of blood flow occurring in the eighth month. Only a single observation was made on each of 100 women in the final trimester of pregnancy. Other studies failed to confirm these findings however. Spitzer (1933), using decholin, found the velocity of blood flow to be the same in the pregnant and non-pregnant states, as did Landt and Benjamin(1936). The cyanide method of Robb and Weiss (1933), which used the nasal flaring response to the central arrival of peripherally injected sodium cyanide to determine flow velocity, was employed by Cohen and Thomson (1936) who carried out 100 measurements on 37 pregnant women. They found the average velocity of blood flow in the upper limb

to be normal in the first trimester, increased in the second trimester of gestation beginning with the seventeenth week, and remained increased until the thirty-fifth week, decreasing again before term. Other similar studies measuring flow times in the upper limb confirmed these findings. Venous pressure studies have also demonstrated marked alterations in the leg veins in pregnancy. McLennan (1943) carried out serial venous pressure studies in pregnancy, inserting needles into the antecubital and femoral veins of both normal and pregnant subjects and recorded intravenous pressures with a manometer. While no gestational changes were observed in the arms, a gradual and sustained elevation in venous pressure was observed in the legs as pregnancy advanced, becoming first apparent at the beginning of the second trimester. Wright et al (1950), injecting saline labelled with ^{24}Na into the dorsum of the foot and timing its appearance at the groin with a Geiger counter, demonstrated parallel changes in blood flow in the leg veins with advancing gestation. The first appreciable increase in foot-groin flow times also occurred at the beginning of the second trimester. Plethysmography studies examining primarily the effect of pregnancy and the oral contraceptive pill on venous distensability also provided further data on lower limb venous blood flow velocity (Goodrich & Wood 1964). In these studies, the mean flow velocity within the examined limb was calculated by dividing the blood flow though the limb (derived from the water plethysmography) by the cross sectional area of the limb. By these rather crude means, a reduction in venous flow velocity was observed in the calf in the third trimester. Using continuous wave Doppler techniques, Ikard et al (1971) found a reduction in femoral venous flow velocity with advancing gestation and in relation to maternal position and Schlunk & Goeltner (1974) observed a reduction in venous blood flow velocity of 43% at term. The described studies provided limited information as to the changes occurring in individual vessels and further studies of blood flow velocity in pregnancy were limited by the need for an accurate, non-invasive technique which enabled scrutiny of individual vessels.

In 1988, Baumann et al published data on femoral vein diameter and flow velocities in pregnancy obtained using duplex Doppler ultrasound techniques. Measuring the diameter of the femoral vein of 21 subjects at 4 weekly intervals between 20 weeks gestation and 12 weeks postpartum, they observed an increase in mean femoral vein diameter from 10.8mm at 20 weeks to 11.9mm at 39 weeks, falling to 7.5mm at 12 weeks postpartum. A reduction in time averaged flow velocity was found to be already present at the beginning of the second trimester, but no further gestation dependent changes were observed.

Reduction in venous bloodflow velocity may be related to increasing venous distensability and pressure and reduced arterial inflow. Venous distensability increases throughout pregnancy (Clark-Pearson & Jelovsek 1981, Goodrich & Wood 1964). This increase occurs early in pregnancy due to decreased venous tone. During pregnancy, venous capacity can increase by up to 50%, with a marked rise in the first and second trimester, but little further increase in the third trimester (Clarke-Pearson & Jelovsek 1981)

Little further contemporary data exists on the normal alterations in venous diameter which occur in pregnancy. However, it can be postulated that venous dilatation occurring as a response to pregnancy associated changes in smooth muscle tone and increased venous pressure secondary to the effects of the gravid uterus on venous return from the deep leg veins, might result in progressive venous dilatation sufficient to cause microtears at the junctions of tributaries with the common femoral vein, thus exposing thrombogenic subendothelial collagen, and initiating thrombogenesis.

2.3.2 Rheology

Pregnancy is associated with a fall in whole blood viscosity secondary to haemodilution of cellular blood components (Lowe 1992). This usually outweighs increases in plasma viscosity (Inglis et al 1982, Huisman et al 1987) and red cell aggregation arising as a result of the rise in plasma fibrinogen (see Chapter 1) until the third trimester, when increases in low shear whole blood viscosity are observed (Lowe 1992) As described earlier, however, lower flow velocity and shear rates can result in local increases in blood viscosity, increasing its resistance to flow. While there are no reported studies of the relationship between blood viscosity and venous thromboembolism in pregnancy, increases in blood viscosity under low shear and low flow conditions may contribute to deep venous thrombosis (Lowe 1984).

2.4 Stasis, venous dilatation and thromboprophylaxis.

Whatever the precise mechanisms by which stasis leads to thrombosis, the efficacy of physical means of thromboprophylaxis underline its importance. The mostly widely used physical means of thromboprophylaxis today are graduated compression stockings and several groups have demonstrated their efficacy in preventing post-operative DVT (Scurr et al 1977, Allan et al 1983, Jeffery & Nicolaides 1990). Early studies on the effect of graduated compression on venous haemodynamics indicated

that their thromboprophylactic effect resulted from an increase in flow velocity within the deep veins of the legs (Sigel et al, 1973). This work provided further clinical evidence for the importance of haemodynamics in thrombogenesis. In recent years, however, the means by which compression stockings prevent thrombosis has come under further examination and while the mechanisms remain uncertain, it appears that they may exert their prophylactic effect by means other than preventing stasis. Coleridge et al have demonstrated that venous distension occurs in lower limb veins during surgical procedures (1991), potentially resulting in the exposure of thrombogenic subendothelial collagen and that intraoperative venous distension can be corrected by the application of graduated compression stockings. The mechanism by which graduated compression stockings effect thromboprophylaxis remains an area of uncertainty and is discussed further in a later chapter. Pneumatic compression has also been demonstrated to be effective in preventing DVT (Nicolaides et al 1983) and recent studies using modern duplex ultrasound methodology suggest their principal effect is to increase deep venous flow velocity (Keith et al 1991). However, other studies have also demonstrated a relative activation of the fibrinolytic system during the use of intermittent compression boots (Guyton et al 1985). Further, there is evidence that pneumatic compression and compression stockings provide a synergistic thromboprophylactic effect, as demonstrated in the studies of Scurr et al (1987) and Nicolaides et al (1983) who showed a reduction in the incidence of postoperative DVT to 1% and 4% respectively when this combination was used. Intermittent pneumatic compression is now widely used to provide intra-operative thromboprophylaxis to women undergoing caesarean section and graduated compression stockings have become an important means of providing thromboprophylaxis in pregnancy and the puerperium. While the evidence for their efficacy in the surgical patients is strong, no studies have yet been published demonstrating their efficacy in preventing DVT in the pregnant and puerperal patient.

2.5 Conclusion

While haemostasis alone has not been shown to cause DVT, the role of haemodynamics in initiating or preventing thrombogenesis can be seen to be crucial both from consideration of the potential effects of haemostasis on the local microenvironment at the vessel wall, and from the clinical evidence reviewed above. Pregnancy is a period of increased risk for DVT, and this may be due in part to gestational changes in deep venous anatomy and haemodynamics. However there is little contemporary data which describes or quantifies these changes.

Chapter 3

Ultrasound in the study of blood flow velocity and vessel size

Summary

Since the discovery of the Doppler effect the application of the Doppler principle to ultrasound equipment in the clinical setting has lead to the development of duplex Doppler ultrasound as a non-invasive means of measuring blood flow velocity, volume flow and vessel size. Pulsed wave Doppler ultrasound allows flow velocity measurements to be made in discrete vessels by Fast Fourier transformation of the Doppler shift detected form a vessel imaged in real-time. True velocity measurements are, however, subject to many potential sources of error. The angle of insonation to that of direction of flow should be minimised and corrected for in calculations of flow velocity. Wall thump artefacts should be minimised by appropriate filter settings. Time average velocity processors are available on most modern ultrasound machines, but are subject to several sources of error. When measuring flow velocity in large vessels with established parabolic flow, there are theoretical advantages in measuring the time averaged maximum flow velocity, although this technique is also prone to certain errors. Transverse imaging of the vessel and measurement of the internal vessel diameter appears to be an accurate and reproducible technique. Calculation of volume flow requires measurement of vessel cross sectional area which is more prone to error. This combined with the difficulties in accurately measuring time average flow velocity in the context of the presented studies renders volume flow measurement unsuitable, and given the relative advantages and disadvantages of the techniques described, the measurements presented in this thesis are of time averaged maximum velocity and cross sectional vessel internal diameter.

3.1 Introduction

Reliable and accurate in-vivo observations of venous anatomy and flow may be recorded using invasive techniques such as direct operative vessel visualisation and the application of mechanical callipers and electromagnetic flow meters to the exposed vessels. Such techniques are clearly not applicable to human physiological studies in pregnancy, where non-invasive, reliable, accurate and reproducible methods are required. Duplex Doppler ultrasound provides a non-invasive means by which deep vessels can be scrutinised for anatomy and flow. This chapter begins with a description of the Doppler effect and its development as a means of velocity measurement. The technical aspects and limitations of Doppler ultrasound as applied

to ultrasound measurement of blood flow velocity are then addressed, and this is followed by a discussion of real-time ultrasound as a means of measuring vessel size.

3.2 Principles of Doppler Ultrasound

3.2.1 The Doppler Effect

The utilisation of the Doppler effect has enabled modern ultrasound machines to provide a means of non-invasively quantifying blood flow velocity. This has revolutionised the study of circulatory physiology and clinical vascular investigation.

The Doppler effect was described by Christian Johanne Doppler, an Austrian professor of mathematics and geometry. In 1843 he postulated that the observed frequency of light or soundwaves depends on the relative motion of the wave source and the observer, thus explaining the shifts in red light from binary stars. He indicated how the observed frequency could be derived mathematically. It was however, a dutchman, BuysBallot who was responsible for the first experimental test of the theory. Working in Utrecht in 1845, he used the newly completed Amsterdam to Utrecht railway line to demonstrate that the pitch of a horn played by a traveller on a moving railway carriage was perceived by a stationary observer to increase as the train approached. The change in pitch became greater as the angle between the railway track and the observer's line of sight became more acute. The variation of the pitch produced by the motion verified Doppler's equations (BuysBallot, 1845, Jonkman, 1980). A short time after this PJ Curie discovered the piezo-electric properties of certain materials, which resonated when subjected to voltage. Curie's pupil, Langevin, used this property of certain ceramics to produce ultrasound which had its first practical application in the detection of submarines in the first world war. The first diagnostic application was described in Austria to visualise intracranial structures using a transmission technique (Dussik 1942). Rapid advances continued through the second world war but it was not until 1957 that the possibility of combining the Doppler effect with ultrasound to identify moving structures was investigated (Satomura 1957). Soon after, the application of ultrasound to obstetrics was established by Ian Donald and his colleagues in Glasgow who produced the first contact B mode scanner. At the same time, Callagan, Rowland & Goldman (1964) and Johnson et al (1965) were working to develop the ultrasonic flow meter to detect fetal heart action. In recent years, technical developments have enabled precision

imaging and measurements. However the principles governing all ultrasound Doppler machines remain the same.

3.2.2 The Doppler Principle

The perceived frequency of sound depends on the number of wavefronts which reach the ear per second. The difference between the emitted frequency and the perceived frequency is called the Doppler shift. Movement of the reflecting object towards the sound source results in an apparent increase in the frequency of reflected sound. Movement away from the source results in an apparent decrease. Echoes reflected from stationary boundaries are received at the emitted frequency, but ultrasonic waves reflected from moving particles, such as red blood cells, undergo Doppler shift that is proportional to the velocity at which the particles are moving.

The Doppler shift (f d)is given by the formula:

$$f\,\mathrm{d} = \frac{2 \times \mathrm{Fo} \times \mathrm{V} \times \cos \text{Ø}}{\mathrm{C}}$$

Fo = the frequency of the emitted ultrasound

V = the velocity of the moving target

Ø = the angle between the ultrasound beam and the direction of movement

C = the velocity of sound in tissue, which is approximately 1540 metres/second

If the Doppler beam is at right angles to the vessel being investigated, no Doppler shift will be recorded, as the cosine of 90 degrees is 0. The size of the Doppler shift increases as the angle of insonation approaches 0 degrees (maximum positive Doppler shift) or 180 degrees (maximum negative Doppler shift). Doppler shifts obtained from flowing blood are in the order of 0-5 kHz, which is within the audible range.

As the Doppler shift is directly proportional to the cosine of the angle of insonation, this angle must be known with accuracy in order to determine the velocity. Errors in the estimation of the angle of insonation can be expected to be less than +/- 5° . The

smaller the angle of insonation, the smaller the error in estimating velocity. The rise in error with increasing angle of insonation is exponential. Angles greater than 85° will cause significant errors (more than 20%) in velocity calculation (Griffin et al, 1983).

Errors in measuring flow velocity may also arise from assumptions related to refraction, the speed of sound in tissue and the speed of sound in blood. For clinical blood velocity measurements, the net error arising from refraction effects is estimated to be between a 2% and 8% overestimation of the actual velocity (Kremkau 1990, Christopher et al 1995).

3.2.3 The Doppler Spectrum

When ultrasound strikes blood it is scattered by the erythrocytes. This scattering is very weak in comparison with that from tissue, as inspection of any ultrasonic image of a vessel will indicate. The 'sample volume' of a Doppler system is the region from which the instrument can receive Doppler shifted echoes. Depending on the design of the machine, it may be as small as 3-4 mm in depth and width, or it may be considerably larger. Since the red cells are in general independent and randomly distributed within the sample volume, their Doppler shifted signals add together randomly to produce the final signal which is detected by the Doppler machine. This process gives the Doppler signal its characteristic 'noise-like' quality.

A further consideration in understanding the nature of a Doppler signal is the fact that the red cells within the sample volume do not, in general, all travel at the same velocity. This gives rise to a 'spectrum' of Doppler shifts, reflecting the range of velocities present in the sample volume.

The dynamics of blood flow have been analysed extensively, both theoretically and experimentally, and it has been shown that the distribution of blood velocity across the diameter of a vessel is complex and highly variable (McDonald, 1974; O'Rourke, 1982). Among other factors, this distribution often called the 'velocity profile' depends on the viscosity of the blood, the time variation of the flow, the presence or absence of turbulence, and any branching or curvature of the vessel.

In a straight non-elastic pipe with an ideal fluid flowing at a constant rate without turbulence, the velocity profile is parabolic, with the maximum velocity being in the

centre and with the blood at the vessel walls scarcely moving. This distribution, referred to as 'laminar flow', is considered to be a reasonable approximation for steady (venous) flow in a relatively straight section of a vessel at points proximal to the entrance of tributaries and in the absence of local pathology.

3.3 Application of ultrasound to flow velocity measurement

3.3.1 Continuous wave Doppler ultrasound

The simplest type of Doppler machine is a continuous wave (CW) Doppler. Here, two separate transducers are used, one to transmit continuously at a fixed frequency, the other to act as a receiver for the back scattered signals. The sample volume of this device is simply the area of overlap of the transmitted beam and the beam pattern of the receiving transducer. In general this sample volume is large. As a consequence, CW Dopplers have relatively poor spatial selectivity, particularly in depth. While this may appear to a severe disadvantage for many applications, it does mean that they can be used 'blind' without imaging guidance, since the positioning of the probe is not as critical as in the systems with better spatial selectivity.

3.3.2 Pulsed wave Doppler ultrasound

A more complex form of Doppler instrument is pulsed Doppler. This uses the relationship between the depth of a scatterer and the time taken for its echo to arrive at the transducer. The transmitted signal consists of a short burst of ultrasound, containing 3-20 cycles at a fixed frequency. Generally the same transducer then acts as a receiver, picking up the back scattered echoes that arise as the transmitted energy travels through the body.

After the weak echo signals have been amplified, a 'range gate' circuit selectively lets through the Doppler shift detector only those echoes which arrive at a given time delay after the transmit burst. This ensures that the signals originate from scatterers, such as erythrocytes, at a fixed depth, with that depth being determined by the time delay between the transmit time and the opening of the range gate. In fact, the sample volume has a finite extent in depth; this is determined by the number of cycles in the transmit burst and the length of time for which the range gate is open. The width of a sample volume is simply the width of the ultrasound beam at that depth.

In view of the limitations of continuous wave ultrasound, especially because of the poor spatial selectivity at depth, deep vessels such as the femoral vein, are better scrutinised using pulsed Doppler systems. As the ultrasound has to travel to the vessel and back, a depth limitation is imposed, since all information from one pulse must be received prior to the next pulse being emitted. The maximum pulsed repetition frequency (PRF) is given by the formula:

$$PRF\ (Hz) = (CxD) / 2$$

where C is the velocity of sound in tissue (generally assumed to be 1540 metres/second) and D is the depth of the structure being investigated.

In addition, if the PRF is less than half the Doppler shifted frequency, an artefact known as aliasing occurs. This phenomenon is readily recognised as the peaks of the Doppler shifted waveform fold round and appear in the lower channel. Aliasing may result in substantial underestimation of systolic velocities (Teague et al, 1985). Although techniques have been developed to reduce frequency aliasing, it is still a significant problem in some applications. A number of machines provide the possibility of switching to continuous wave Doppler when aliasing cannot be eliminated, since CW Doppler does not suffer from this limitation. Aliasing constitutes less of a problem when measuring venous blood flow, as the velocities are considerably lower, and unlikely to exceed the PRF of a pulsed wave Doppler machine.

3.3.3 Doppler signal processing

While aural monitoring of the signal can be part of the examination, providing the operator with feedback regarding the quality and nature of the signal, spectral analysis by means of the fast Fourier transform (FFT) has become established as the method of choice for analysing and displaying the signals, and virtually all equipment now provides this option. The FFT is a high speed algorithm which computes the spectral content of a sampled signal by transforming incoming Doppler signals from the time domain to the frequency domain in real time. The analyser first samples and digitizes the audio- frequency, time domain signal with a sampling rate sufficient to prevent aliasing (usually 20 to 200MHz, corresponding to sample lengths of 50 to 5 ms) and then displays the information on a rolling screen. The spectral display shows the signal in considerable detail indicating the frequency components of the Doppler spectrum, the relative intensity of these components and their time variation.

Various derived values may also be available, including the peak and instantaneous mean frequencies, and time average maximum values. Variation in flow patterns can be readily observed, such as occurs in venous flow during the respiratory and cardiac cycles.

Duplex Doppler ultrasound also provides a non-invasive means of quantifying venous flow velocity. There are however different means of analysing the Doppler spectrum in order to extract information about flow velocity in the scrutinised vessel. The two principal means are calculation of the time-average velocity (TAV), achieved by computation of the mean Doppler frequency, and the time averaged maximum flow velocity (TAMV), calculated from the maximum frequency envelope of the Doppler waveform. Both are subject to machine based and observer based sources of error. Machine based errors may be systematic or random, or a combination of both (Gill 1985). Random machine-based errors are difficult to differentiate from random observer errors, so machine based error are usually considered to be systematic. These errors are difficult to measure in-vivo (Gill 1985). However, the potential machine based errors associated with TAMV and TAV measurement are discussed below.

3.3.4 Measurement of Time Average Velocity

Most modern ultrasound machines contain software which allows computation of the mean frequency over a given time. Under ideal conditions, this derived frequency is proportional to the mean velocity of flow within the scrutinised vessel. If the angle between the subtended ultrasound beam and the axis of the blood vessel is known, the mean flow velocity can be calculated.

If a true mean velocity within a vessel is to be calculated, then analyses of the Doppler frequencies at every point across the vessel diameter is required. The sample volume should include the entire lumen of the vessel, both axially and laterally. In reality, this may not be attainable (Evans 1982). Duplex scanners usually use the same beam for Doppler ultrasound as for real-time imaging, and the beam is made narrow at its focus in order to improve lateral resolution of the real-time image. Even low frequency (eg: 2MHz) transducers produce a beam width whose lateral extent is small compared with the diameter of large vessels such as the common femoral vein (Burns & Jaffe 1995). Cobbald et al (1983) and Evans (1985) have demonstrated that the use of an ultrasound beam that is narrower than a blood vessel containing a parabolic velocity profile may cause an over-estimation of the mean velocity of up to 33% as the lower frequencies at the lateral edges of the vessel may be excluded from

the computation of the mean frequency. In addition, the differential rates of beam attenuation in soft tissues and blood mean that echoes returning from different parts of the blood vessel may undergo different rates of attenuation if they traverse different proportions of soft tissue and blood. Signals from the centre of the vessel are stronger than those at the lateral edges of the vessel where the beam traverses more soft tissue and less blood. Higher velocities obtained at the centre of the vessel are therefore accentuated and the effective beam width is reduced (Cobbald et al 1983) therefore accentuating the higher velocities at the centre of the vessel.

The recorded Doppler spectrum comprises not only the moving blood but also the pulsating vessel wall. Vessel wall motion is low in frequency, but is high in intensity (Reneman 1981). Doppler devices therefore contain high pass filters designed to remove high amplitude low-frequency signals which can arise from movement of vessel walls. These filters will however, not only remove unwanted noise but will also reject low frequency signals, thus biasing the mean frequency estimate upwards. The margin of error thus introduced has been shown to be around 3%. (Gill 1979).

A further important limitation of mean frequency calculation is the inability of the processor to distinguish between signal and noise. This is of particular importance when the signal to noise ratio is reduced, as may occur when the Doppler angle is large. Unless noise is removed from the spectrum, the mean velocity calculation will be biased by the inclusion of non-signal derived frequencies.

Many of these limitations do not, however, apply to the calculation of maximum frequencies.

3.3.5 Measurement of Time Averaged Maximum Velocity

Many modern ultrasound machines also contain processors which can automatically extract the maximum frequency envelope from the Fast Fourier Transformed spectrum. Knowledge of the angle between the subtended beam and the direction of flow at the centre of the vessel enables calculation of the maximum velocity. In many instances, the maximum frequency envelope is manually traced on screen by the operator. In neither case is the calculation of maximum frequency and hence maximum flow velocity prone to the same errors described in relation to the calculation of the time averaged mean velocity as derived by mean frequency processors. In relation to the effect of non-uniform insonation discussed above, provided some part of the ultrasound beam passes through the part of the vessel

containing the maximum velocity (the central segment in veins containing parabolic flow) then the output will not be significantly influenced by the shape of the ultrasound beam or the ratio of the beam width to the vessel diameter. Further, differential attenuation of the ultrasound beam between blood and tissue is of less importance since the effective ultrasound beam shape is not critical to the ability to recognise and analyse maximum frequency shifts within the vessel.

With respect to the effect of wall filters, provided the maximum frequency in the Doppler signal does not fall below the frequency of the filter, the calculation of time averaged maximum velocity from the maximum frequency will be unaffected by its action; again, in contrast to the derivation of mean velocity by the mean frequency processor. However, given the low flow velocities present within large veins, it is important that the wall filter is set as low as is practical in order to avoid removal of the maximum frequencies themselves.

A further major advantage of calculating time averaged maximum velocities is their relative immunity to noise. Provided the signal can be visually differentiated from background noise, then the effect of noise can be virtually eliminated from the velocity calculations. The human eye is very sensitive to pattern recognition, and allows an operator to monitor the performance of an automatic maximum frequency follower if installed in the machine. The threshold level can be adjusted to ensure that it follows the required signal (Prytherch & Evans 1985).

A source of error that is more likely to affect maximum than mean velocity calculation is that imposed by intrinsic spectral broadening (ISB). Intrinsic spectral broadening does not affect the mean frequency of a spectrum because the broadening is symmetrical. However since the effect of ISB is to blur the Doppler spectrum, it will not fall off rapidly at the frequency corresponding to maximum flow, but will fall off gradually, depending on the amount of ISB present. This may make determination of the true maximum frequency within the spectrum difficult to judge with certainty (Biascom et al, 1986).

In determining which means of spectrum analyses to use to measure venous flow velocity in the presented studies, consideration was given to the above advantages and disadvantages of each method. For volumetric blood flow measurements, the calculation of time-averaged mean velocity using a mean frequency processor has been the usual method of choice. For velocity calculations however, the technique

least sensitive to noise and other distorting influences is the calculation of time averaged maximum flow velocity from analyses of maximum Doppler shifts.

When larger vessels are interrogated, accurate sampling of the complete vessel is difficult to achieve. In addition, different segments of a vessel may have different flow characteristics. Sampling the middle third of the vessel lumen will minimise errors arising from incorrect assumptions over the form of flow and avoid the difficulties in sampling larger vessels. Clearly the time averaged flow velocity cannot then be calculated as a only a proportion of the flowing blood is sampled. However, it is reasonable to assume that the maximum flow velocities will be present in the middle third of the lumen. Additionally, if only the mid-lumen is sampled, wall thump artefacts (discussed below) are reduced.

Measurement of the TAMV is therefore recommended as the better technique for velocity measurement when the velocity profile is established, parabolic and relatively non-pulsatile, and the maximum velocities can be assumed to occur in the middle segment of the vessel (Burns & Jaffe 1985, Evans et al 1989, Tortoli et al 1994). Such is the case in large veins at points distant to the entry of tributaries. The accuracy of TAMV as a means of measuring flow velocity has been verified experimentally. Li et al (1993) employed a computer-controlled string phantom to compare Doppler measured TAMV with actual mean flow velocity in a straight tube under pulsatile and non-pulsatile flow conditions. The TAMV was found to be within 5% of the actual velocity. Error arising from spectral broadening was less than 3%. Although few studies report the clinical reproducibility of duplex Doppler TAMV measurement in the deep leg veins, data derived from other venous measurements indicate that good inter- and intra- observer agreement can be obtained using this technique (Lomas 1994).

3.3.6 Measurement of volume flow

The potential of Duplex Doppler ultrasound to provide a non-invasive means of measuring volume flow has been explored by many workers (Gill 1979, 1982, Eik-Nes et al 1984, Gill et al 1984, Evans 1986). In order to calculate volume flow, the blood vessel is visualised, allowing the accurate placement of the Doppler sample volume to totally encompass the vessel while avoiding signals from adjacent structures. The angle between the ultrasound beam and the axis of the blood vessel is measured, as is the area of the vessel. The mean velocity of flow parallel to the vessel

axis is calculated and multiplied by the cross sectional area to give the mean volumetric flow.

The errors which may arise in the calculation of mean velocity vessel cross sectional area (discussed below) can be reduced to 6% for certain arterial measurements by careful attention to technique (Gill, 1985). However, for smaller vessels, accurate measurement of vessel size is difficult, and for larger vessels, uniform insonation becomes progressively more difficult to achieve.

In view of the increased potential for error in volumetric flow measurement, the author elected to measure flow velocity only, and after consideration of the previously discussed advantages and disadvantages of time average mean velocity and time averaged maximum velocity measurements, the latter method was elected for the presented studies.

3.3.7 Measurement of Wall Shear Rate

Given the important role played by wall shear stress and shear rate in the pathogenesis of venous thrombosis (see Chapter 2), the ability to quantitate wall shear rate using pulsed Doppler ultrasound is of great potential interest. Hughes and How (1993) have described the calculation of wall shear rate using a 20MHz Doppler system to obtain steady flow velocity profiles in cylindrical tubes. Comparing the obtained wall shear rates with those expected from theoretical considerations, an average error in measured wall shear rate was obtained. of 46% measured velocity profiles. Carrying out similar studies under conditions of pulsatile flow, error in wall shear rate calculations of 28% were reported by the same authors (1994). At the time of designing the studies presented in this thesis, the means of measuring wall shear rates in-vivo with Doppler ultrasound were not available. This technique requires further development and refinement before meaningful clinical measurements can be made.

3.4 Ultrasound Measurement of Vessel Size.

The ability of modern ultrasound machines to image deep blood vessels combined with on-board software allowing the use of superimposed 'callipers' offers the possibility of non-invasive and accurate vessel diameter measurement. This technique has found widespread use in echocardiography, vascular surgery and obstetrics, where the ability to measure the size of fetal vessels is of considerable importance in the

field of prenatal diagnosis. In view of the potential clinical utility of vessel size measurement, the technique has been subject to examination of its accuracy and reproducibility.

There are several potential sources of error which may affect the accuracy of vessel size measurement using ultrasound techniques. Imaging the vessel in the sagittal plane introduces the potential for underestimation of the vessels diameter as the transducer may slide from the central, widest section of the vessel, producing a false image of the true vessel size. This potential for error can be removed by imaging the vessel in the transverse plane, where the maximal diameter can readily be determined.

Because of the low intra-luminal pressure and relatively thin walls, veins collapse readily on the application of external pressure. Indeed, this property constitutes the basis for ultrasound techniques in the diagnosis or exclusion of deep venous thrombosis (see Chapter 1). Superficial vessels are particularly vulnerable to compression by the application of an ultrasound transducer to the skin and this may result in artefactual reduction in measured diameter by the technique itself. To overcome this, some workers have used apparatus designed to hold the transducer against the skin while applying minimal pressure (Camerota et al 1989). While such devices have found use in anaesthetised paralysed patients, they are of less practicality in the conscious patient. Other workers have shown that such devices may not be required if careful technique is employed (Buchbinder et al, 1987). The liberal application of sonic gel allows excellent sonic transmission with minimal direct contact between the transducer and the skin. Suitable images for analysis can be obtained by withdrawing pressure on the applied transducer to the point at which sonic contact is lost and then gently reapplying the transducer to the minimal pressure required for return of the image.

Measurements of arterial diameters are complicated by the changes in vessel diameter that occur during the cardiac cycle. Some authors have advocated taking the mean of several measurements to minimise uncertainty as to the 'true' diameter (Evans et al 1989). Eik-Nes et al (1984) attempted to overcome this potential uncertainty in arterial measurements by taking the mean of 10 on-screen measurements of randomly frozen images.

More recent developments in the field of non-invasive vessel diameter measurement include an ultrasound phase-locked echo-tracking system which has been shown to

allow the measurement of pulsatile vessel diameter changes. (Hansen et al, 1993). In addition Magnetic Resonance Imaging (MRI) has been shown to be a valuable tool in measuring vessel diameters that alter with cardiac pulsation. The importance of pulsatile changes in vessel diameter as a source of measurement error is questionable however. At the femoral artery radial dilatation during systole is small (McDonald1974) and M Mode ultrasound studies of pregnant patients have demonstrated this to be in the order of 5% regardless of gestational age . No significant systole related radial dilatation was demonstrated in the CFV, SFV or popliteal vein (Baumann et al, 1988).

The reproducibility and accuracy of real-time ultrasound measurement as compared to direct methods of vessel measurement has been established by many studies. In a prospective study undertaken to assess the reliability of ultrasound imaging of the greater saphenous vein, Buchbinder et al (1987) performed pre-operative imaging on 15 patients prior to saphenous bypass, and compared the ultrasound measurements with intraoperative findings. In addition to reporting 100% accuracy in the detection and location of valve sites, they found the actual venous diameter to be consistently within 0.5mm of that measured by realtime ultrasound. Using realtime ultrasound they were also able to demonstrate the correct anatomic location of the vein in all patients.

The superficial location of the greater saphenous vein in the proximal leg renders it more vulnerable to compression during ultrasound measurement than the deeper lying CFV, SFV and popliteal veins. The accuracy of the technique in the hands of Buchbinder et al demonstrates that with careful technique, errors in measurement caused by vessel compression can be minimised. Head & Brown (1995) have further validated ultrasound vessel diameter measurement in 100 patients undergoing coronary artery bypass grafting. They demonstrated a close correlation between imaged and in-vivo measurements. However, a non-statistically significant increase in the in-vivo measurement was noted, possibly reflecting comparison of the internal diameter measured by ultrasonography to the external diameter measured at operation. This difference was observed to be of a similar magnitude at all levels of the saphenous vein. Of further interest was the absence of differences found in vein measurements based on age, sex, diabetes or obesity, or in measurements obtained by five observers. Real-time ultrasound would therefore appear to be an accurate and reproducible means of non-invasive vessel measurement.

In-vivo versus in-vitro comparison of real-time ultrasound has further confirmed the accuracy of the technique. Rasmussen (1987) has measured fetal vessels in-vivo and in-vitro preparations and reported a close correlation in results, describing an under estimation of vessel diameter of only 1.1% in-vivo.

The above described studies relate to simple vessel diameter measurement. However, vessel area is the important parameter for those wishing to measure volume blood flow. While vessel area can be calculated from vessel diameter by applying the formula:

$$\text{Vessel Area} = (\Pi \times \text{vessel diameter}/2)^2$$

several assumptions are made which may not be applicable in vivo. The first is that the vessel concerned is circular in cross section. Veins are usually oval in cross section and errors may therefore enter the calculation.

Inter- and intra- observer error has been shown to be non-significant in the measurement of the diameter of the superficial femoral vein. Studies assessing the reproducibility of vessel area measurements have shown less clear results. Ellis et al (1992) have studied the inter- and intra-observer error arising in measurements of the external vessel diameter, luminal diameter and internal diameter (the diameter within the internal elastic lamina) in both longitudinal and cross sectional views of the common femoral arteries. They also assessed the reproducibility of cross sectional area measurements. They found cross sectional and longitudinal diameter measurements to be similarly reproducible, with measurement of the internal diameter showing the greatest inter- and intra- observer agreement (limits of agreement;-0.67 to +0.25mm). They concluded that a real difference in vessel diameter of greater than 0.86mm would be required to enable detection by different observers. This represented a change of less than 10% in the measured vessel. Cross sectional area measurements, however, showed a wide variation with limits of agreement ranging from -25.4% to +30.2%, demonstrating the inferior reliability and reproducibility of vessel area measurements.

3.5 Conclusion

All ultrasound methods of measuring vessel size and blood flow velocity are subject to error, the principal sources of which have been discussed in this chapter.

Appropriate selection and careful use of technique can reduce the impact of these errors. For the studies presented in this thesis the technique deemed most suitable for flow velocity measurement was time averaged maximum velocity (TAMV). Volume flow measurements were not attempted. In view of the reported reproducibility of internal diameter measurements, and the above described data demonstrating the accuracy of the ultrasound diameter measurements, this method was selected for the studies presented in this thesis. Systematic errors are of less importance when serial measurements at the same site are made to detect changes in vessel size or flow velocity rather than absolute values. Similarly, random observer based errors can be reduced if all observations are carried out by the same observer under the same experimental conditions. However, in order to assess the reliability of transverse sectional diameter and flow velocity measurements as measured by the author using the ultrasound machine to be employed for the presented studies, a study was undertaken by the author together with a consultant radiologist with expertise in vascular ultrasound to assess the inter- and intra-observer error of measurement of deep leg veins using our own ultrasound machine (Acuson 128). These data are presented in Chapter 4.

Chapter 4

Duplex ultrasound measurement of flow velocity and vein diameter: a reproducibility study

Summary

A reproducibility study is presented where-in the inter and intra-observer variation between ultrasound measurements of cross-sectional vessel diameter and time averaged maximum velocity were calculated. Using Pearson's Coefficient of Correlation, the inter-observer variability for these measurement techniques was found to be good with correlation coefficients of 0.96 for vessel diameter and 0.90 for time averaged maximum flow velocity. At an interval of one hour between measurements, the intra-observer agreement was also good with correlation coefficients of 0.89 for vessel diameter and 0.87 for flow velocity measurements. At an interval of 10 days the respective correlation coefficients were 0.71 and 0.77. Physiological alterations in hormonal status of the female subjects examined may underlie the difference in levels of agreement obtained at 1 hour and 10 days (mean) intervals. The presented data indicate that the techniques employed are reproducible.

4.1 Introduction

The reproducibility of realtime ultrasound measurement of venous diameter and duplex Doppler measurement of time averaged maximum velocity has undergone previous evaluation, as discussed in the previous chapter. However, most of the studies addressing the reproducibility of vessel measurement and duplex Doppler flow velocity have been carried out in vessels other than those studied in the work presented in this thesis.

In order to assess the reproducibility of the methods employed by the author, studies were carried out into the inter-observer and intra-observer reproducibility of transverse section vessel diameter measurement with real-time ultrasound and time averaged maximum flow velocity measurement using duplex Doppler ultrasound.

4.2 Methods

4.2.1 Inter-observer variation

10 healthy women of low parity at different stages of pregnancy (range of gestation: 24-39 weeks, mean: 33 weeks) were recruited for this study. None had any previous history of thromboembolic disease. Each woman rested in the semi-recumbent position for 15 minutes prior to the scans being performed. The following protocol

was followed by two observers, each blinded to the measurements of the other. Both observers were experienced in duplex Doppler ultrasound. The first observer was the author (NM) and the second (AR) a consultant radiologist with a special interest in vascular ultrasound.

With the subject lying supine and with her back raised at an angle of 15°, the right common femoral vein was imaged in the longitudinal axis, at a point on the common femoral vein 2 cm below the junction with the long saphenous vein. The image was frozen after minimising the transducer pressure near to the point of losing contact. The distance between the inner aspects of the anterior and posterior vessel walls was recorded and the mean of three measurements calculated. The Doppler gate was then placed across the middle third of the vessel lumen, and a spectral Doppler recording of the flow wave form was made over a period of 15 seconds of quiet respiration. In order to minimise velocity calculation errors from the Doppler shift, the angle of insonance was electronically steered to subtend an angle less than 60° to the axis of flow and the velocities measured were angle corrected by aligning the cursor to the direction of flow. These measurements were then repeated at the popliteal vein, distal to its junction with the short saphenous tributary. All measurements were recorded directly by each observer, who was blinded to the results of the other observer at the time of performing the measurements.

The inter-observer variation was assessed by calculating Pearson's Correlation Coefficient between the sets of data obtained by each observer. Calculations were performed using the SPSS Statistics Programme for Windows.

4.2.2 Intra-observer variation

For the first part of the study, 8 subjects were recruited. The subjects were non-smoking members of staff and none were pregnant or had any history of thromboembolic disease or other significant medical history. Each subject was allowed to rest in the semi-supine position for 15 minutes prior to undergoing the same measurements as described above, with the same technique. The values obtained were recorded directly from the screen at the time of measurement. After an interval of at least one hour, the same protocol was followed on each subject by the same observer (NM), and the results again recorded directly at the time of measurement. In order to further test the reproducibility in the author's hands, the protocol was repeated on 10 further subjects similarly recruited, with a mean interval

of 10 days (range 8-11 days) between observations, by the same observer. On each occasion the observer was blinded to the previously obtained measurements.

The intra-observer variation was assessed by calculating Pearson's Correlation Coefficient between the sets of data obtained by the same author observer. Calculations were performed using the SPSS Statistics Programme for Windows. The coefficients of variation between the measurements carried out at an interval of 1 hour were calculated, as were the coefficients of variation between the measurements carried out more than a week apart.

4.3 Results

4.3.1 Inter-observer variation

The mean measurements obtained by each observer for each parameter are shown in **Table 4.1,** The correlation coefficient between observers for vessel diameter measurement was 0.964 and that for time averaged maximum flow velocity was 0.904. These studies demonstrate good reproducibility for TAMV and vessel diameter measurements in the patients studied.

4.3.2 Intra-observer variation

Two sets of data were obtained. **Table 4.2** show the mean results obtained on each subject from the first examination and that carried out 1 hour later. **Table 4.3** shows the data obtained when the interval between measurements was more than a week.

The correlation coefficient for vessel diameter between the examinations made at an interval of 1 hour was 0.89, while that for measurement of time averaged maximum flow velocity was 0.87.

When the measurements were carried out at a mean interval of 10 days, the level of agreement was found to be less good, with correlation coefficients for vessel diameter measurement and TAMV measurement of 0.71 and 0.77 respectively.

4.4 Discussion

A coefficient of correlation value of greater than 0.8 indicates a good agreement between observations, while that above 0.9 indicates very good agreement (Altman 1991).

We have demonstrated very good inter-observer agreement for the techniques of vessel diameter and maximum flow velocity measurement. Our findings in this regard are consistent with previous studies assessing similar techniques on other vessels (Rasmussen 1987, Lomas et al 1994, see Chapter 3). The results for inter-observer agreement were similar to those obtained for intra-observer agreement. However, the slightly higher coefficients of correlation obtained between observers may reflect the closer temporal proximity of the measurements as these were carried out consecutively. Transient alterations in vessel size and flow velocity were less likely to occur than in the intra-observer study, where intervals of 1 hour and a mean of 10 days occurred between observations. The lower level of intra-observer agreement seen at 10 day intervals may reflect a true weakness in the reproducibility of the techniques employed. However, given the good reproducibility observed in the 1 hour study, a more likely explanation may underlie the lower coefficient of correlation observed for both vessel diameter and maximum flow velocity at a 10 day interval: the compliance of the veins has been shown to alter in pregnancy and in women taking the oral contraceptive pill (Goodrich & Wood 1969, Clarke-Pearson & Jelovsek, 1981) and a changing hormonal milieu has been proposed as the cause. The subject groups for the intra-observer studies consisted of non-pregnant pre-menopausal women. Over a 10 day period, cyclical changes in the oestrogen and progestogen levels occur and may affect venous compliance and hence capacitance, diameter and blood flow velocity. This variable, related to the menstrual cycle may be reflected in the results obtained. Clearly, such a variable is unlikely to exert a significant influence at an interval of 1 hour, and resultant agreement between measurements by the same observer is unlikely to be thus affected. The significance of these findings for the interpretation of the data presented in later chapters is two fold. Firstly, the technique employed for measuring vessel diameter and blood flow velocity has been demonstrated to have good reproducibility. Secondly, any trend revealed in the change of these measured parameters with gestation is less likely to be a chance event, since the poorer correlation coefficient observed over periods of around 10 days would tend to conceal such a trend.

4.5 Conclusion

The techniques employed in the ultrasound studies presented in this thesis appear to have good reproducibility in the author's hands on the equipment employed.

Table 4.1

The three values obtained by two observers (NM and AR) for vessel diameter (d) in mm and time averaged maximum flow velocity (v) in cm/sec at the common femoral (CFV), superficial femoral (SFV) and popliteal veins (POP) in five patients are given below.

Patient	Parameter	NM1	NM2	NM3	AR1	AR2	AR3
1	CFVd	15.5	16.2	15.5	14.3	14.2	14.8
1	SFVd	8.0	8.0	8.3	7.6	7.5	7.5
1	POPd	7.8	7.7	7.5	7.1	6.9	6.8
1	CFVv	7.3	7.1	7.1	8.9	8.6	10.0
1	SFVv	6.5	5.8	5.4	4.6	5.6	6.2
1	POPv	4.6	4.4	4.4	5.6	5.4	5.3
2	CFVd	12.8	12.0	12.3	11.9	11.5	12.6
2	SFVd	9.9	9.9	9.9	8.1	8.1	8.0
2	POPd	4.9	4.8	5.6	5.9	5.6	5.7
2	CFVv	12.1	12.4	12.0	17.6	15.4	17.4
2	SFVv	5.1	4.3	3.5	6.1	3.3	3.3
2	POPv	5.1	6.1	4.8	7.0	7.0	5.1
3	CFVd	11.8	12.3	12.0	17.6	15.4	17.4
3	SFVd	8.3	8.3	8.2	8.4	9.0	8.4
3	POPd	7.3	7.6	7.3	6.8	7.2	6.9
3	CFVv	6.0	4.5	4.8	5.	3.9	4.7
3	SFVv	2.8	2.9	2.6	3.6	3.0	3.3
3	POPv	3.5	2.9	3.2	3.7	2.3	3.3
4	CFVd	7.8	7.1	7.0	8.5	8.0	7.6
4	SFVd	7.3	7.3	7.2	7.5	7.8	7.8
4	POPd	4.6	4.9	4.7	5.8	6.2	4.7
4	CFVv	15.7	13.9	12.2	16.1	15.2	11.2
4	SFVv	5.1	5.5	4.5	7.6	7.0	7.1
4	POPv	4.9	3.7	3.6	5.6	5.6	5.8
5	CFVd	12.5	12	11.7	12.3	12.3	12.3
5	SFVd	8.2	7.7	7.6	8.5	7.9	7.4
5	POPd	-	-	-	-	-	-
5	CFVv	13.0	12.4	10.5	11.1	9.5	9.1
5	SFVv	6.2	6.3	6.2	5.5	5.2	4.8
5	POPv	-	-	-	-	-	-

Table 4.2

The initial three values obtained by one observer (NM) for vessel diameter (**D1**) in mm and time averaged maximum flow velocity (**V1**) in cm/sec and those obtained after an interval of one hour (**D2 and V2**) at the common femoral (**CFV**) and popliteal veins (**POP**) in eight subjects are given below.

	CFV				POP			
Subject	**D1**	**D2**	**V1**	**V2**	**D1**	**D2**	**V1**	**V2**
1	10.0	10.2	4.6	5.2	6.1	6.3	1.3	3.0
1	10.5	10.0	4.0	5.6	6.5	5.6	2.5	2.4
1	11.3	10.2	3.0	4.7	5.5	6.2	1.4	1.8
2	9.9	10.7	7.1	5.8	6.0	6.9	2.7	2.2
2	9.9	10.7	6.6	5.5	6.1	6.9	2.1	2.5
2	9.5	11.0	5.6	5.6	6.1	6.9	2.3	2.5
3	10.9	11.0	5.0	6.0	5.2	5.2	3.1	3.8
3	10.9	10.9	5.0	6.5	5.2	4.9	3.4	4.7
3	10.2	10.9	5.0	6.5	5.3	5.0	2.8	4.6
4	11.8	11.5	4.7	5.3	5.9	5.4	4.3	5.8
4	11.9	11.0	5.0	6.1	5.9	5.6	4.4	5.3
4	12.5	11.8	4.5	4.8	5.9	5.6	4.3	5.8
5	13.3	12.5	6.3	7.4	5.2	5.1	3.8	3.9
5	13.2	13.5	5.6	5.9	5.5	5.6	3.8	4.2
5	13.7	13.5	4.5	5.9	5.3	6.4	3.8	4.4
6	9.4	9.9	9.3	7.7	5.5	5.6	5.3	4.4
6	9.3	10.2	9.9	7.7	5.9	5.9	5.1	5.4
6	9.8	10.4	11.6	8.0	5.4	5.4	5.0	5.1
7	14.8	14.4	4.4	4.9	7.4	6.8	2.7	2.0
7	14.5	14.6	3.7	4.3	7.0	6.8	2.2	1.7
7	14.4	15.1	4.6	4.3	7.5	7.9	2.2	2.1
8	11.3	11.2	7.5	7.4	6.5	7.2	7.7	6.9
8	11.8	11.5	9.2	7.9	7.1	7.8	9.8	8.1
8	11.8	11.7	9.4	7.0	6.9	7.3	7.9	6.1

Table 4.3

The initial three values obtained by one observer (NM) for vessel diameter (**D1**) in mm and time averaged maximum flow velocity (**V1**) in cm/sec and those obtained after a mean interval of 10 days (**D2 and V2**) at the common femoral (**CFV**) and popliteal veins (**POP**) in ten subjects are given below.

	CFV				POP			
Subject	**D1**	**D2**	**V1**	**V2**	**D1**	**D2**	**V1**	**V2**
1	10.7	7.9	8.2	12.5	5.2	4.8	3.7	3.4
1	11.5	8.5	9.1	9.3	5.6	5.4	2.9	3.3
1	10.9	8.2	10.0	6.8	5.0	5.1	2.1	2.7
2	9.5	8.5	5.5	7.5	3.9	4.4	5.3	6.7
2	9.1	8.7	5.8	6.6	4.2	4.8	5.2	5.1
2	9.1	7.9	9.6	9.7	4.1	4.5	4.3	5.5
3	6.3	7.0	25.0	21.6	4.5	4.7	6.5	4.9
3	6.0	6.4	27.9	19.4	4.6	5.0	5.0	4.3
3	5.8	5.8	27.5	19.4	5.0	4.6	3.5	3.8
4	8.4	8.6	14.8	11.1	5.9	5.8	5.0	7.1
4	8.0	8.5	13.0	11.8	6.1	5.8	6.5	7.3
4	7.3	8.5	13.8	11.4	6.0	5.6	6.1	7.3
5	11.2	9.1	12.0	14.0	7.0	6.8	6.0	4.6
5	11.4	9.1	11.5	14.7	6.7	6.3	6.4	4.8
5	11.3	9.7	11.8	15.3	6.5	6.6	5.7	6.7
6	9.3	8.2	9.1	9.9	5.8	3.2	9.3	7.0
6	7.9	8.1	4.5	9.5	4.8	3.2	7.4	7.6
6	8.1	8.0	9.0	9.6	4.8	3.2	6.5	8.3
7	7.8	6.4	14.5	15.9	5.4	5.3	3.1	4.7
7	7.3	6.9	12.9	15.1	5.7	5.4	3.9	3.1
7	7.4	6.5	13.7	12.3	5.8	5.6	3.4	3.0
8	8.9	9.7	12.7	14.8	5.4	5.3	5.2	7.3
8	10.0	10.0	11.3	14.5	5.1	5.0	4.8	7.0
8	10.1	9.5	12.3	16.1	4.9	5.3	6.4	6.1
9	12.6	8.4	12.8	13.2	4.8	4.8	4.0	4.5
9	12.5	8.2	13.5	12.1	5.0	5.0	4.3	4.1
9	12.5	8.1	12.6	12.5	5.0	5.0	5.0	4.5
10	11.6	9.0	5.7	10.1	5.1	5.1	3.3	3.9
10	11.0	9.0	5.7	10.1	5.1	5.1	3.3	3.9
10	11.3	9.2	4.9	8.5	4.9	4.9	2.3	4.3

Chapter 5

Methods

Summary

In this chapter the practical procedures carried out in order to obtain the ultrasound derived data presented in later chapters are described. All the studies were carried out by the author in the same Ultrasound Unit, employing the same ultrasound apparatus. All subjects were recruited from the staff and patients of the hospital in which the studies were performed. The ultrasound machine settings were set as advised in the manual supplied with the machine as appropriate for peripheral venous studies. Protocols for patient preparation, scan performance and data collection were designed and are described below.

5.1 Introduction

The studies presented in chapters 7 to 11 of this thesis were performed in the Ultrasound Department of Glasgow Royal Maternity Hospital. Full ethical approval was obtained from the Hospital Ethics Committee prior to commencing the studies. A 5 MHz linear array transducer, suitable for vascular studies, was purchased using monies from the grant awarded to Professor Greer and the author. This was coupled to an Acuson 128 ultrasound machine with real-time, spectral Doppler and colour Doppler facilities made available to the author by the Ultrasound Department.

5.2 Recruitment

Subjects were recruited from four main sources.

A. Women were seen by the author at their booking visit. After carrying out the booking procedure, those with a singleton pregnancy and no complicated past obstetric history or medical history were informed about the study and invited to take part. No other exclusion criteria were applied. Full informed consent was obtained, and arrangements were made for shared antenatal care between the author and the woman's GP.

B. A small number of antenatal patients with a history of DVT in pregnancy were referred to the author at booking by their consultant for screening throughout

pregnancy. Full informed consent to the study was obtained, and a protocol for scans was offered similar to those antenatal subjects with no history of DVT.

C. The subjects entered solely into post-natal studies were recruited directly from the postnatal wards. Women who were suffering postnatal complications limiting their mobility were excluded, as were any with a complicated medical history. No other restrictive criteria were applied, and full informed consent was obtained on the third or fourth post-operative day, the day of the first scan.

D. Subjects entered into the study into support stockings were recruited from among staff. This group was restricted to the following criteria:

- no previous history of DVT
- no risk factors for DVT
- no current medical illness

Full informed consent was obtained.

5.3 Ultrasound Scanning Equipment and Settings

5.3.1 Transducer

A 5 MHz linear array transducer (L 558 Acuson, Mountain View, Calif.) was employed for all studies. The linear array format is the preferred type for peripheral vascular studies as it is possible to place the entire transducer face on the patient. Additionally, colour flow mapping is not altered artefactually by relative changes in flow direction with respect to the subtended beam, in a vessel running parallel to the skin surface as may occur when employing the sector array format.

5.3.2 Machine Settings

The following parameters were set to enhance venous imaging prior to each scan. The settings were stored in the system software. All power settings were set at levels less than or equal to the acoustic output guidelines for "Peripheral Vessel" of the United States Food and Drug Administration (FDA).

Real time 2D image

Transmit Power:	-9bB; equivalent to SPTA
	<2.9mW/cm^2 (minimum output)
Log compression (grey scale dynamic range):	45 decibels (midrange setting)
Postprocessing curve:	Low contrast (level 2)
Preprocessing:	Moderately sharp border (level 1)
Image persistence:	Moderate (level 3)

Spectral Doppler Mode

Doppler Power (SPTA):	718mW/cm^2 (Standard setting)
Log compression:	25dB (a dynamic range displaying reduced extraneous signals or noise)
Postprocessing:	(D curve) Linear relationship between echo amplitude and displayed pixel intensity.
Wall thump filter	50MHz

Colour Doppler Imaging Mode

Transmit power (SPTA):	345 mW/cm^2
Preprocessing:	High colour resolution (level 0)
Persistence:	Moderate temporal averaging of colour samples (level 1)
Postprocessing:	Velocity only colour map (level V5)
Velocity filter:	For low velocities (level 2)

5.4 Subject Preparation

In order to allow the effects of recent ambulation on venous flow to diminish, all subjects rested for 20 minutes on the examination couch in a semi-supine recumbent position (back tilted to 45 degrees). In pregnant patients, urinalysis was carried out, a blood pressure recording was taken and a fetal scan was performed during this rest period. In order to reduce environmental effects on peripheral venous dilatation, the examination room was maintained at a temperature between 22-25^{o}C.

The back rest was then adjusted to apply 15 degrees of reverse Trendelenberg tilt, and sonic coupling gel applied to the skin over the femoral triangle. The subject was asked to externally rotate the leg at the hip, thus exposing the femoral triangle to easy

access with the transducer. The CFV and SFV were examined with the subject thus positioned (**Plates 5.1 & 5.2**). In order to examine the popliteal vein without causing collapse of the vessel, the subject was asked to flex the knee slightly while maintaining a degree of external rotation at the hip **(Plates 5.3).**

5.5 Vessel diameter measurements

The tranducer was applied to the skin over the common femoral vein at the junction with the long saphenous tributary, imaging the vessels in longitudinal section. The CFV was identified by its position medial and deep to the visibly pulsing common femoral artery (CFA), its junction anteriorly with the great saphenous tributary, its diameter (the largest of these vessels) and, if visible, the distal to proximal streaming artefact indicating venous blood flow within the vessel. If doubt persisted as to the identification of the CFV, the vessels of the femoral triangle were scrutinised with colour Doppler. This clearly demonstrated pulsatile flow in the CFA. A real-time ultrasound examination was made of structures in the vicinity of the CFV such as lymph nodes, to exclude causes of extraneous vessel compression. By means of gentle manipulation of the transducer and angle of insonation, a view of the CFV at its maximum diameter was obtained. The transducer was then rotated through 90 degrees to obtain a transverse view of the vessel.

The close proximity of the CFV to the skin, coupled with its readiness to collapse on application of pressure by the transducer made accurate assessment of the distance between the posterior and anterior vessel walls difficult. In order to minimise compression artefacts, once a maximal diameter had been imaged, the transducer was gradually lifted from the point of application until the image was lost. The lightest pressure to obtain an image was then applied, and the image frozen. The distance between the inner aspect of the anterior wall and the inner aspect of the posterior wall of the CFV was then measured at a point 1 cm distal to the saphenofemoral junction **(Plate 5.4)**. Where the deep circumflex tributary joined immediately posterior to this point, the diameter was measured immediately distal to the latter junction. This procedure and measurement was repeated twice and three transverse diameter assessments were recorded.

Continuing the imaging in the longitudinal view, compression was applied until dimpling of the overlying skin occurred, and the posterior and anterior walls of the

CFV was examined. Complete obliteration of the vessel lumen was interpreted as thrombus free segment as discussed in chapter 1.

5.6 Flow velocity measurements

The time averaged maximum flow velocity (TAMV) was chosen as the best means of assessing venous flow velocity. In order to avoid the effect of shearing effects on calculating the flow velocity, the pulsed Doppler gate was placed so as to interrogate flow velocity in the middle third of the vessel lumen in all cases. This had the additional benefit of minimising wall thump artefacts **(Plate 5.5)** (see Chapter 3).

Distal to the saphenofemoral junction, the CFV runs a parallel course to the skin. A combination of electronic beam steering and manual angling of the transducer was applied to reduce the angle of insonation to the direction of venous flow as much as possible below 60^{o} without distorting the vessel under scrutiny **(Plate 5.5)**. If the angle subtended to the direction of blood flow was greater than 60 degrees, the measured data regarding venous flow velocity was discarded.

The angle of insonation was reduced to less than 60 degrees by means of the techniques described earlier, and the flow direction indicator on the screen was lined up parallel to the direction of blood flow. Flow direction was most accurately assessed when the streaming artefact was visible. If not present, then the direction of flow was assumed to be in parallel to the axis of the vessel. The flow through the gate as indicated by a realtime spectral representation on screen was then recorded onto video tape for later analysis. Each recording continued until a 15 second period of technically acceptable wavefroms were obtained. Analysis of the wavefrom was performed by measuring the maximum flow velocity and minimum flow velocity during each 15 second period **(Plate 5.6)**. The outline of the spectral representation of the waveform was then traced onto the screen and a built in soft-ware package used to calculate the TAMV of the 15 second period **(Plate 5.7)**. The VVI was calculated as described earlier. Mean values for the TAMV and VVI obtained over three consecutive 15 second periods were recorded.

A realtime image of the vessel under examination was then obtained in the longitudinal axis and flow through the vessel was imaged using colour Doppler. The angle subtended by the ultrasound beam was maintained below 60^{o} to the direction of

blood flow either by manual manipulation of the transducer or by electronically steering the beam.

On achieving a colour Doppler image the colour gain was increased to the point where spontaneous flow was seen to fill the insonated segment of vein, while preventing artefactual extravascular colour signals from enlarging the perceived diameters of the vessel. Evidence of spontaneous venous blood flow filling the vessel lumen was recorded, as was fluctuation of flow velocities associated with respiration. If venous flow velocities were below the range of detection of ultrasound machine (less than 0.9cm/sec), no colour signal was detected during spontaneous respiration, and flow was then augmented by means of gentle manual compression of the ipsilateral calf. If no thrombus occluded the vessel between the calf and CFV, a colour signal filled the vein with colour confirming patency of the vessel. Moving distally from the CFV, every part of the CFV and SFV was thus examined down to the distal segment of the popliteal vein. Further methodological details are described as they apply to the studies reported in the following chapters.

Plate 5.1 The transducer is placed over the CFV in the longitudinal axis, after the leg has been externally rotated at the hip.

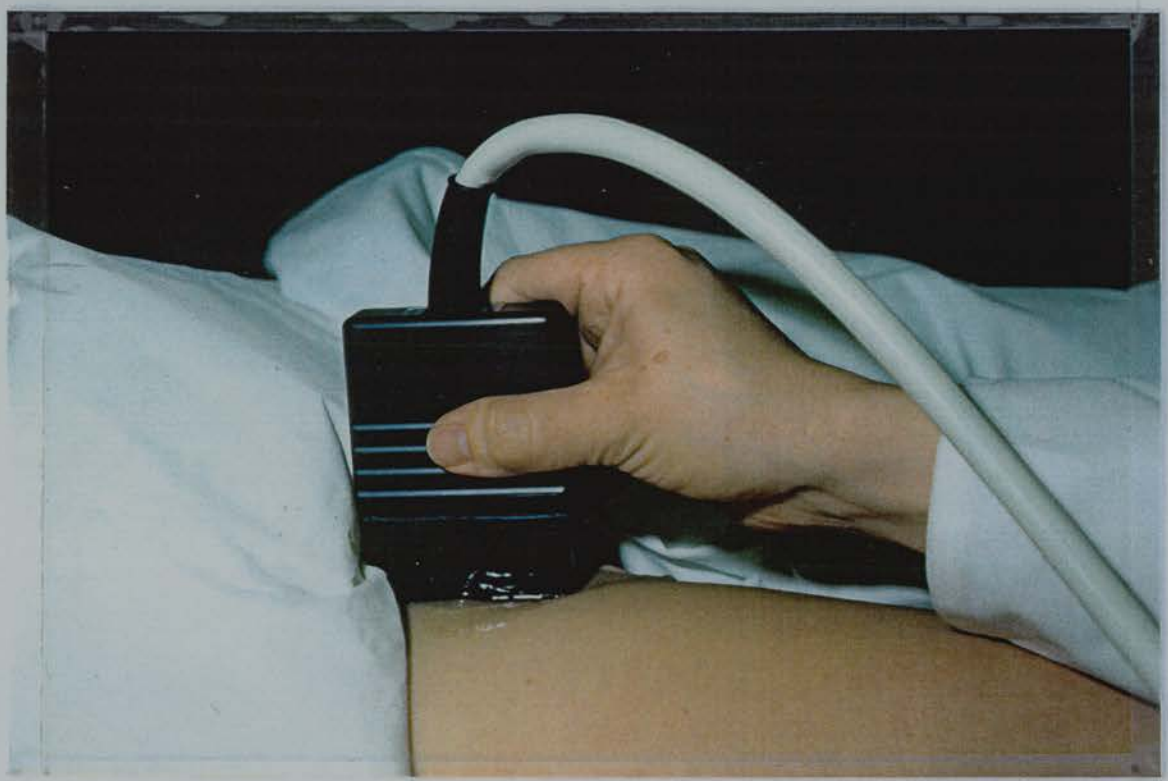


Plate 5.2 The transducer is positioned in the longitudinal axis, at the point where it emerges from the adductor canal.

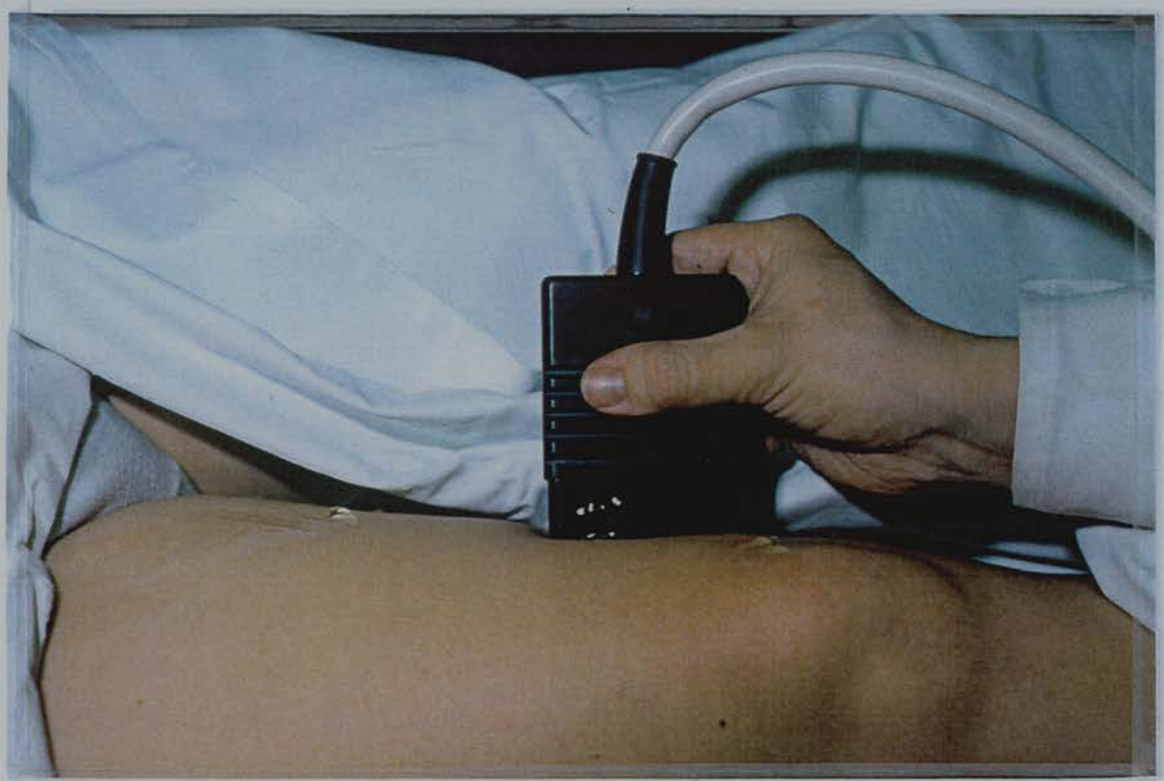


Plate 5.3 Collapse of the popliteal vein on application of the transducer is prevented by a moderate degree of knee flexion.

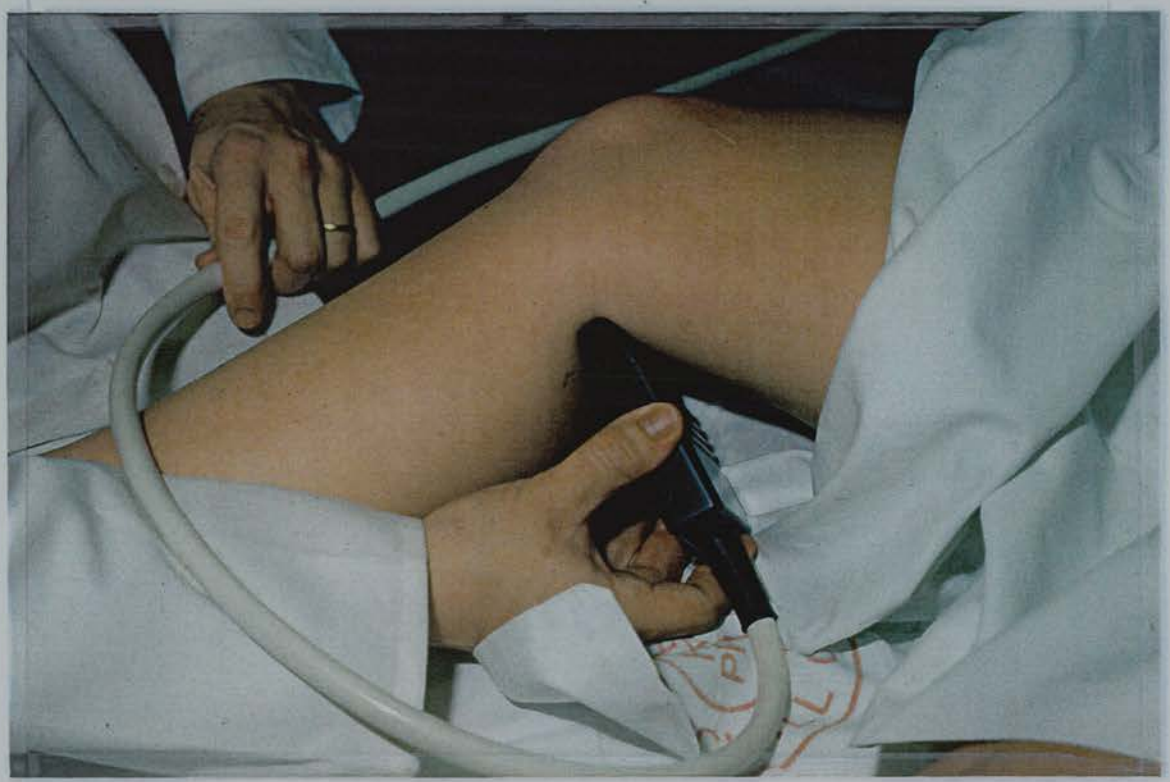
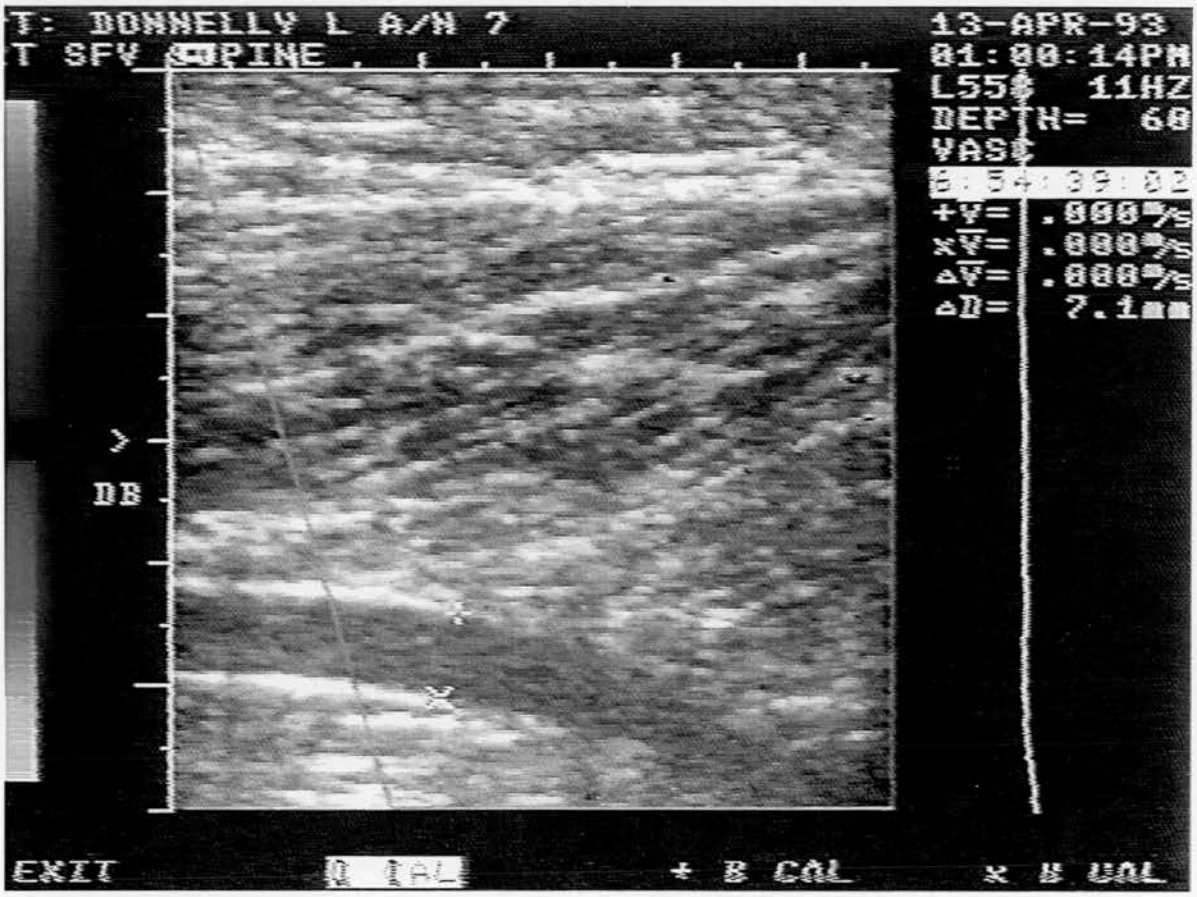


Plate 5.4

The vessel diameter is measured between the two callipers shown.



ADVANCED TECH LABS.

Plate 5.5 The Doppler gate is placed to interrogate flow velocity in the middle third of the vessel lumen.

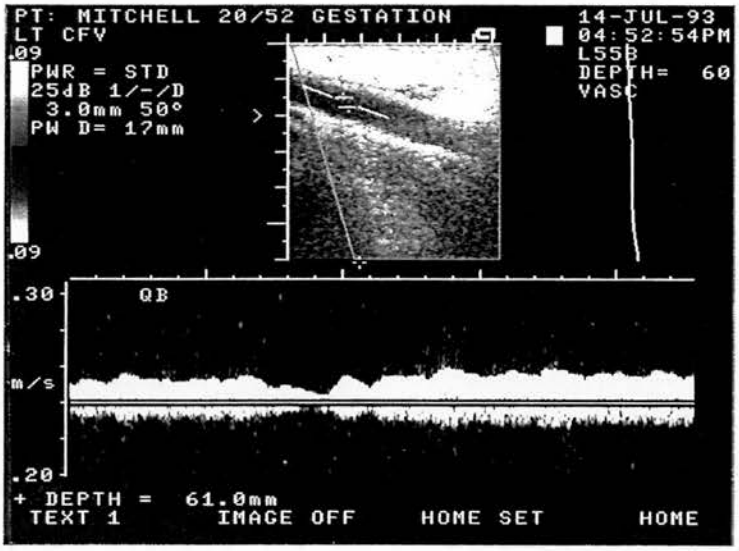
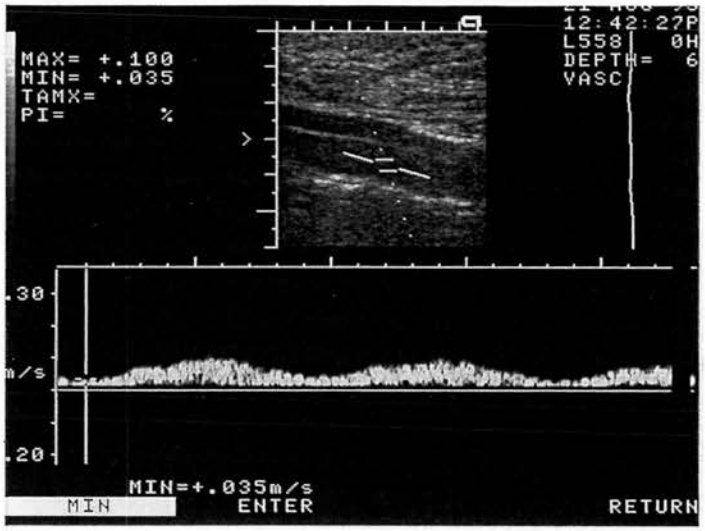


Plate 5.6 The maximum and minimum flow velocities are measured using on-screen callipers.



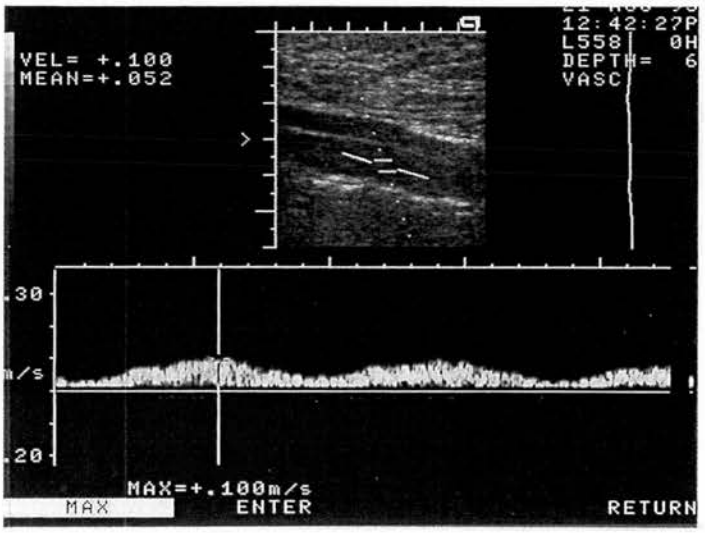
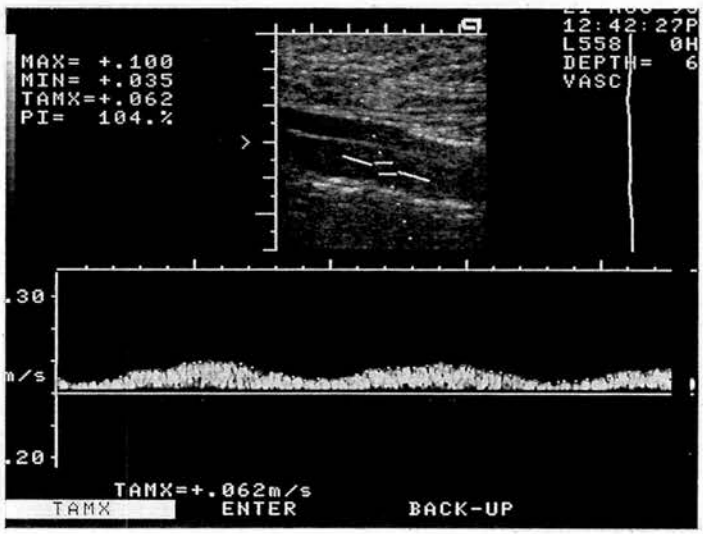


Plate 5.7 The spectral representation of the Doppler waveform is traced over 15 seconds and the TAMV calculated.



Chapter 6

Venous thromboembolic disease in obstetrics:

The Scottish experience.

Summary

The incidence and pattern of thromboembolic complications in obstetric and gynaecological patients in Scotland between 1981 and 1992 was investigated by analysing I.C.D. coded data retrieved from the SMR1 and SMR2 database. The effect of mode of delivery and maternal age over 35 on risk of thromboembolism in pregnancy was also assessed. 0.076% of gynaecological episodes were subsequently complicated by thromboembolic events. 19% of those suffering thromboembolic complications within 2 weeks of discharge were referred back to gynaecology. The incidence of deep venous thrombosis (DVT) in those under 35 years and over 35 years was 0.615/1000 maternities and 1.216/1000 maternities respectively. Respective figures for postnatal DVT were 0.304/1000 and 0.720/1000 and for pulmonary thromboembolism (PTE), 0.108/1000 and 0.405/1000. In both age groups, emergency caesarean section was associated with a higher incidence of DVT than elective caesarean section and vaginal delivery.

6.1 Introduction

In response to concern over the continuing major contribution of venous thromboembolism to obstetric mortality and morbidity, guidelines covering the assessment for and appropriate institution of thromboprophylaxis have recently been published (THRIFT Consensus Group 1992, RCOG 1995). However many obstetricians do not prescribe thromboprophylaxis to patients at risk because of the perceived low incidence of thromboembolic disease in their practice (Greer & De Swiet 1993). Information concerning the risks of DVT associated with pregnancy (Letsky and De Swiet, 1984) is available but the true incidence of thromboembolic complications in pregnancy remains unclear. Apart from a recent study employing duplex Doppler ultrasound which found no cases of DVT among 140 asymptomatic women at low to moderate risk screened in the early puerperium (Macklon & Greer 1995), no other accurate contemporary data based on objective screening techniques has been published. In order to assess the incidence of recorded thromboembolic complications in obstetric practice in Scotland, we analysed data for the years 1981 to 1992 provided by the Information and Statistics Division of the Common Services Agency for the National Health Service in Scotland.

6.2 Methods

Data were extracted from the SMR 2 database (Obstetrics) held by the Information and Statistics Division of the Common Services Agency for the National Health Service in Scotland. The data related to all patients treated in Scottish hospitals and covered the inclusive period of 1983 -1992. Thus data concerning over 700,000 maternities were analysed. Analyses on specified ICD9 codes were carried out for specific thromboembolic complications:

Superficial Thrombophlebitis	ICD9-671.2
Antepartum Deep Venous Thrombosis	ICD9-671.3
Postpartum Deep Venous Thrombosis	ICD9-671.4
Pulmonary Embolism	ICD9-673.2

Data relating to the above thromboembolic complications were obtained with information regarding mode of delivery (elective caesarean section, emergency caesarean section or vaginal delivery) and patient age (under 35 years, 35 years and over). All postnatal admissions for thromboembolic complications were to obstetric units and these data were also stratified for age. The obstetrical data were analysed using chi-squared tests for statistical significance between rates of thrombotic events per 10,000 deliveries.

6.3 Results

During the period 1983 to 1992 inclusive, there were 645,663 recorded maternities in Scotland. 44,410 were to women over the age of 35 years; 6.88% of the total number of maternities. The proportion of maternities to women over 35 rose significantly over the study period, however, from 6.25% in 1983 to 8.5% in 1992 (**Figure 6a**). 89,618 caesarean sections were recorded over the 10 year period, constituting a caesarean section rate of 13.88%. Among those over 35 the rate of caesarean section was 20.77% compared to 13.37% in those under 35. 37.7% of the caesarean sections were performed as elective procedures, although this figure rose to 47.87% in those over 35 years of age, probably reflecting repeat elective procedures.

The figures obtained and the relevant denominators for the numbers of antenatal and postnatal DVTs, PTE and superficial thromboses over the 10 year period are given

in **Table 6.1**, which also shows the annual incidences of each thrombotic event per 1000 maternities.

The incidence of antenatal DVT was 0.615/1000 maternities in those under 35 years of age but was significantly higher in those aged over 35 years of age where the incidence was 1.216/1000 ($p<0.005$) **(Figure 6b)**. A similar age related effect was seen in those presenting with DVT postnatally, with a rate of 0.304/1000 maternities under 35 years and 0.72/1000 over 35 years ($p<0.005$). Age over 35 was also associated with a significantly greater risk of pulmonary thrombembolism (PTE), occurring with an incidence of 0.405/1000 maternities as opposed to 0.108/1000 in those under 35 years ($p<0.05$). A similar age related increase was observed for superficial thrombosis with an incidence of 1.67/1000 under 35 years and 5.38/1000 over 35 years ($p<0.005$).

In summary, age over 35 years was associated with a near doubling in the incidence of deep venous thrombosis and pulmonary thromboembolism, and an increase by a factor of three in the incidence of superficial thrombosis.

The incidence of postnatal DVT was affected by mode of delivery. Delivery by caesarean section was associated with a rate of 0.424/1000 compared to a rate of 0.173/1000 following vaginal delivery. Emergency caesarean section was associated with a higher postnatal DVT rate than elective caesarean section in both the under 35 age group (0.431/1000 vs. 0.238/1000 respectively, $p<0.005$) and the over 35 age group (1.248/1000 vs 0.680/1000, $p<0.005$) **(Figure 6c)**. While caesarean delivery was associated with a higher incidence of PTE than vaginal delivery in both age groups **(Table 6.2 and Figure 6d)**, a significantly higher incidence associated with emergency versus elective caesarean section was only demonstrated in the over 35 age group. The association with mode of delivery of superficial thrombosis was in marked contrast to that seen with DVT and PTE in that the highest incidence in both age groups were associated with vaginal delivery **(Table 6.2)**. The data for postnatal readmissions showed that 38% of postnatal DVTs and 22% of cases of PTE presented after discharge from hospital.

6.4 Discussion

The data presented requires a substantial degree of caution in its interpretation as it is not known to what extent objective tests were employed to reach the diagnoses. Obstetricians remain reluctant to use the traditional 'gold standard' objective test, contrast venography, because of the perceived risk to the fetus. Despite poor sensitivity and specificity, clinical diagnosis may often be relied upon in the absence of the availability of non-invasive tests such as compression ultrasound, and the clinical signs arising from conditions such as popliteal cysts or groin lymphadenopathy may be misinterpreted and misdiagnosed. Given the poor reliability of clinical diagnosis (Genton & Turpie 1980) and that 70% of those who suffer a fatal PTE have no previous documented evidence of DVT (Department of Health et al 1994), it is unlikely that the data presented represent the true incidence of DVT. In addition, women with a thromboembolic complication may go unrecognised both in hospital and the community. These data remain of value, however as they reflect the incidence of these conditions as diagnosed under current clinical practice. In addition, such data may be required to guide practice with regard to diagnosis and prevention of thrombotic complications. Thus, this study maybe of value, particularly as there is a paucity of published information in this field, and because of the large numbers analysed.

The appropriate degree of thromboprophylaxis in individual cases is normally determined by the presence of certain risk factors for thromboembolic disease. In obstetrics, previous guidelines have advised that age over 35 years be considered a risk factor, but this was considered by many to be an arbitrary 'cut off'. Our data clearly demonstrate this factor to be associated with a significant increase in the incidence of antenatal and postnatal DVT, pulmonary embolism and superficial thrombosis. Delivery by caesarean section has been demonstrated to increase the risk of PTE, and this risk is considered to be greatest after an emergency procedure. The presented data support this view. It is interesting to note, however, that the incidence of DVT after emergency caesarean section in women under 35 years of age was similar to that after a vaginal delivery and less than that after elective caesarean section in women over 35 years . Age over 35 may, therefore, be a more important risk factor than mode of delivery. While superficial thrombosis is not considered to put the patient at immediate risk of PTE, it is considered a risk factor for the development of DVT. The increased incidence in reported cases of superficial thrombosis after vaginal delivery in both age groups when compared to delivery by

caesarean section may reflect an influence on the interpretation of leg signs such as calf tenderness by knowledge of the relative risk of DVT associated with the mode of delivery; clinicians may take signs suggestive of DVT more seriously in patients who have undergone emergency caesarean section than in those who have delivered vaginally. Unless clinical suspicion is tested objectively, incorrect diagnoses may be reported.

In the recent Confidential Enquiries into Maternal Deaths in the U.K. 46% of fatal cases of PTE occurred after delivery (DHSS et al 1994). A significant proportion of the reported cases of postnatal DVT and PTE analysed here, presented after discharge from hospital. Vigilance during the puerperium is difficult, and the responsibility for this falls, in part, to those providing community based postnatal care. However, correct identification of those at risk and appropriate thromboprophylaxis prior to and following discharge, may help to reduce the number suffering potentially fatal thromboembolic events in the late puerperium.

6.5 Conclusion

Thromboembolic disease is frequently encountered by individual obstetricians and gynaecologists, but the consequences of a missed diagnosis can be grave. The data presented provides information as to why the condition is perceived to be rare in clinical practice, and highlights high risk groups for targeting appropriate thromboprophylaxis.

Acknowledgements

The author is grateful to Mr Bruce Whyte and the staff of the Health Analytical Services Unit of the Information and Statistics Division, CSA, Edinburgh, for their assistance in obtaining the data.

Table 6.1 The annual incidence of antenatal DVT (AN DVT), postnatal DVT (PN DVT), PTE and superficial thrombosis (Sup. Thromb.) in women aged under 35 years and 35 years or over in Scotland, 1983 to 1992.

							Rates per 1000 maternities			
Year	Age	Maternities (Years)	AN	PN DVT	PTE DVT	Superficial Thromb.	AN	PN DVT	PTE DVT	Sup. Thromb.
1983	<35	59964	47	18	6	151	0.784	0.300	0.100	2.518
1983	>35	3982	5	2	3	35	1.256	0.502	0.753	8.790
1984	<35	60214	43	15	10	123	0.714	0.249	0.166	2.043
1984	>35	3991	11	1	4	28	2.756	0.251	1.002	7.016
1985	<35	60874	23	9	3	97	0.378	0.148	0.049	1.593
1985	>35	4081	3	4	2	28	0.735	0.980	0.490	6.861
1986	<35	60535	36	14	6	100	0.595	0.231	0.099	1.652
1986	>35	4159	3	4	0	26	0.721	0.962	0.000	6.252
1987	<35	60842	56	18	4	97	0.92	0.296	0.066	1.594
1987	>35	4084	3	1	3	19	0.735	0.245	0.735	4.652
1988	<35	61051	35	12	6	83	0.573	0.197	0.098	1.360
1988	>35	4381	5	4	0	15	1.141	0.913	0.000	3.424
1989	<35	58556	38	28	11	90	0.649	0.478	0.188	1.537
1989	>35	4424	9	6	1	13	2.034	1.356	0.226	2.939
1990	<35	59878	38	26	7	84	0.635	0.434	0.117	1.403
1990	>35	4686	7	4	2	25	1.494	0.854	0.427	5.335
1991	<35	60556	21	28	5	88	0.347	0.462	0.083	1.453
1991	>35	5183	3	3	1	25	0.579	0.579	0.193	4.823
1992	<35	58783	33	15	7	108	0.561	0.255	0.119	1.837
1992	>35	5439	5	3	2	25	0.919	0.552	0.368	4.596

Table 6.2 The influence of mode of delivery on the incidence of postnatal DVT (PN DVT), superficial thrombosis (Sup. Thromb.) and PTE in women aged below 35 years and 35 years and over in Scotland, 1983 to 1992.

						Rates per 1000 deliveries		
Delivery	Age	Total	PN	Sup DVT	PTE Thromb.	PN	Sup. DVT	PTE Thromb.
Elective C/S	<35	29364	7	25	10	0.238	0.851	0.341
Elective C/S	>35	4415	3	16	3	0.680	3.624	0.680
Emergency C/S	<35	51031	22	41	14	0.431	0.803	0.274
Emergency C/S	>35	4808	6	12	5	1.248	2.496	1.040
Vaginal Delivery	<35	520853	82	910	23	0.157	1.747	0.044
Vaginal Delivery	>35	35187	14	203	6	0.398	5.769	0.171

Figure 6a. The number of maternities in those over 35 years of age as a proportion of all maternities in Scotland over the years 1983-1992.

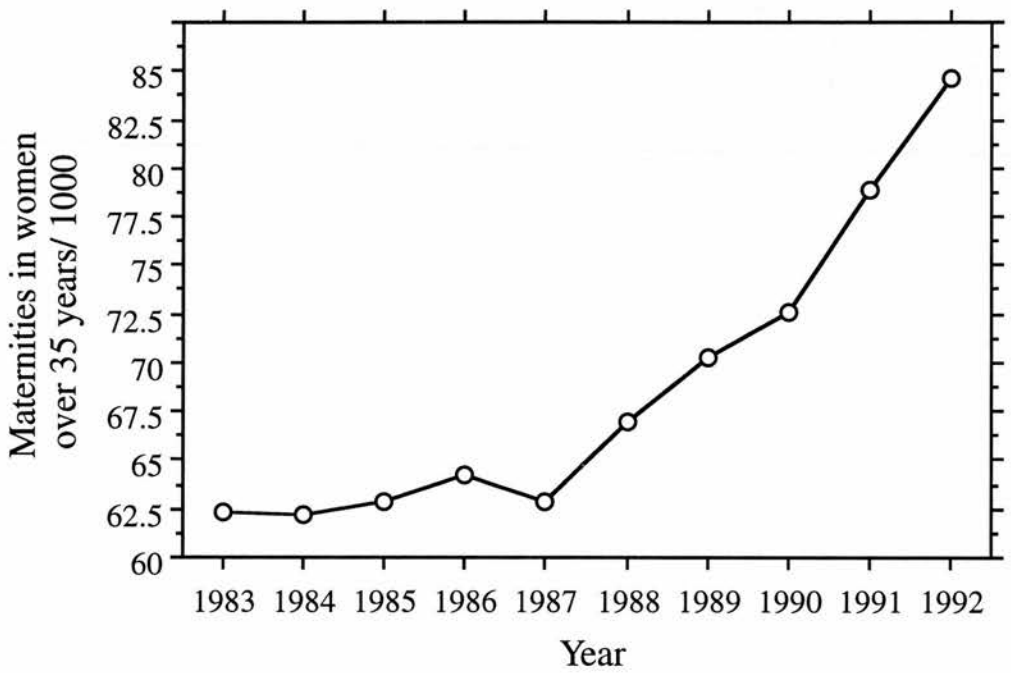


Figure 6b The effect of age on the incidence of antenatal DVT, postnatal DVT and PTE.

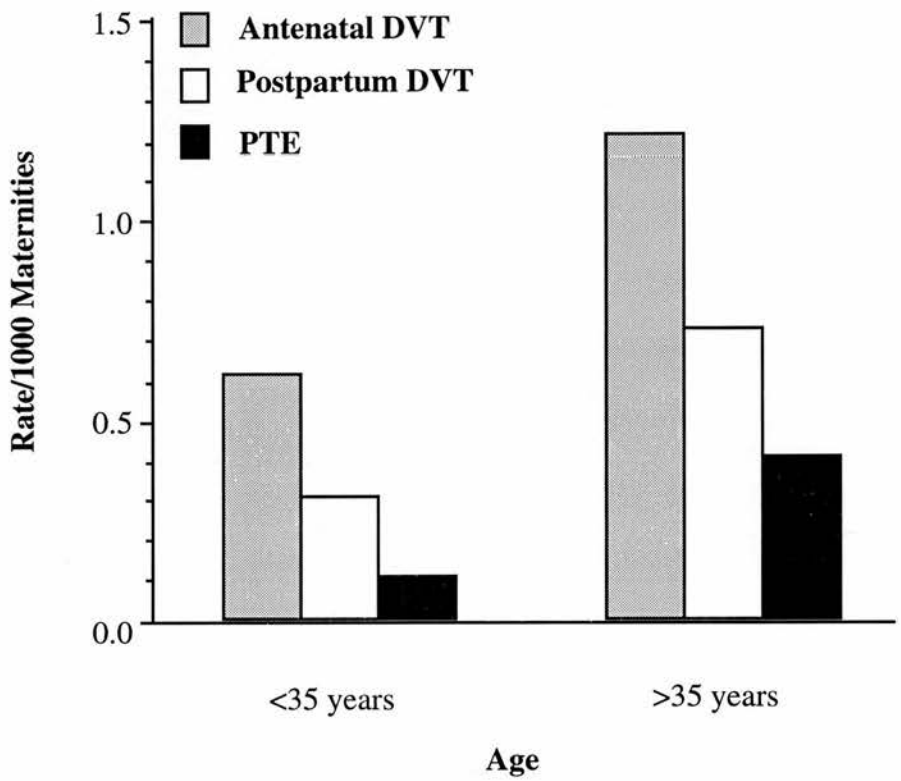


Figure 6c The effect of mode of delivery on the incidence of postnatal DVT in women under 35 years of age , over 35 years of age and in total. (CS: caesarean section)

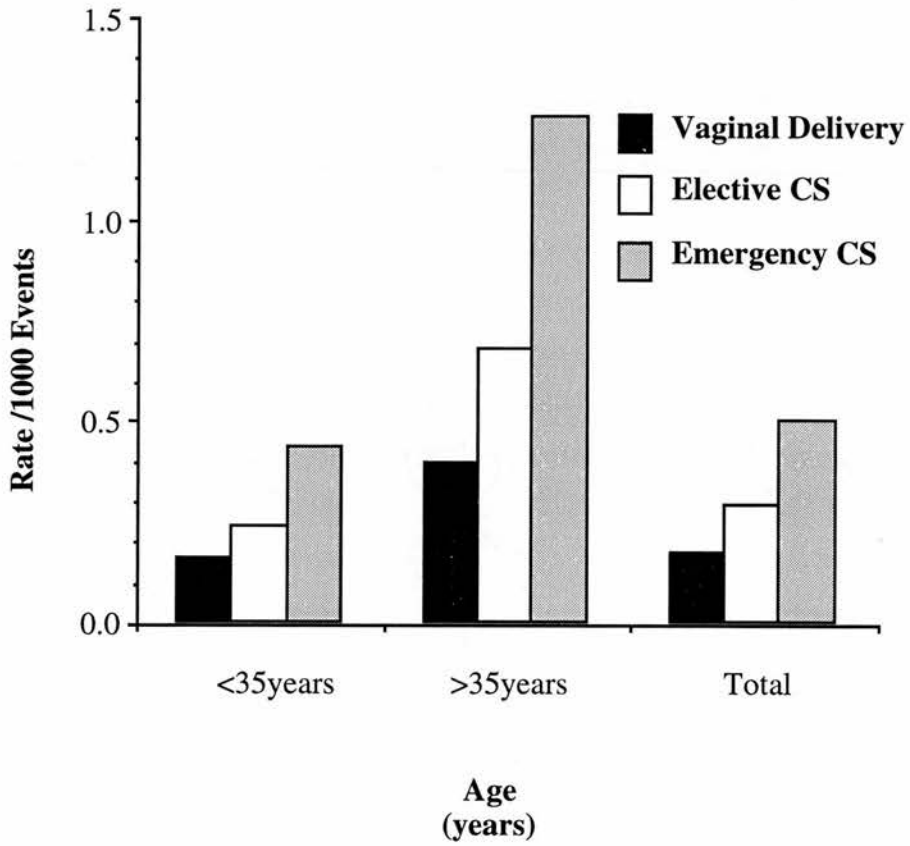
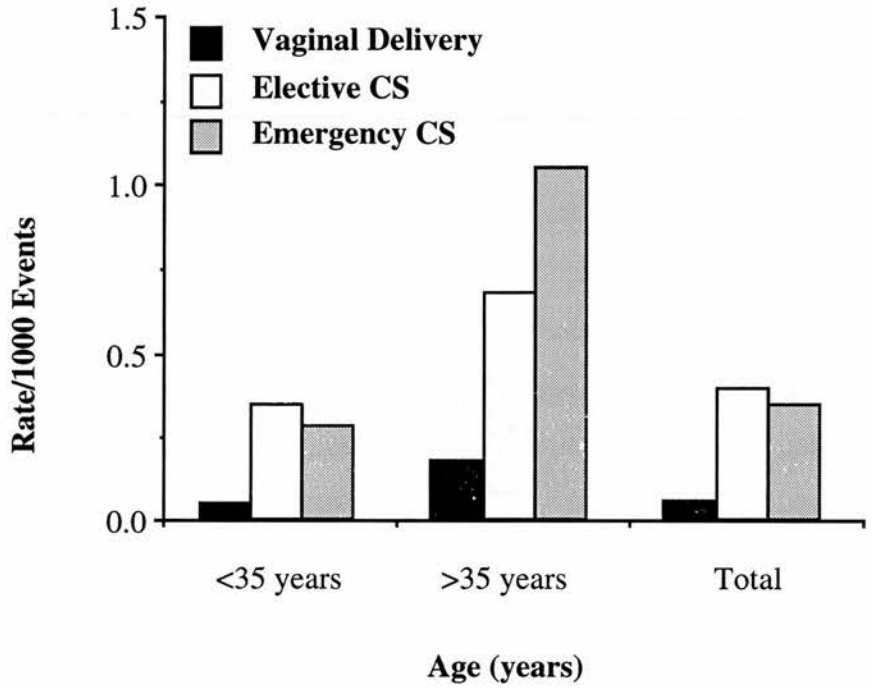


Figure 6d The effect of mode of delivery on the incidence of PTE in women under 35 years and over 35 years (CS: caesarean section)



Chapter 7

The deep venous system of the leg in pregnancy: an ultrasound study.

Summary

The objective of this study was to investigate gestational and postural changes in diameter and blood flow in the proximal deep leg veins during pregnancy. 24 healthy women with uncomplicated singleton pregnancies were recruited to this longitudinal, prospective observational study. Realtime and duplex Doppler ultrasound assessments of the vessel diameter, flow velocity and respiratory flow fluctuation in the proximal deep leg veins of women were serially measured from the first trimester of pregnancy to six weeks postnatally. An increase in vessel diameter and a fall in flow velocity with increasing gestation was observed. However, no change in venous flow variation was demonstrated. After delivery these effects were seen to reverse. Flow velocity was slower in the left than the right legs, but on adoption of the left lateral position an increase in flow velocity and venous flow variation was observed in both legs during pregnancy. These data are consistent with the observed increase in incidence and pattern of deep venous thrombosis in pregnancy and may aid in the interpretation of duplex Doppler ultrasound examinations for deep venous thrombosis in pregnancy. Postural changes should be part of this evaluation. The gravid uterus may not be the sole cause for postural changes in deep venous flow velocity.

7.1 Introduction

Thromboembolic disease remains a major cause of maternal mortality (DHSS 1994). Clinical diagnosis of deep venous thrombosis (DVT) has been shown to be insensitive and nonspecific (Genton & Turpie 1980) and objective means of diagnosing DVT are normally required. Venography remains the 'gold standard' test, but is avoided in pregnancy because of the perceived radiation risk to the fetus. In recent years, real time ultrasound has been shown to be of use in pregnancy (Greer et al 1990, Polak et al 1991) and, with the aid of duplex and colour Doppler, is now considered to be the first line investigation for suspected DVT in pregnancy. However, alteration of venous flow occurs in pregnancy (Wright et al 1954). The interpretation of ultrasound examination of the deep veins of the leg has therefore been hampered by a lack of information regarding the normal gestational changes in the deep venous system. Thus, the aim of this study was to follow longitudinally the gestational alterations in vessel diameter, flow velocity and respiratory variation in flow (termed the Venous Variation Index (VVI)) using duplex Doppler ultrasound. In addition the effects of

adopting the supine, left lateral and upright postures on these same indices from early pregnancy to the late puerperium were serially examined.

7.2 Methods

24 subjects were recruited on attendance for booking at the antenatal clinic. Inclusion criteria were a viable singleton pregnancy on booking ultrasound scan and no obstetric risk factors. 20 subjects had no past history of thromboembolic disease and 4 had a previous history of DVT in pregnancy. The median gestation at which they entered the study was 12 weeks (8-24). The median age of the subjects was 25 years (18-34) and parity ranged from 0 to 2. Each subject underwent a duplex Doppler ultrasound scan of both legs by means of the technique described below at the time of the booking visit and at approximately monthly intervals throughout pregnancy. Further scans were carried out 4 days and 6 weeks postnatally. The following method was employed for each scan.

Prior to each scan, each subject was allowed to rest supine for 15 minutes. The ultrasound examinations were carried out using an Acuson 128 Ultrasound scanner (Acuson, Mountain View, Calif.) equipped with spectral and colour Doppler facilities, and a 5 MHz linear array transducer. The room temperature was maintained between 22 and 25°C. With the subject lying supine with 15° of head up tilt, the right common femoral vein was imaged in the longitudinal axis, at a point on the common femoral vein 2 cm below the junction with the long saphenous vein. The image was frozen after minimising the transducer pressure near to the point of losing contact. The distance between the inner aspects of the anterior and posterior vessel walls was recorded and the mean of three measurements calculated. The Doppler gate was then placed across the middle third of the vessel lumen, and a spectral Doppler recording of the flow wave form was made over a period of 15 seconds of quiet respiration. In order to minimise velocity calculation errors from the Doppler shift, the angle of insonance was electronically steered to subtend an angle less than 60° to the axis of flow and the velocities measured were angle corrected by aligning the cursor to the direction of flow. The wave form recording was then analysed for maximum and minimum flow velocities, time averaged maximum velocity (TAMV) over 15 seconds, and for the presence of respiratory and cardiac fluctuation. The degree of flow fluctuation with respiration was calculated by dividing the difference between maximum and minimum velocity by the TAMV, giving the Venous Variation Index

(VVI), a measure of venous 'pulsitility'. These measurements were repeated at the superficial femoral vein proximal to its exit from the adductor canal, and at the popliteal vein, distal to its junction with the short saphenous tributary. This protocol was repeated in the left leg. The subject then adopted the left lateral position and the same measurements were carried out at the left and right common femoral vein.

Prior to statistical analysis the data were assigned to one of nine gestational 'stages' depending on gestation or postpartum date at which it was collected. The grouped data were pooled and then analysed for variance by means of a repeated measurements model which allows for variation among patients and for correlated errors across time.

7.3 Results

7.3.1 The semisupine position.

Vessel Diameter

Analysis of the data relating to diameter of the CFV, SFV and popliteal vein demonstrated no significant difference between the legs and the data were pooled across legs for further analysis. The CFV diameter at booking measured 9.1mm (SEM± 0.3mm) and was found to increase throughout pregnancy to a maximum of 12.7mm (± 0.2mm) between 36 weeks gestation and delivery. By the fourth postpartum day the mean diameter had fallen to 9.8 mm (± 0.2mm) and a further fall to a mean of 9.0mm (±0.2mm) was recorded 6 weeks postnatally. The presence of changes over time was highly significant ($p<0.001$). A similar but less marked gestational pattern was observed at the superficial femoral vein, rising from a mean diameter at booking of 7.7mm (±0.3mm) to a maximum of 8.4mm (± 0.2mm) in the late third trimester before falling to a diameter of 7.5mm (±0.2mm) postnatally. Again, the presence of changes over time was highly significant ($p<0.001$). At the popliteal vein a similar marked pattern was again observed with the rise in diameter occurring from 5.8mm (±0.2mm) at booking to 6.8mm (± 0.2mm) prior to delivery before returning to a lower value of 5.3mm (0.2mm) at 6 weeks postnatal **(Figure 7a).**

Flow Velocity

Analysis of the data in the right and left legs showed the time averaged maximum flow velocity (TAMV) to be significantly slower in the left than in the right CFV and popliteal veins. The gestational fall in TAMV demonstrated a similar pattern in both limbs. At the right CFV a mean TAMV of 14.8cm/s (SEM±2.0cm/s) was recorded at booking, falling by over 60% to 4.5cm/s (±0.4cm/s) by the mid third trimester ($p<0.001$). A similar pattern was seen in the left CFV where the fall was from 11.2cm/s (±1.2cm) to 4.9cm/s (±0.5cm/s). The difference in TAMV between the right and left CFV was demonstrated in early pregnancy and six weeks postnatally **(Figure 7a)** when significant increases in flow velocity were seen in both right and left legs to 15.0cm/s (±0.8cm/s) and 13.4cm/s (±0.7cm/s) respectively ($p<0.01$). The popliteal vein demonstrated similar changes with gestation **(Figure 7a)**. Here, the fall in flow velocity appeared complete by the mid second trimester and showed no significant further increase until delivery had occurred. Although a similar trend was evident at the SFV, the gestational changes in flow velocity were less marked and did not reach statistical significance.

Venous variation index

While there was a suggestion of a slight gestationally related reduction in VVI **(Figure 7b)** the observed changes failed to reach statistical significance in any of the vessels examined and no significant difference between the right and left legs was demonstrated.

7.3.2 Left lateral position

On adopting the left lateral position, clear differences were recorded in vessel diameter, flow velocity and VVI when compared with the supine position and these changes were evident at most gestational and postnatal stages.

Vessel Diameter

In contrast to the semi-supine position, differences in vessel diameter were evident between the left and right CFV in the left lateral position, and the data were analysed separately. At the right CFV adoption of the left lateral position resulted in a fall in diameter from 9.0mm (±0.4mm) to 7.9mm (±1.7mm) at booking. In contrast to the semi-supine position, no significant gestational changes in right CFV were recorded in the left lateral position until delivery when a significant fall in diameter from 5.9mm (±0.6mm) prenatally to 4.8mm (±0.3mm) was observed. The postural difference in diameter was therefore observed to increase slightly as gestation

advanced **(Figure 7c)** A statistically significant fall in diameter was also observed in the left leg on adoption of left lateral position ($p<0.01$) but this fall was significantly less than that observed in the right CFV ($p<0.01$) **(Figure 7c)**. The postnatal measurements showed a reversal in this relationship, with an increase in diameter being recorded at the left CFV on adoption of the left lateral position **(Figure 7c).**

Time averaged maximum flow velocity

Adoption of the left lateral position resulted in an increase in flow velocity in the right CFV which while clearly evident throughout pregnancy became more marked after delivery ($p<0.001$). **(Figure 7d).** In the left CFV, the adoption of the left lateral position resulted in a rise in flow velocity over the semi-supine position from mid-pregnancy. However, the left lateral position was associated with a fall in flow velocity when measured postnatally **(Figure 7d)**.

Venous Variation Index

The adoption of the left lateral position resulted in a significant increase in VVI in both the right and left CFV during pregnancy ($p<0.01$). However, after delivery no significant changes was demonstrated in the right CFV on altering posture whereas in the left CFV, adopting the left lateral position the postnatal phase resulted in a more profound increase in VVI than was observed during pregnancy **(Figure 7e)**.

7.4 Discussion

The development of duplex Doppler ultrasound techniques as a noninvasive, accurate and reliable means of measuring blood flow velocity has enabled a review of the previously held assumptions concerning the effects of pregnancy on the cardiovascular system. *In vitro* and *in-vivo* studies on the venous system have shown Doppler ultrasound to be capable of accurate measurement of flow velocity (see Chapter 3) and the technique has been validated in the arterial system by comparison with the Fick principle, showing high correlation in the measurement of cardiac output in non-pregnant patients undergoing cardiac catheterisation (Robson et al, 1987). Several studies have since been published demonstrating the effects of pregnancy on cardiac output (Robson et al 1989).

Early studies of the venous system in pregnancy indicated that the pressure in the femoral vein increased through gestation to a maximum at term, by which time it had

doubled (McLennan 1943). The flow rate studies of Wright (1954) indicated a parallel effect, with a doubling in the time taken for saline labelled with ^{24}Na injected into a vein on the dorsum of the foot to be detected by a counter at the groin. Unlike previous studies which assessed venous flow in the limb as a whole, we have specifically examined the proximal deep venous collecting system of the leg and our findings suggest that the gestational changes in the deep leg veins maybe more profound. A feature of our results was the variable degree to which the different vessels altered with advancing gestational age. When measured in the supine position, an increase in diameter was detected from the early second trimester in all three vessels (CFV, SFV and POP). However, these changes were most marked in the CFV. Similarly, while a fall in flow velocity was demonstrated in all three vessels from the second trimester, this was again most profound in the CFV where a reduction of more than 60% in flow velocity was observed from the first trimester to term. Such a reduction in flow velocity is likely to result in relative stasis of the blood. Additionally, marked vessel distension may result in damage to the endothelium and the exposure of the blood to subendothelial collagen and triggering of the extrinsic pathway of coagulation (Stewart et al 1987). Further, increased stretch of endothelial cells may cause activation of prothrombotic changes on the endothelium (Bodin et al 1994). Thus the CFV in late pregnancy may provide more favourable conditions for thrombus formation than the more distal deep veins of the leg. These findings are consistent with the observations that in contrast to the nonpregnant state where thrombus formation is thought to begin in the soleal sinuses of the calf, in pregnancy, the ileofemoral segment of the deep venous system is the commonest site of thrombus formation (Berqvist & Hedner 1981).

In the nonpregnant, 55% of DVT affect the left leg. In pregnancy, this predominance rises to 85% (Lindhagen et al 1986). This is thought to be due to the compression of the left iliac vein by the right iliac artery and the ovarian artery which crosses the vein on the left side only. The presented findings confirm that flow velocity is significantly slower in the left leg when measured in the supine position. This difference was also evident in the left lateral position. The observed difference in flow velocity between the left and right legs may explain the increased risk of DVT on the left side.

The adoption of the left lateral position had striking effects on CFV diameter, flow velocity and VVI which were not confined to the third trimester. Previous studies have demonstrated a clear compressive effect of the gravid uterus on the inferior vena

cava in late pregnancy and it may be completely occluded in the supine position, with venous return being diverted through the ascending lumber veins (Kerr et al 1964). Adoption of the left lateral position relieves the observed obstruction in the inferior vena cava, and is recommended in late pregnancy to prevent the 'caval syndrome'. These data suggest that the 'lifting' of the gravid uterus off the IVC, while contributing to the improvement in venous return, may not be the principal mechanism by which venous return is increased on adoption of the left lateral position and that other abdominal organs, such as the liver, may have a postural dependent effect on flow in the IVC. The minimal effect of advancing gestation on the VVI in the supine position suggests a limited dampening effect of the gravid uterus on the transmission of respiratory changes in thoracic pressure. This is in contrast to the marked increase in VVI seen in both the left and right CFV on adoption of the left lateral position. This positional increase in VVI may provide a means of increasing the specificity of reduced respiratory fluctuation in flow as an indicator of proximal DVT. Additionally, we have demonstrated that adoption of the left lateral position results in a greater increase in flow velocity in the right CFV than that observed after the application of graduated support stockings in non-pregnant women (Macklon & Greer 1995). The observed increase in flow velocity in both the left and right CFV in the left lateral position in pregnancy may therefore provide the basis of a simple thromboprophylactic manoeuvre for those at increased risk of thromboembolic disease, with implications for the care of the patient following delivery by caesarean section, a recognised risk factor for DVT (Macklon & Greer 1996).

7.5 Conclusion

Duplex Doppler and colour Doppler ultrasound are now established as the first line method of diagnosis for suspected DVT in pregnancy. The physiological changes which take place in the deep veins of the leg during and after pregnancy have been elucidated and may aid in the interpretation of venous ultrasound examinations. Our data have confirmed the profound changes in the diameter and flow velocity and pattern within the deep veins of the leg on adoption of the left lateral position, and have shown that these effects are not confined to late pregnancy. The gravid uterus appears not to be the only factor underlying postural alterations in venous return. The alterations in venous flow characteristics described on adoption of the left lateral position may also aid in the diagnosis or exclusion of suspected DVT. The left lateral position may also have thromboprophylactic effects.

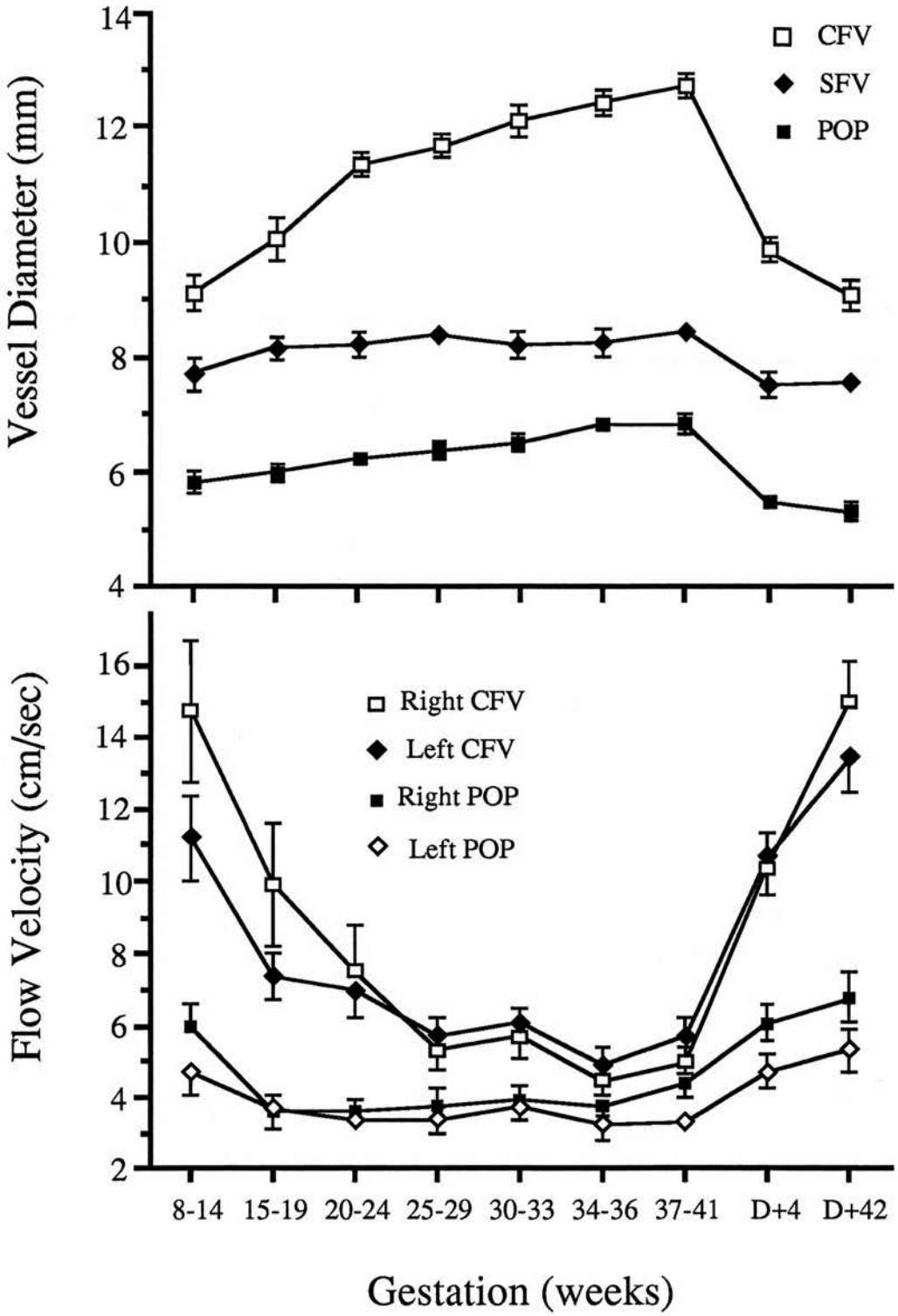


Figure 7a Top Panel: The gestational changes in diameter in the left and right CFV, SFV and popliteal veins.

Bottom Panel: The TAMV in the right and left CFV and popliteal vein. D+4 and D+42 indicate the 4th and 42nd postnatal day respectively. Data shown are mean (SE).

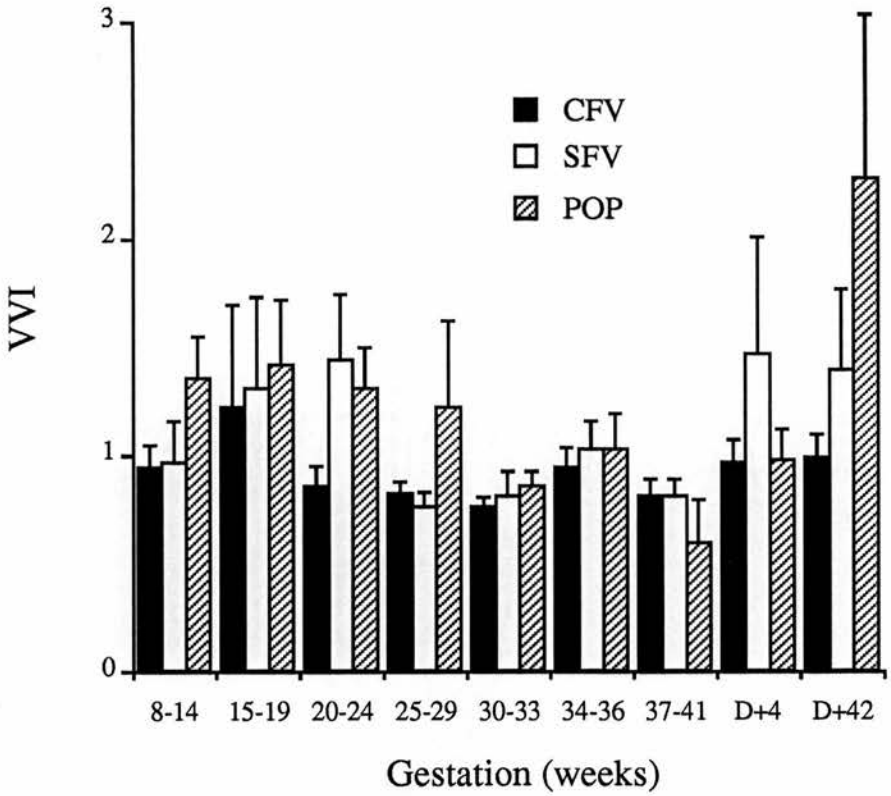


Figure 7b Gestational changes in the venous variation index (VVI) in the CFV, SFV and popliteal vein (POP) Data shown are mean (SE).

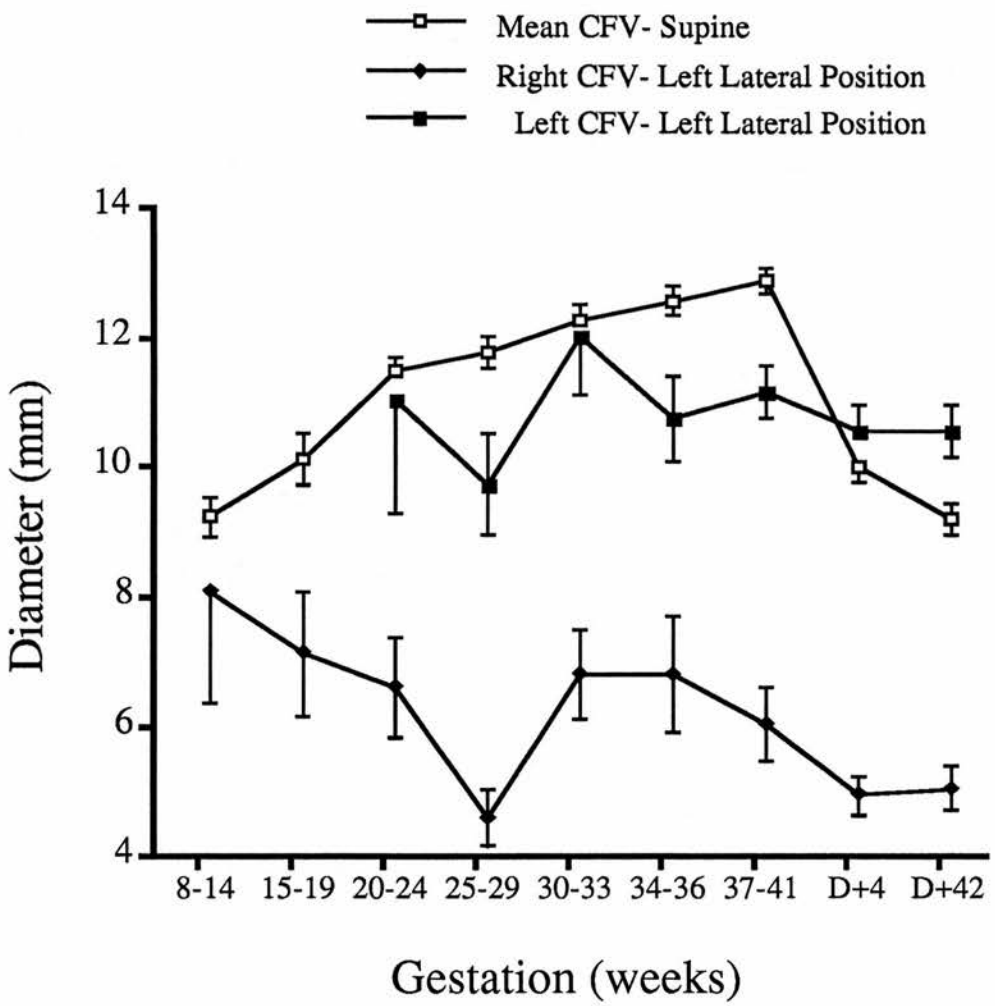


Figure 7c Gestational changes in the diameter of the right and left CFV as measured in the left lateral position, compared with the mean CFV diameter as measured in the semi-supine position.

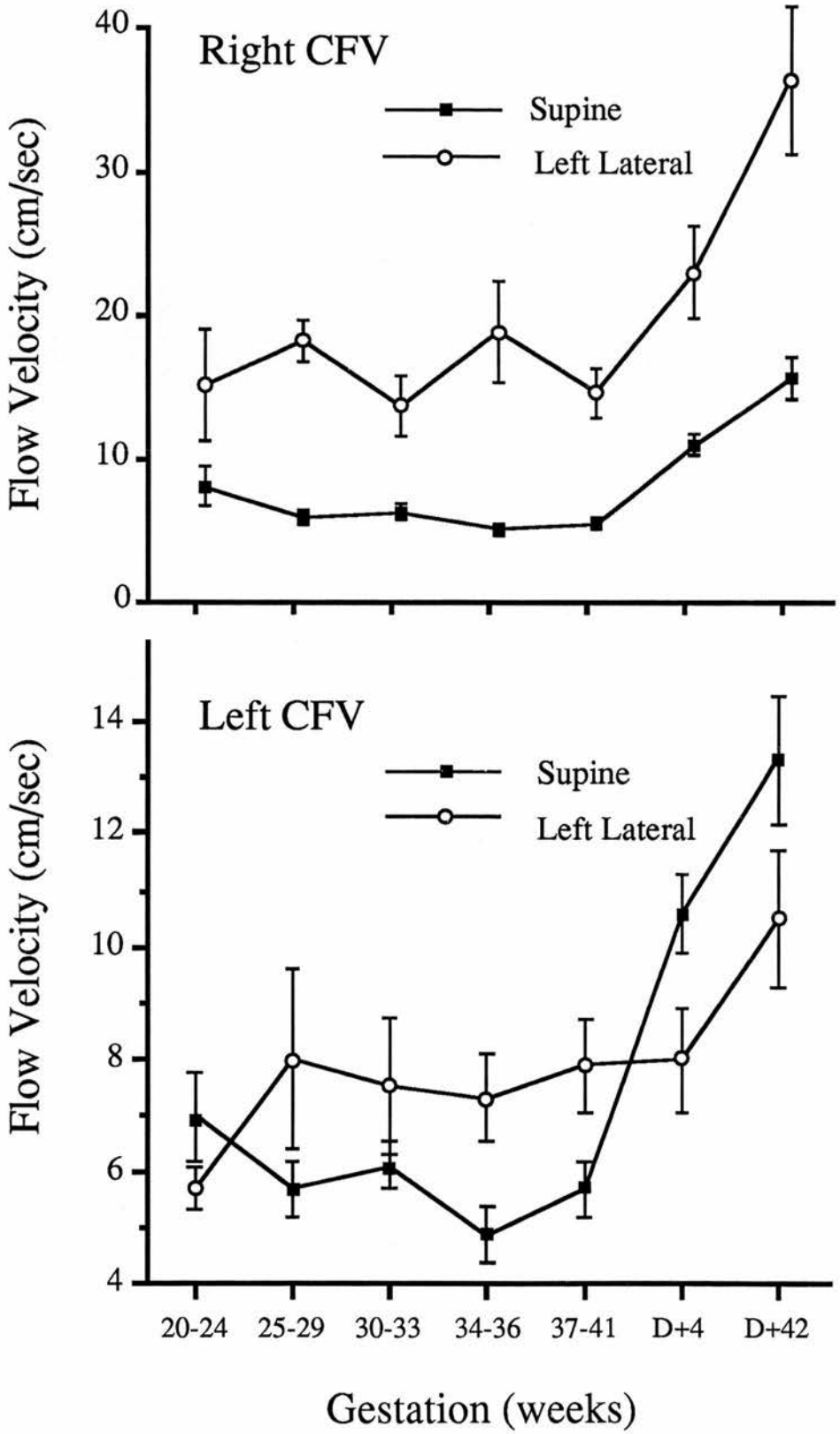


Figure 7d The effect of adopting the left lateral position on flow velocity in the right and the left CFV from 20 weeks gestation to 42 days postnatally (Bars: SEM). Data shown are mean (SE).

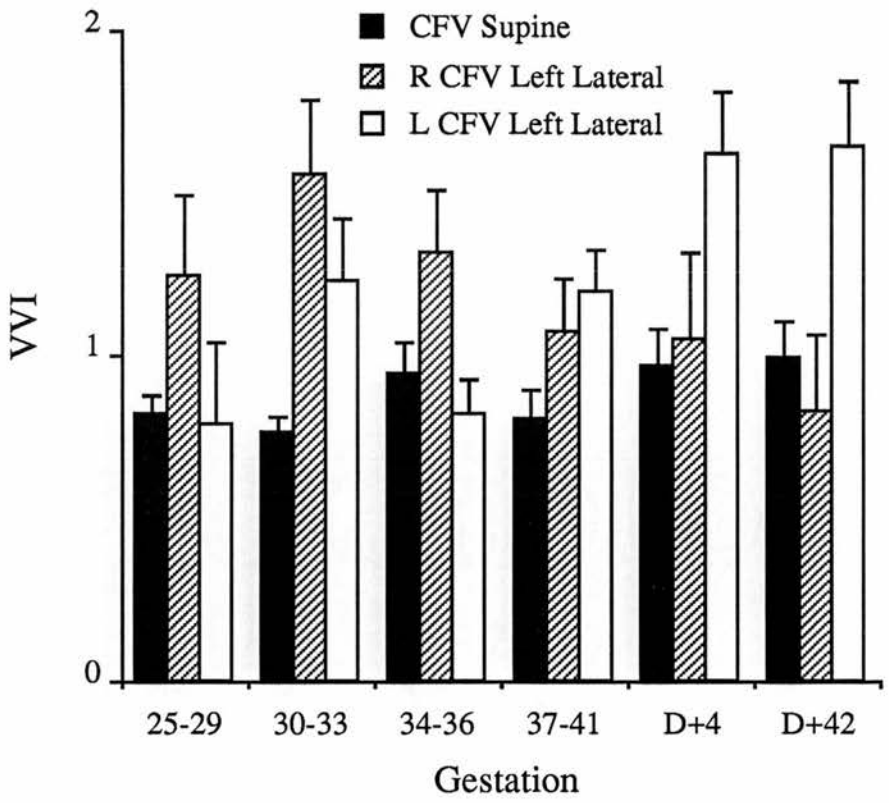


Figure 7e The venous variation index (VVI) in the left and right CFV in the supine (mean values) and left lateral position from 25 weeks gestation to 42 postnatal days. Data shown are mean (SE).

Chapter 8

The deep venous system in the puerperium: an ultrasound study.

Summary

The objective of this study was to determine the vessel wall diameter and blood flow velocity within the proximal deep venous system of the leg in the puerperium and compare these parameters with respect to the left versus right leg, 4th versus 42nd postnatal day and vaginal versus caesarean delivery. A reduction in vessel diameter and an increase in flow velocity was observed between the 4th and 42nd postnatal day. Vessel diameter was greater and flow velocity was reduced in the left as compared to the right leg. In those delivered by caesarean section, a trend towards reduced flow velocity in the proximal deep leg veins was observed when compared to those delivered vaginally. These data suggest possible physiological mechanisms behind previous clinical observations relating to the period of greatest risk of DVT in the puerperium, the relative preponderance of left sided DVT and the risk of DVT associated with caesarean section.

8.1 Introduction

Pulmonary thromboembolism remains the major cause of maternal mortality (DHSS et al 1996). The puerperium is considered to be the period of greatest risk from pregnancy associated thromboembolism, and guidelines have recently been published in the U.K. for the administration of thromboprophylaxis to those at risk (RCOG 1995). In the review of reported thromboembolic complications of pregnancy and the puerperium in Scotland presented in Chapter 6, 38% of postnatal DVT and 22% of postnatal PTE presented after discharge from hospital while caesarean section was associated with a reported incidence of DVT more than double that after vaginal delivery (Macklon & Greer 1996). The physiological response to pregnancy results in thrombogenic alterations to the blood coagulation system and relative stasis of blood in the deep leg veins. The third component of Virchow's classical pathophysiological triad for thrombosis (1856), vascular damage, may then arise from vessel distension and endothelial tearing (Stewart et al 1987). Knowledge of the changes in deep venous flow in the legs after delivery may be of value not only to our understanding of the pathophysiology of venous thromboembolic disease in the puerperium, but also in the design of future thromboprophylactic practice. We employed duplex Doppler ultrasound techniques to study the diameter and blood flow velocity in the proximal deep leg veins. Data for left versus right leg, 4th versus 42nd postnatal day and vaginal versus caesarean delivery were compared.

8.2 Methods

The approval of the local Research Ethics Committee was obtained prior to commencement of the study. Subjects were recruited from the postnatal wards of the maternity unit in which the study was carried out. Inclusion criteria included delivery by spontaneous vertex delivery (SVD) or by caesarean section for obstetric reasons such as fetal distress, breech presentation, and previous caesarean section. Postpartum heparin thromboprophylaxis received in line with our unit protocol was not considered an exclusion criterion, but women with a history of pre-eclampsia or major antepartum haemorrhage were excluded from the study. Given the previously demonstrated sensitivity of the measurement technique proposed, it was considered that clinically meaningful differences in the studied parameters would be evident in a combined sample size of 40 subjects. Complete data was obtained from 20 who had been delivered by SVD and 22 who had been delivered by caesarean section, of which 12 had undergone emergency delivery. The mean parity in each group was 1. The mean age in the caesarean group was 28 years as opposed to 26 in the SVD group but this small difference was not considered significant.

The subject preparation and methods employed were as previously described. All measurements were made with the patient lying supine with a 15° head up position. The diameter and blood flow velocity (measured as the time averaged maximum velocity, (TAMV)) were recorded at the common femoral vein, superficial femoral vein and popliteal veins according to the previously described protocol. Measurements were performed in both legs on the 4th and again on the 42nd postnatal day.

The data were found to be normally distributed. The data were subjected to two factor analysis of variance and tested for significance using Fishers Protected LSD test. $p<0.05$ was taken to indicate a statistically significant result.

8.3 Results

8.3.1 Effect of time

Between 4th and 42nd postnatal day, there was a mean reduction in the diameter of all vessels except the left SFV. However, only the CFV showed a statistically significant reduction . An increase in flow velocity was seen in all vessels between

the 4th and the 42nd postnatal day. Again, however, statistical significance was only demonstrated at the CFV (**Table 8.1**).

8.3.2 Difference between left and right legs

Comparison of the vessel diameter and flow velocity demonstrated significant differences between the left and right legs. The mean diameter of the left CFV was significantly greater than that of the right CFV. Conversely, the flow velocity was lower in the left CFV than in the right, although the difference did not reach statistical significance. While a similar trend was demonstrated at the level of the SFV, the differences between left and right did not reach significance. At the popliteal vein, however, the vessel diameter in the left leg was significantly greater and the flow velocity significantly slower than that demonstrated in the right leg (**Table 8.1**).

8.3.3 Effect of mode of delivery

A trend towards reduced flow velocity at the CFV and SFV was observed in those delivered by caesarean section (**Table 8.2**). However, the influence of mode of delivery on vessel diameter and flow velocity did not reach statistical significance at any of the venous segments studied.

8.4 Discussion

Our data indicate that following discharge from hospital, most women retain a degree of stasis within the proximal deep veins of the leg. This may contribute to the ongoing risk of thromboembolism in the puerperium and reflect persistent increased vessel wall compliance (Clarke-Pearson & Jelovsek 1981) or relaxation of vascular smooth muscle in the continuing presence of hormonal factors. It is not certain to what extent observations made on the 42nd postnatal day reflect the non-pregnant situation. However, in Chapter 7 it was demonstrated that by the 42nd postnatal day, deep venous diameter and flow velocity have returned to levels observed in early pregnancy .

Between the 4th and 42nd day, the most profound changes in deep venous diameter and flow velocity were seen in the CFV. Our data suggest that the CFV is the segment of the deep venous system of the leg most affected by the physiological and mechanical stresses provided by pregnancy and delivery. Why this should be the case is not clear. The superficial position of the vessel leaves it relatively unsupported

compared to the superficial femoral vein where changes in compliance of the vessel wall and venous pressure may not result in changes readily detected with ultrasound. Additionally, any observed effect of the uterus on venous flow will decrease as the distance between the vessel and the pelvis increases. These data are consistent, however, with the observation that most pregnancy related DVT are ileofemoral in origin, reflecting these thrombogenic alterations in the CFV, rather than of calf vein origin as is the case outside pregnancy (Bergqvist & Hedner 1983, Polak & Wilkinson 1991).

Thrombosis tends to occur more frequently in the left leg than in the right in both pregnant and non-pregnant patients (Markel et al 1992). In Chapter 7 blood flow within the deep veins of the leg was shown to be slower in the left leg during pregnancy supporting the suggestion that relative stasis in the left leg may account for the observed predominance of left sided DVT in pregnancy (Lindhagen et al 1986). The data presented here demonstrate the presence of relative stasis in the deep veins of the left leg in the early puerperium and six weeks after delivery. The increased diameter and reduced flow velocity on the left side would appear to indicate the presence of a proximal obstruction. One factor that may contribute to this is the compression of the left common iliac vein by the right common iliac artery. (Cockett & Thomas 1965). In addition, venous webs have been reported to form more commonly at the left than the right iliac vein (Ferris et al 1983) and changes in the left iliac vein itself have been described in post-mortem studies, further supporting this as a potential site for the development of acute DVT (Krumbhaar & Ehrich 1942). Hormonal factors may contribute to the pregnancy associated increase in left sided predominance, since the effect has been observed to be related to oestrogen dose in users of higher oestrogen-containing oral contraceptives (Bergqvist et al, 1982). A trend towards relative stasis in the proximal deep leg veins was observed in those who had undergone caesarean delivery, suggesting that the increased incidence of DVT observed after caesarean section may be due in part to relative stasis.

8.5 Conclusion

These data suggest possible physiological mechanisms behind previous clinical observations relating to the period of greatest risk of DVT in the puerperium, the relative preponderance of left sided DVT and the risk of DVT associated with caesarean section. Current thromboprophylactic guidelines tend to advise the

institution of prophylactic measures only until the patient is mobilised or discharged. The presented data suggest that this approach may merit review. This is further supported by the data presented in Chapter 6 showing that a high proportion of cases of thromboembolism present after discharge and data from the Confidential Enquiry which shows that many fatal cases of PTE occur between 7 and 42 days postnatally (DHSS et al 1996). It may therefore be advisable that those women receiving thromboprophylaxis should continue to use this following discharge. For example, anti-thromboembolic stockings may be indicated for at least six weeks postnatally, particularly following caesarean delivery.

Table 8.1

Vessel diameter and time averaged maximum flow velocity (TAMV) are given for the right (R) and left (L) common femoral vein (CFV), superficial femoral vein (SFV) and popliteal vein (POP) on the 4th and 42nd postnatal day. The statistical significance of the differences between the 4th and 42nd day **(4 v 42)** and the right and left leg **(R v L)** are given as p values.

				p value	
	Vessel	**Day 4**	**Day 42**	**4 v 42**	**R v L**
Diameter mm(SEM)	R CFV	9.6(0.2)	8.6(0.3)	0.02	0.02
	L CFV	9.9(0.2)	9.4(0.2)		
	R SFV	7.6(0.2)	7.3(0.3)	0.85	0.07
	L SFV	7.7(0.2)	7.9(0.2)		
	R POP	5.4(0.2)	5.0(0.4)	0.30	0.03
	L POP	5.8(0.2)	5.7(0.2)		
TAMV cm/s(SEM)	R CFV	10.6(0.6)	13.9(0.7)	0.04	0.07
	L CFV	10.0(0.6)	12.0(0.7)		
	R SFV	5.4(0.4)	6.2(0.5)	0.15	0.17
	L SFV	5.1(0.3)	5.5(0.4)		
	R POP	5.9(0.4)	7.0(0.5)	0.06	0.04
	L POP	5.3(0.4)	5.9(0.5)		

Table 8.2

Mean vessel diameter and flow velocity (TAMV) at the common femoral vein (CFV), superficial femoral vein (SFV) and popliteal vein (POP) on the 4th and 42nd postnatal day are given for the group delivered by spontaneous vertex delivery (SVD) and the group delivered by caesarean section (C/S). The statistical significance of the differences between the groups delivered by SVD and C/S **(SVD v C/S)** are given as p values.

	Vessel	Day	SVD	C/S	p value SVD v C/S
Diameter	CFV	4	9.7(0.2)	9.7(0.2)	0.44
mm(SEM)	CFV	42	9.2(0.2)	8.8(0.2)	
	SFV	4	7.7(0.2)	7.6(0.3)	0.76
	SFV	42	7.5(0.2)	7.7(0.2)	
	POP	4	5.4(0.2)	5.7(0.4)	0.33
	POP	42	5.3(0.2)	5.4(0.2)	
TAMV	CFV	4	10.4(0.6)	10.3(0.7)	0.27
cm/s(SEM)	CFV	42	13.7(0.5)	12.3(0.4)	
	SFV	4	5.4(0.4)	5.1(0.3)	0.36
	SFV	42	6.3(0.3)	5.5(0.5)	
	POP	4	5.9(0.4)	7.0(0.5)	0.29
	POP	42	6.1(0.4)	6.8(0.5)	

Chapter 9

Deep venous flow and posture; qualitative studies of respiration and cardiac phasicity in pregnancy

Summary

Fluctuation in deep venous flow velocity with respiration may be an important means by which early thrombi are removed form valve pockets. The duplex Doppler study presented shows this phasicity of flow to be present throughout pregnancy. While adoption of the upright posture does not remove respiratory fluctuation, it does result in a reversal in the phase of respiration. These findings indicate the importance of caval occlusion in altering venous return to the chest. Fluctuations in deep venous flow velocity with the cardiac cycle are rarely seen in normal pregnancy.

9.1 Introduction

In pregnancy, the gravid uterus has been shown to cause collapse of the IVC in the supine position (Kerr et al 1962). The data presented in chapter 7 indicates that when present, the amplitude of respiratory phasicity of venous flow in the deep leg veins is not significantly altered even in late pregnancy. As previously discussed this may have implications for the ultrasound diagnosis of proximal occlusive DVT. Respiratory phasicity may also be of thromboprophylactic importance. It has been suggested that the presence of respiratory phasicity in non-pregnant subjects may act to prevent the formation of DVT by 'washing out' early thrombi forming in venous valve pockets (Sigel, 1973). The presence of respiratory flow phasicity may be seen to be beneficial in this regard. Conversely, the presence of cardiac phasicity (that is fluctuation in venous flow velocity with the cardiac cycle) is rare in healthy non-pregnant subjects. It's presence may be associated with haemodynamic pathology such as cardiac failure (Willeput et al 1984).

The mechanism by which respiration causes phasic changes in venous return and evident fluctuations in maximum flow velocity have been subject to previous study. Before the advent of modern non-invasive measurement techniques, venous return to the heart in the non-pregnant state was thought to increase during inspiration and decrease during expiration. This was considered to be the result of two factors. The inspiratory fall in intrathoracic pressure increases the pressure difference between the periphery and the right atrium, so aspirating blood into the thoracic veins. Secondly, the descent of the diaphragm compresses visceral organs, propelling splanchnic blood toward the inferior vena cava. These concepts are, however, derived from canine experiments involving surgical exposure of the vessels in order to insert flowmeters

(Brecher & Hubay 1955, Brecher & Mixter 1953). The application of these data to the human situation has been questioned, since the pattern of inspiratory muscle contraction is different in dogs and humans; while dogs use parasternal intercostal muscles to breath in (Road et al 1982), in humans the diaphragm is responsible for most of the volume change (Sharp et al 1975). Since the veins from the lower extremities traverse the abdominal cavity and the diaphragm before entering the thorax, the inferior vena cava may be squeezed by the contracting diaphragm or collapse as a result of a rise in intrabdominal pressure. In non-pregnant subjects, Doppler studies have shown that the semi-recumbent position inspiration is associated with a fall in venous return whereas expiration is associated with an increase (Willeput et al 1984). There is to the author's knowledge no data indicating whether this effect is maintained in the standing position. However, it can be hypothesised that the standing position may result in a head of venous pressure sufficient to prevent collapse of the IVC which can occur during inspiration. The patent IVC could then transmit the increased negative intra-thoracic pressure generated during inspiration to the infra-abdominal venous collecting system, thus resulting in an increase in venous return, during inspiration compared to expiration. This effect may be detectable as increased venous flow velocity at the CFV.

The physiological effect of pregnancy on these parameters remains unclear. The aims of this study were to assess the effects of advancing pregnancy gestation on the presence or absence of respiratory and cardiac flow phasicity and the phase of inspiration associated with maximum venous flow velocities. In order to test the hypothesis stated above regarding the effect of the standing position on the phase of respiration associated with maximum flow velocity, the studies were carried out in the semi-supine and upright position.

Duplex Doppler ultrasound was used to assess the common femoral veins (CFV), superficial femoral veins (SFV) and popliteal veins (POP) of the left and right leg in the supine and upright position in pregnant subjects from the first trimester until the 42nd postnatal day. In addition to recording the presence and phasicity of respiratory flow fluctuations, the presence or absence of flow fluctuation with the cardiac cycle was recorded.

9.2 Methods

The same cohort of women studied in the study presented in chapter 8 were investigated and the data presented below were collected during the same ultrasound examinations. These 24 women had a viable singleton pregnancy, were aged 18-34 years (median 25 years) of low parity (0-2) and free from any respiratory and cardiovascular diseases . The mean gestation at which the subjects entered the study was 12 weeks (8-24). Each subject had a duplex Doppler scan performed at booking and at approximately monthly intervals thereafter until delivery. Further ultrasound assessments were carried out on the 4th and 42nd postnatal day. Data were recorded on the 42nd postnatal day as an approximation to the non-pregnant state.

Prior to each scan, each subject rested in the semi-supine position for 15 minutes. All the ultrasound examinations were carried out using an Acuson 128 Ultrasound scanner (Mountain View, Calif.) and 5 MHz tranducer. The subjects were prepared and positioned by means of the protocol described in Chapter 5. The vessel to be scrutinised was visualised in the longitudinal axis and the Doppler gate placed across the middle third of the vessel lumen. A spectral Doppler recording of the flow waveform was made during a 15 second period of deep breathing during which the subject was observed for phase of respiration by monitoring chest wall and abdominal wall excursion. Measurements were carried out at the CFV, SFV and popliteal veins of the right and left leg in the semi-supine position (head up 15^{o}) and the right CFV in the upright position. The following observations were made:

a. The presence of respiratory and/or cardiac fluctuations in venous flow.

b. The timing of maximum flow velocity in relation to the phase of the respiratory cycle.

In order to simplify the analysis of the effect of increasing gestation on flow phasicity, three stages of pregnancy were defined:

Stage 1	8 to 32 weeks gestation.
Stage 2	33 weeks to delivery.
Stage 3	The puerperium up to the 6th postpartum week.

Stage 2 was defined to indicate late pregnancy, when any effect of the gravid uterus was likely to be detected. At gestations prior to this, the effect of the gravid uterus was considered likely to be of less importance, and thus they were grouped as Stage 1. A total of 155 assessments were made, although technically adequate scans of all vessels in all postures were only obtained in a total of 142 subject assessments. The discrepancy was due to cases where the amplitude of phasicity was too low to discern the relationship with respiratory phase. The categorical data obtained was analysed using Chi-squared tests for significance.

9.3 Results

In the supine position, respiratory variation in flow velocity was present at the CFV in 150/155 scans (**Plate 9.1**). Cardiac variation in flow velocity was also present in 15 scans (**Plate 9.2**) and was the only form of phasicity of flow in 5/155 scans. Similar results were obtained at the SFV and popliteal vein (**Figure 9a**). During deep breathing, maximal flow velocity through the CFV occurred during expiration in 130/142 of the assessments (**Figure 9b**), a further 3 showing a biphasic flow pattern with peak velocities occurring in both inspiration and expiration, 3 showing peak flow during inspiration and 6 showing no respiratory variation in flow velocity. Again, similar patterns were observed at the SFV and the popliteal veins. No significant differences were evident in flow phasicity between the left and right legs. On adoption of the upright position, 128 of 142 examinations demonstrated respiratory variation in flow at the CFV (**Figure 9c**). However, in contrast to the supine position, maximum flow velocities were observed in inspiration alone during deep breathing in 102 of 142 examinations (**Plate 9.3**). A biphasic waveform demonstrating peak velocities during inspiration and expiration was observed in a further 8 examinations, and expiration was associated with maximum flow velocities in 16 examinations. The difference in respiratory phase of peak flow between the supine and upright position was statistically significant ($p<0.02$).

The postural effects on flow phasicity described above were stratified for early pregnancy, late pregnancy and the puerperium. While respiratory phasicity was almost always present in both the supine and upright positions regardless of stage of pregnancy, cardiac phasicity appeared to diminish with advancing gestation when measured in the supine position. Prior to 33 weeks gestation, 10% of assessments of flow in the right CFV demonstrated cardiac phasicity superimposed on respiratory

fluctuation. This fell to just 3% after 33 weeks gestation, rising to 25% in the puerperium **(Figure 9c).** There was no significant change with gestation in the effect of adopting the upright posture on respiratory phase of maximum venous flow velocity **(Figure 9d).**

9.4 Discussion

The present data indicate that in pregnancy and the puerperium, inspiration reduces the velocity of venous flow through the deep veins of the legs. These findings are consistent with those of Willeput et al (1984) who used continuous wave Doppler techniques to measure flow velocity at the CFV in 10 non-pregnant subjects in the supine position. The presented data, like that of Willeput et al (1984) contrasts with previous studies such as that of Wexler et al (1968) who used an electromagnetic transducer positioned in the intrahepatic portion of the inferior vena cava. They reported increased caval flow velocities during inspiration. This discrepancy may reflect differences in the pattern of inspiratory muscle use by the subjects examined. Konno and Mead (1967) have demonstrated the partition of breathing between the diaphragm and rib cage, and different individuals may engage different components as the principal means of effecting inspiration. Sharp et al (1975) have shown that during quiet breathing, most normal subjects are diaphragmatic breathers when supine and thoracic breathers when upright. If it is accepted that diaphragmatic excursion tends to cause collapse of the inferior vena cava, whereas thoracic excursion does not, then their findings would be consistent with our observations. Advanced gestation did not appear to influence the pattern of respiratory phasicity observed. However, cardiac pulsations were observed most frequently in the puerperium, and least frequently in late pregnancy. It might be postulated that the gravid uterus exerts a dampening effect on the transmission of cardiac pulsations to the CFV which increases with advancing gestation. After delivery, the return of the uterus to a size near to its non-pregnant state removes this dampening effect.

9.5 Conclusion

The present study shows respiratory fluctuation in venous flow through the deep leg veins to be present throughout pregnancy and demonstrates a reversal in the respiratory phase of maximal flow velocity when the upright position is adopted, a phenomenon observed in both the pregnant and non-pregnant state, as indicated by the measurements taken on the 42 post-natal day. The hypothesis that adoption of the upright position results in a head of pressure in the abdominal segment of the inferior vena cava sufficient to resist occlusion by increased intrabdominal pressure during inspiration is supported by our findings. The presented data also indicate that cardiac pulsations can be observed in healthy pregnancy but are unusual. Their presence may indicate an additional degree of haemodynamic disturbance, but further work is required to determine whether they are more prevalent in pregnancy affected by additional haemodynamic stress such as that imposed by pre-eclampsia.

Figure 9a

The percentage of assessments demonstrating respiratory, cardiac and both respiratory and cardiac phasicity, and those assessments where no phasicity of venous flow was demonstrated, are shown for the right (R) and left (L) common femoral vein (CFV), superficial femoral vein (SFV) and popliteal vein (POP) in the supine position.

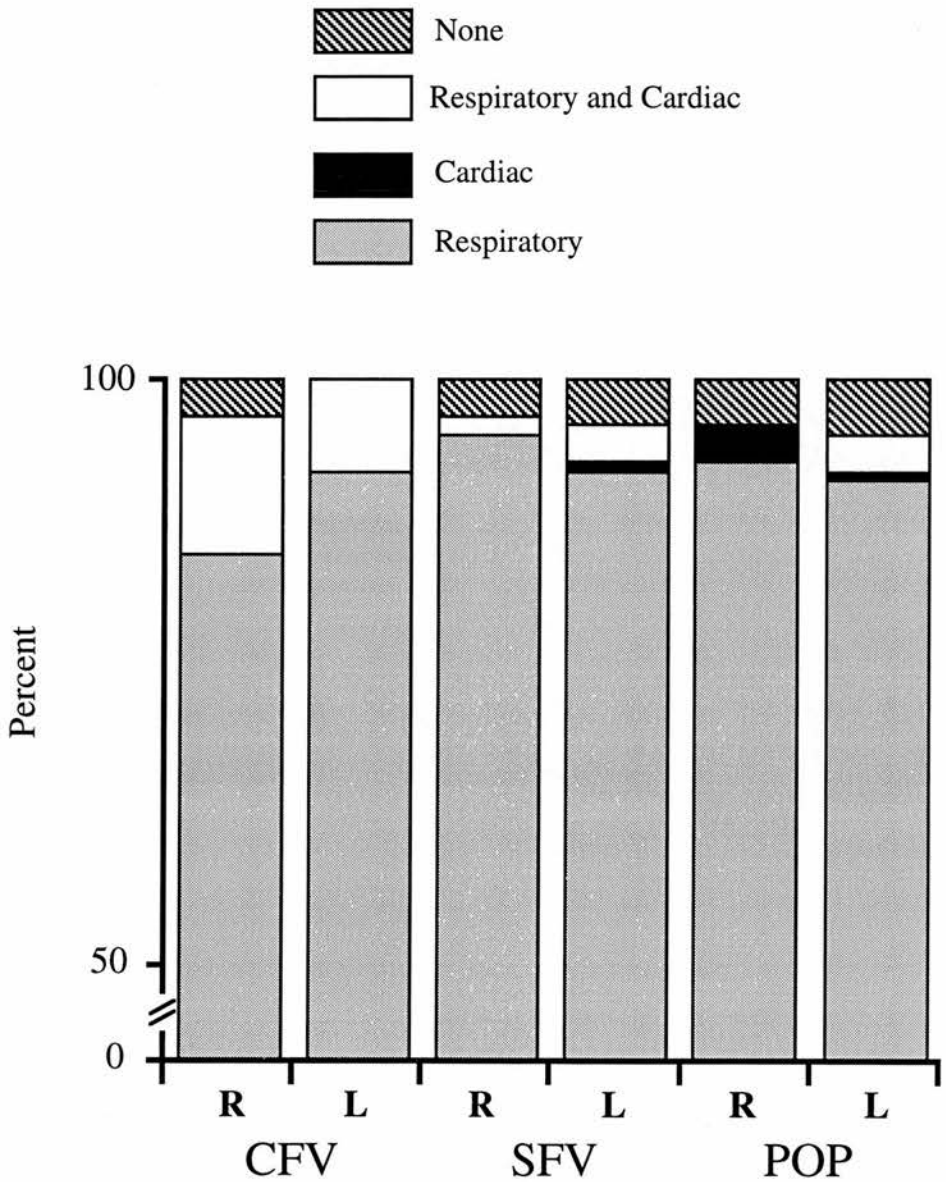


Figure 9b

The percentage of assessments where maximum flow velocity was demonstrated during expiration, inspiration, both expiration and inspiration (demonstrating abiphasic waveform), and where no flucuation was observed with respiration (None). Observations are shown for the right (R) and left (L) common femoral vein (CFV), superficial femoral vein (SFV) and popliteal vein (POP) in the supine position.

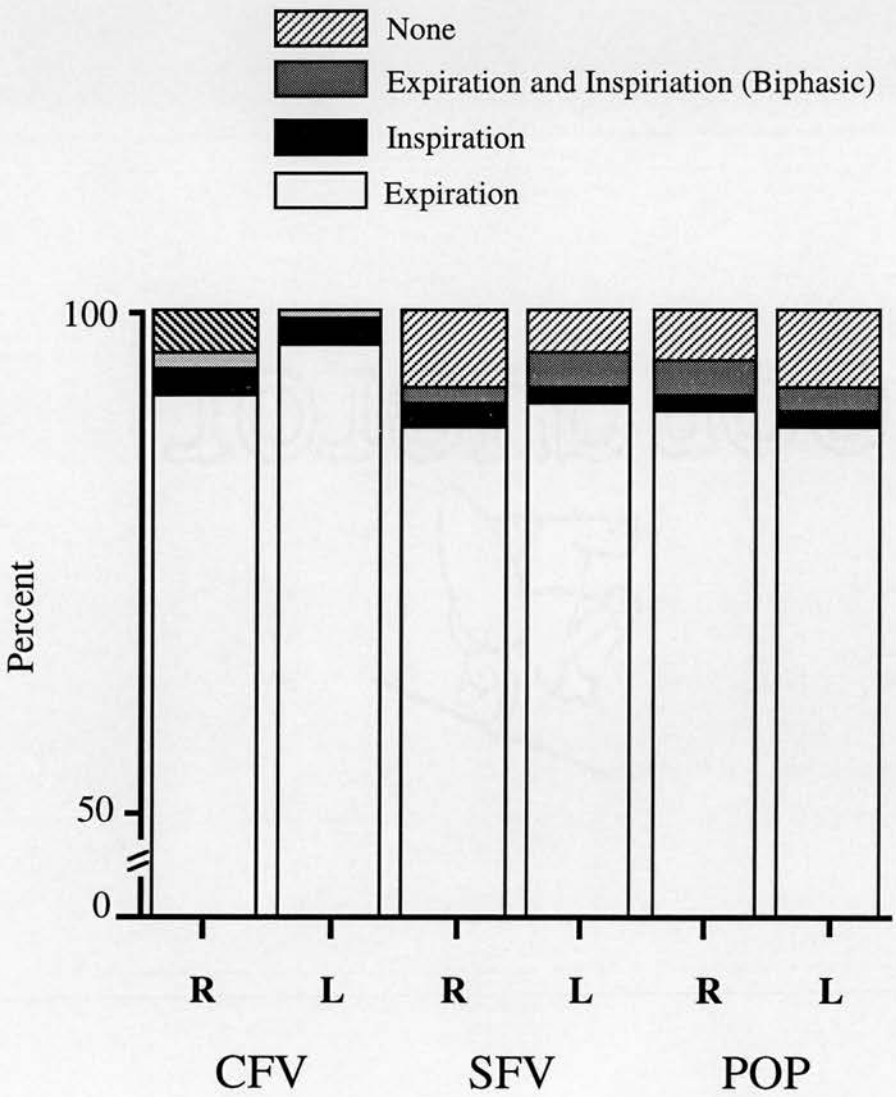


Figure 9c

The percentage of assessments demonstrating respiratory, cardiac and both respiratory and cardiac phasicity, and those assessments where no phasicity of venous flow was demonstrated, are shown at the right common femoral vein in the supine and upright positions in early pregnancy (EP), late pregnancy (LP) and the puerperium (PM).

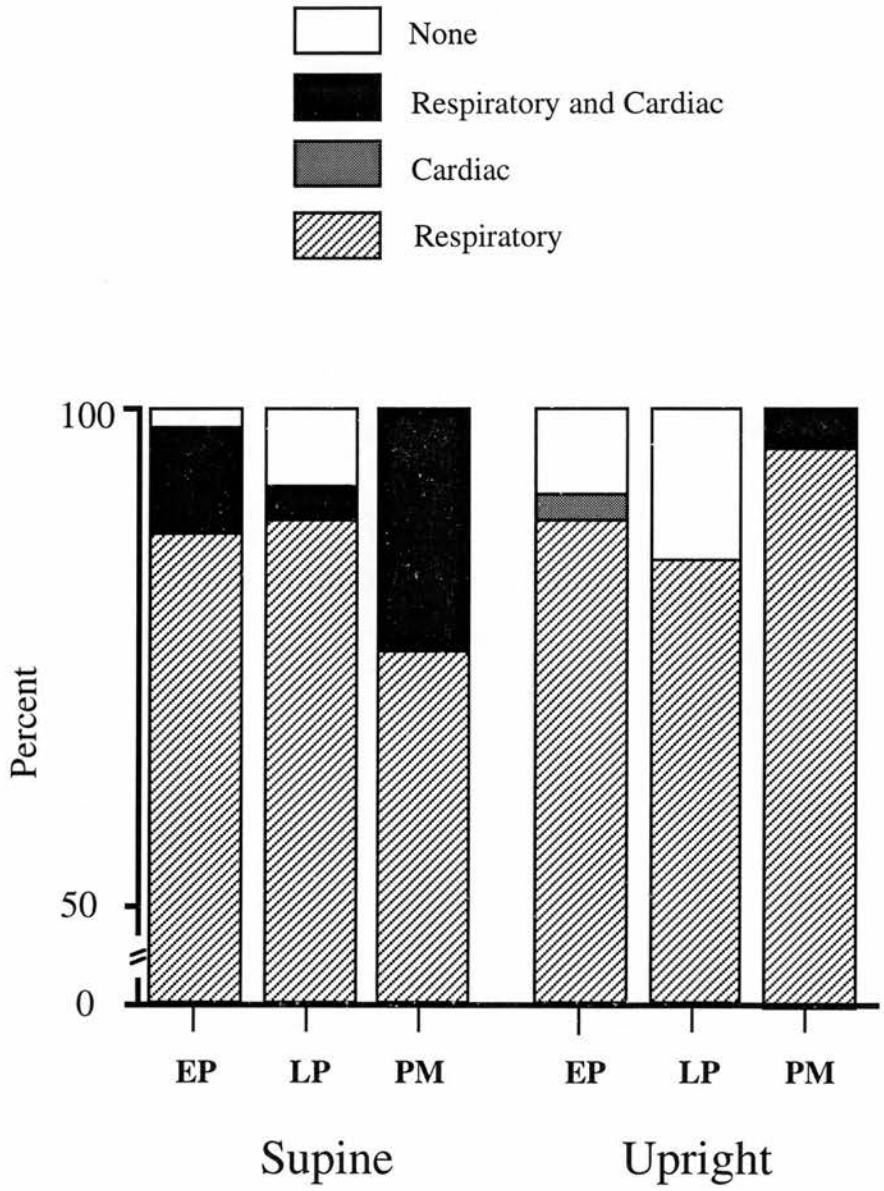


Figure 9d

The percentage of assessments where maximun flow velocity was demonstarted during expiration, inspiration, both expiration and inspiration (demonstrating a biphasic waveform), and where no fluctuation was observed with respiration (None). Observations are shown at the common femoral vein in the supine and upright positions in early pregnancy (EP), late pregnancy (LP) and the puerperium (PM).

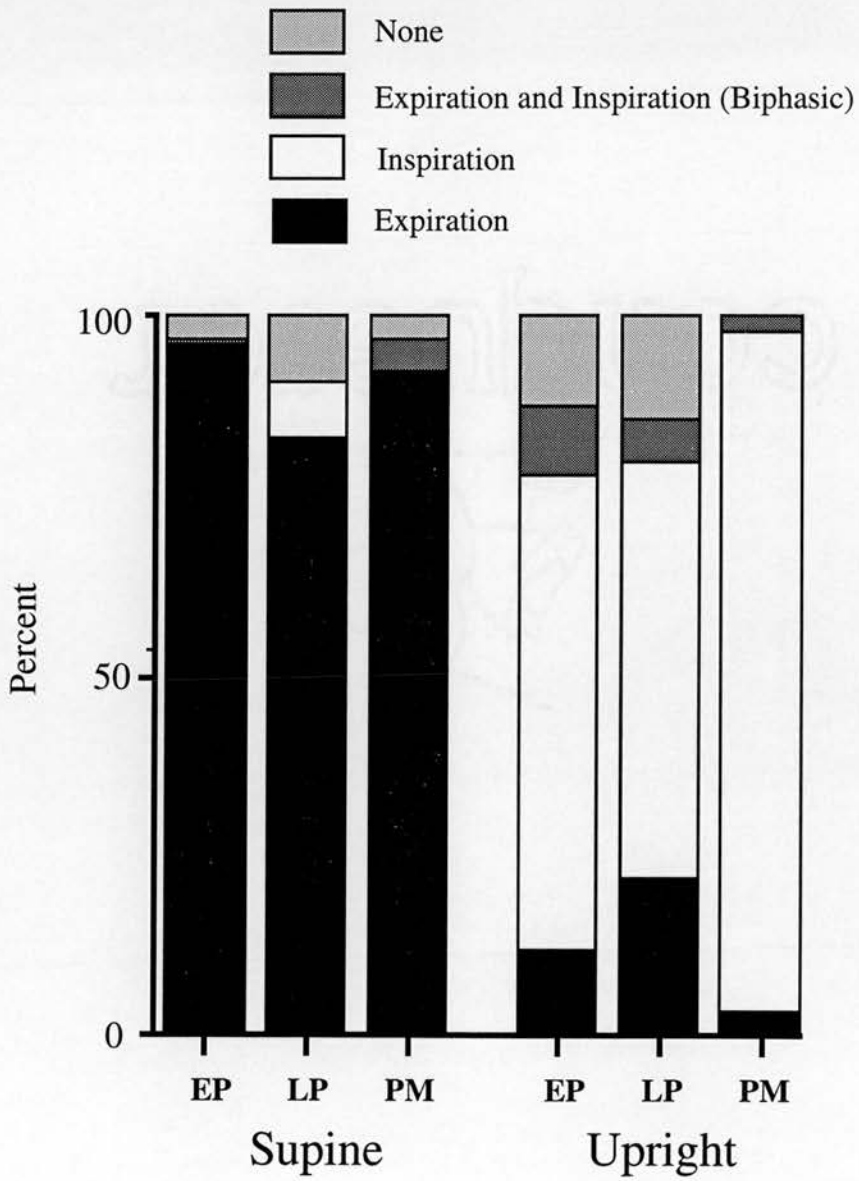


Plate 9.1 Respiratory variation in venous flow at the CFV in the supine position. Maximum flow velocity occurs during expiration.

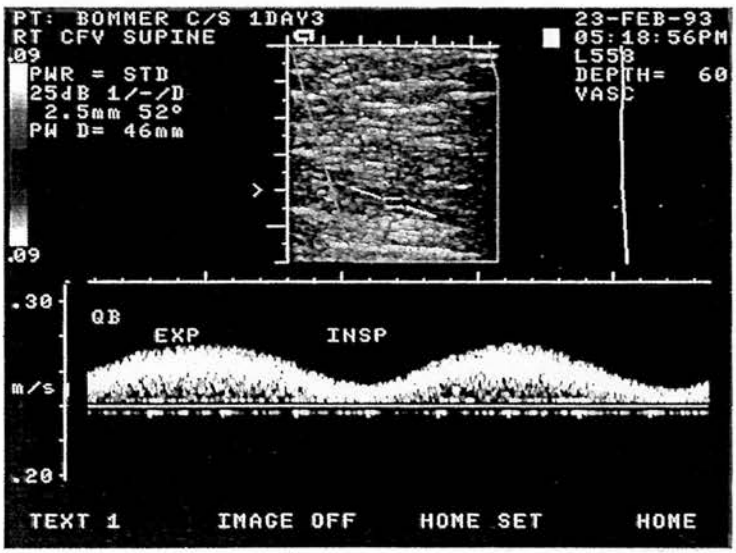


Plate 9.2 Variation in flow velocity related to the cardiac cycle is superimposed on respiratory variation (S = cardiac systole).

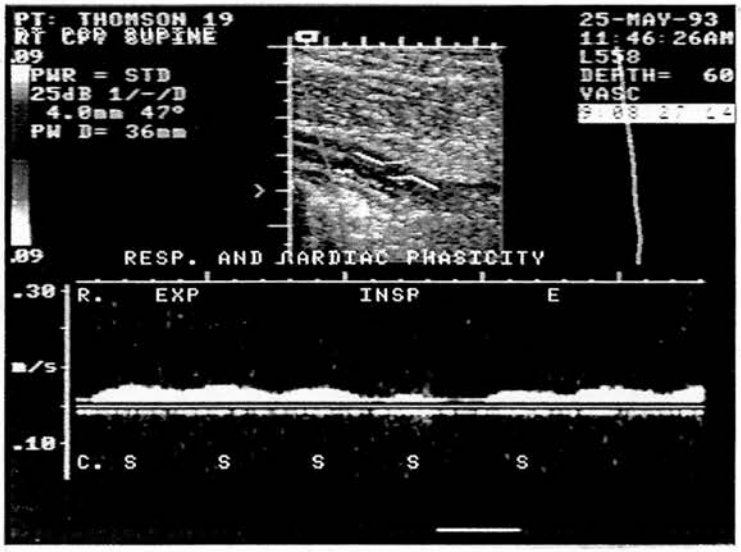
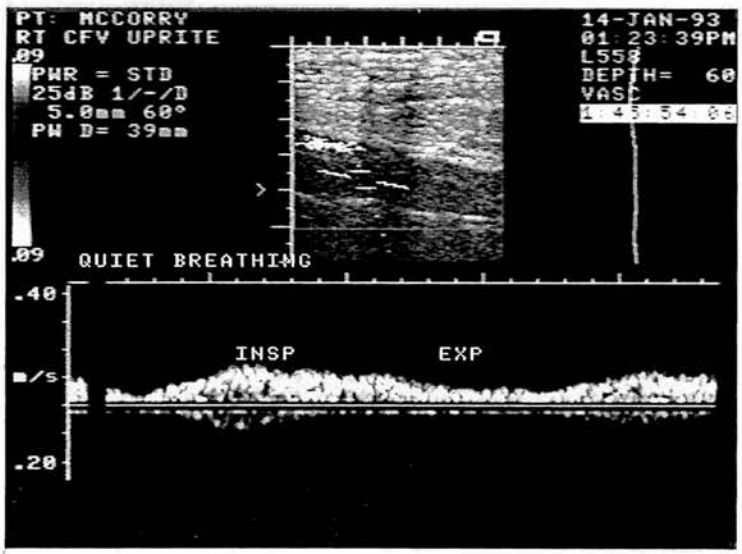


Plate 9.3 Respiratory variation demonstrates maximum flow velocity during inspiration at the CFV in the upright position.



Chapter 10

Duplex ultrasound screening for deep venous thrombosis in the puerperium

Summary

Although the role of duplex Doppler ultrasound as a screening tool for DVT in asymptomatic patients remains to be established, it is of considerable potential utility in pregnant and puerperal women. In order to determine whether a significant number of women at low to moderate risk of developing puerperal DVT had subclinical thrombosis, the previously described duplex techniques for detecting deep venous thrombosis in the proximal veins of the leg were applied to 140 such women. No DVT were detected and all the subjects remained asymptomatic at follow up 6 weeks later. These findings indicate that there is unlikely to be a large number of subclinical DVT in this group of women, and are consistent with other data regarding the incidence of DVT in the puerperium. Current guidelines for thromboprophylaxis in this group are appropriate.

10.1 Introduction

The puerperium is recognised as a period of increased risk from thromboembolism, and additional factors known to increase the risk include caesarean section, pre-eclampsia, obesity, age over 35 years, and multiparity. While the incidence of pulmonary embolism in the puerperium is well documented, that of deep venous thrombosis remains uncertain as no contemporary data based on non-invasive objective and accurate screening techniques exists. The development of Duplex doppler ultrasound as a means of diagnosing DVT offers a potential non-invasive means of screening for DVT in asymptomatic patients deemed to be at risk. In such patients, particularly those at low to moderate risk, invasive techniques such as contrast venography would not be acceptable to most patients. However, duplex Doppler ultrasound screening can only be of value if demonstrated to have sufficient sensitivity and specificity when compared with a gold standard test such as contrast venography. As discussed in an earlier chapter, the sensitivity and specificity of ultrasound in detecting proximal DVT in symptomatic patients has been shown to approach that of venography, and has replaced it as the first line investigation in many centres. Less certainty exists as to the accuracy of duplex ultrasound in detecting DVT in asymptomatic subjects, and no validation studies have been carried out on pregnant or puerperal patients. The majority of studies designed to assess the accuracy of Duplex ultrasound as a screening test have been carried out in post-operative orthopaedic patients. This prospective screening study of 140 asymptomatic

women who had been delivered four days previously describes the use of duplex Doppler ultrasound techniques to screen for subclinical deep venous thrombosis in the early puerperium.

Initial studies suggesting a low sensitivity for the detection of asymptomatic DVT were hampered by small numbers (Monreal et al, 1989) and selective use of comparison to confirm positive Duplex tests (White et al, 1990). In a study of 158 post-operative total hip arthroplasty patients, Barnes et al (1991) demonstrated a sensitivity and specificity for duplex scanning of 79% and 97% respectively against venography as the gold standard. Cronan et al (1991) were able to achieve 100% sensitivity and specificity for compression ultrasound against venography in detecting 12 DVT in 86 patients who had sustained a hip fracture. A meta-analysis of comparitive studies published between 1982 and 1993 (Wells et al 1995) cast doubt on the true value of duplex ultrasound in asymptomatic patients however. Analysing those studies where bias in study design had been minimised, they calculated a sensitivity of 62% and a specificity of 97% for duplex Doppler against venography, and suggested that duplex ultrasound may therefore have only a limited role in screening. In coming to this conclusion they included data from papers that had employed colour Doppler as the means of screening. Colour Doppler appears of little value in assessing the asymptomatic patient (Davidson et al, 1992), and some authorities believe it to be inferior to duplex ultrasound in this role (Camerota, 1993). The reason for this is unclear, but since colour Doppler renders the examination of the deep veins easier in most cases, it may encourage a less diligent search in the asymptomatic patient. Restricting their studies to duplex ultrasound versus venography, Grady & Benson (1994a) recently assessed duplex ultrasonography in 79 patients who had undergone total knee arthroplasty, and showed 100% sensitivity and specificity in the detection of proximal DVT against venography. For the detection of distal thrombosis, the sensitivity of duplex ultrasound fell to 88% with a specificity of 98%. Amongst a cohort of 51 hip arthroplasty patients a sensitivity of 91% and specificity of 98% was reported by the same authors (1994b). However Jomgbloest et al (1994) were unable to confirm such impressive figures, reporting a sensitivity of just 40% in detecting proximal DVT in 13 of 100 patients who had undergone craniotomy. In the absence of meta-analyses of more recent data, the true value of duplex ultrasound in screening the asymptomatic at risk patient remains uncertain. Discrepancies in published results may reflect differing degrees of expertise among the sonographers. Prior to carrying out this study, the author underwent intensive training in the technique from experienced experts (see Acknowledgements). While

no formal assessment of the authors expertise was carried out, all DVTs detected by him in symptomatic patients were subsequently confirmed by venography, and to the author's best knowledge, no thromboembolic sequelae occured amongst the many women on whom he reported a negative scan during the period of data collection.

Accepting the limitations of the technique, the published data appears sufficiently encouraging to merit utilisation of duplex ultrasound as a screening tool among subjects on whom venography would be difficult to justify. Such a group constitutes the study group presented in this chapter; asymptomatic woman at low to moderate risk of postpartum DVT.

In order to ascertain the true incidence of DVT in this group of patients, previous data would indicate the need for screening study of several hundred patients. The aim of this study, however was to employ duplex Doppler ultrasound to determine whether a large number of women at low to moderate risk were sustaining subclinical untreated DVT prior to discharge from hospital. Thus a study of similar size to those previously published in the application of other techniques in pregnancy (Bergqvist et al 1979) was undertaken.

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10.2 Methods

The screened population consisted of two groups: 94 women delivered by caesarean section and 46 delivered vaginally. Although unselected, the presence of additional risk factors for deep venous thrombosis were recorded, including age older than 35 years, weight over 80 kg at booking, previous history of deep venous thrombosis, parity greater than four, and pre-eclampsia affecting the index pregnancy.

Each subject was examined in the semi-supine position using an Acuson 128 ultrasound scanner (Mountain View, California, USA) fitted with a 5 MHz linear array transducer or a Hitachi EUB 415 ultrasound scanner (Tokyo, Japan) fitted with a 5 MHz curvilinear transducer. The proximal deep vein collecting system of each leg was examined for evidence of thrombus formation from the ileofemoral vein to the popliteal vein. Thrombus was excluded if the vein appeared undistended, was easily compressible and was free of intraluminal echogenic material. Exclusion of occlusive deep venous thrombosis proximal and distal to the venous segment under scrutiny respectively required the demonstration of spontaneous respiratory flow

fluctuation and augmentation of flow on Doppler ultrasound on distal calf compression. Since direct scrutiny of the superficial femoral vein as it passed through the adductor canal was not possible in many cases, the latter criteria were applied to infer patency in this segment.

10.3 Results

One hundred and forty asymptomatic women were screened. Of those delivered by caesarean section, 21 subjects (22%) had one additional risk factor for deep venous thrombosis and four (4.3%) had two additional risk factors. Of those delivered vaginally, ten (22%) had one risk factor and one (2%) had two risk factors. **Table 10.1** summarises the risk profile of the screened population. No cases of subclinical deep venous thrombosis were identified in any of the subjects.

10.4 Discussion

Recently, guidelines on thromboprophylaxis in pregnancy and the puerperium have been published (THRIFT Consensus Group 1992), but obstetricians remain reluctant to prescribe prophylaxis in those at risk, partly because of the perceived rarity of clinical deep venous thrombosis in their practice (Greer & De Swiet 1993). Clinical diagnosis has estimated the incidence of deep venous thrombosis following vaginal delivery between 0.08 and 1.2 %, rising to 2.2 to 3.0 % following caesarean section (Husni et al 1967). However, clinical diagnosis is unreliable (Genton & Turpie 1980). A postpartum study using I-labelled fibrinogen (Friend & Kakkar 1970) reported an incidence of 2.6 % following vaginal delivery. Most of the cases of deep venous thrombosis detected were situated in the calf and were of debatable clinical significance.

The present study found no positive diagnosis in the women studied, although the majority had either none or only one additional risk factor. While limited by the relatively low number of women examined, this suggests that the incidence of proximal deep venous thrombosis is unlikely to be higher, and may even be lower than previously reported in low risk women. Since previous studies were published, developments in modern obstetric practice towards shorter admissions and the encouragement of early ambulation may have contributed to the lower incidence of

deep venous thrombosis suggested by the present results. A more recent study using plethysmography to screen 169 women following caesarean section found an incidence of deep venous thrombosis of 1.8 % (Bergqvist et al 1979). Plethysmography is, however, an indirect means of diagnosis and inferior in sensitivity and specificity to the traditional diagnostic gold standard, X-ray venography. The invasive nature of venography and I-labelled fibrinogen scanning, coupled with the risks of viral transmission and questionable accuracy associated with the latter (Lensing & Hirsh 1993), render these techniques unsuitable for screening.

Ultrasound techniques have been demonstrated to offer excellent sensitivity and specificity when measured against venography for the diagnosis of symptomatic proximal leg vein thrombosis (Aitken & Godden 1987) and have become widely used for this purpose in pregnancy. As discussed above, however ,in asymptomatic subjects the sensitivity may be reduced. When considered with the difficulty in assessing the calf veins, ultrasound appears less attractive as a screening tool. In pregnancy and the puerperium these limitations may not apply. As is the case with plethysmography, interpretation of ultrasound findings may be complicated by pregnancy associated physiological changes and necessitate different criteria for the diagnosis of deep venous thrombosis. Additionally, in contrast to the nonpregnant state, obstetric deep venous thrombosis frequently initiate in the common femoral vein (Bergqvist & Hedner 1983, Polak & Wilkinson, 1991) and poor visualisation of the calf veins may, therefore, be less important.

Our results are consistent with those of previous indirect noninvasive screening studies and serve to confirm the perceived low incidence in modern obstetric practice of subclinical deep venous thrombosis in the early puerperium in women at low to moderate risk. These data are also compatible with the epidemiological based incidence. Validation of the techniques as a screening tool in this patient group will remain difficult, however, given the relatively low incidence of DVT reported compared to that amongst post-operative orthopaedic patients. The application of this technique to larger numbers with multiple risk factors may, however be valuable in the further assessment of ultrasound as a screening tool in pregnancy and the puerperium and may aid further in the drawing up of guidelines for thromboprophylaxis.

8.5 Conclusion

On the basis of this study, there is no evidence that a large number of subclinical thromboembolic complications are being missed by not offering routine DVT screening to women at low to moderate risk. In the absence of data from large screening studies of women at high risk, and in view of the 10-fold incidence of DVT reported in those considered under current guidelines to be at risk (see above and chapter 6) current thrombprophylaxis guidelines (see chapter 1) should not be altered.

Table 10.1

The number (n) and percentage (%) of subjects screened with none, 1, 2, and 3 risk factors for deep venous thrombosis (DVT) in addition to their puerperal status are shown. Delivery by caesarean section is designated an additional risk factor.

Risk factors for DVT	n	%
None	35	25
1	79	56.5
2	22	15.5
3	4	3

Chapter 11

Compression stockings and posture: a comparative study of their effects on the proximal deep veins of the leg at rest.

Summary

Graduated compression stockings have been shown to reduce the incidence of deep venous thrombosis. While they are thought to act primarily by increasing venous flow velocity, their mode of action remains uncertain. Doppler ultrasound was employed to study the relative effects of three types of support stocking on the deep venous diameter, flow velocity and pulsatility in 10 non-pregnant female subjects. In addition, the effect of altered posture on the same parameters was assessed. Significant effects of the graduated stockings were found at the level of the popliteal vein, where a reduction in both the diameter and the amplitude of respiratory phasicity was recorded ($p<0.05$). No significant increase in flow velocities was recorded. Adopting the left lateral position significantly increased flow velocity in the right common femoral vein ($p<0.05$). The application of stockings in this position produced no additional increase in flow velocities, but did alter the amplitude of respiratory phasicity. These data do not support the widely held view that graduated compression stockings increase flow velocities at rest. Adopting a lateral recumbent position significantly increases flow velocity in the non-dependent leg.

11.1 Introduction

Venous thromboembolism remains a major cause of post-operative mortality and morbidity. Eighty percent of those who die from pulmonary thromboembolism (PTE) are asymptomatic (Sandler & Martin 1989), and emphasis is therefore placed on appropriate prophylaxis (Lowe et al 1992). Elasticated stockings are now the most widely used physical means of preventing DVT.

The use of local compression to increase venous flow through the limbs was first described by Stanton and colleagues (1949) who observed an increased clearance of Evans Blue dye from the leg. Later, continuous wave Doppler flow studies demonstrated that a pressure gradient applied from 18mm Hg at the ankle to 8 mm Hg at the thigh optimised flow velocity in the proximal veins of the leg (Sigel et al 1975). Graduated elasticated stockings designed to apply this compression profile have been shown to prevent post-operative deep venous thrombosis (Holford 1976, Allan et al 1983, Scurr et al 1977) and a recent meta-analysis has confirmed their efficacy in this regard (Wells et al 1994). Initial studies indicated that compression stockings acted to increase venous clearance from the limb. However more recently, this mode of action

has been questioned (Keith et al 1992) and the precise mechanism by which they achieve their thromboprophylactic effect remains unclear.

The aims of this study were firstly to assess whether the compression stockings used in our hospital could be demonstrated to exert a measurable effect on venous flow velocity, and whether any one could be demonstrated to have superior effect. The second aim of the study was to assess whether adoption of the left lateral position, recommended in the third trimester to improve venous return, could be shown to have an effect on venous flow velocity in non-pregnant patients, and to compare any positional effect on venous flow velocity and vessel diameter with those effects exerted by compression stockings. Duplex Doppler ultrasound was employed to measure the diameter and flow velocity within the common femoral and popliteal veins of non-pregnant subjects. We elected not to extend the study to pregnant patients for the reasons given below.

The stockings assessed were the T.E.D. Thigh-Length Stocking (Kendall Company, U.K.), the Brevet TX Anti-Embolism Stocking (Brevet Hospital Products, U.K.) and the Tubigrip Stocking (Seton Healthcare, U.K.) **(Plate 11.1)**. The T.E.D. stocking was selected for study as it is the only stocking which objective data shows to be effective in preventing DVT. The Brevet stocking was studied as it is widely used and is one of the main competitors to the T.E.D. stocking. Since the Tubigrip stocking is still widely used in clinical practice it was also subject to the studies presented. The T.E.D. and Brevet stockings studied provide an ankle to thigh compression gradient of 30-40 torr, whereas the Tubigrip is worn below the knee and is not graduated.

11.2 Methods

The study protocol required multiple measurements to be made in 3 postures in the first instance without the application of a support stocking and then 1 hour after the application of each stocking. To ensure each examination was of acceptable duration to the subjects measurements for each stocking were made at separate sessions at 2 or 3 day intervals. Compliance of out-patients was expected to be poor, while possible effects of the varying types and degree of pathology necessitating their admission rendered in-patient women likely to have confounding factors of a heterogeneous nature. Given the proposed study period of a week for each subject, gestational changes in vessel diameter and flow velocity could occur, themselves affecting the

data obtained. Given the problems associated with standardisation of pregnant subjects, non-pregnant members of staff were recruited to the study.

Ten fit, non-pregnant pre-menopausal women, with no history of venous disease volunteered. Initial measurements were made with the subject wearing no stocking and, in order to limit the duration of each examination, all investigations were confined to the right lower limb.

All support stockings were fitted one hour before the ultrasound measurements were made and all fittings were carried out by physiotherapists with expertise in fitting the correct size of stocking to achieve the intended pressure gradient. The tubigrip stockings were however not designed to exert a pressure gradient, and were fitted purely for comfort and adequate compression as judged by the physiotherapist.

The following protocol was followed. Prior to each scan, each subject was allowed to rest supine for 5 minutes. The ultrasound examinations were carried out using an Acuson 128 Ultrasound scanner (Acuson, Mountain View, Calif.) equipped with spectral and colour Doppler facilities, and a 5 MHz linear array transducer. With the subject lying supine with 15^{o} of head up tilt, the right common femoral vein was imaged in the longitudinal axis, at a point on the common femoral vein 2 cm below the junction with the long saphenous vein. The image was frozen after minimising the transducer pressure near to the point of losing contact. The distance between the inner aspects of the anterior and posterior vessel walls was recorded and the mean of three measurements calculated. The Doppler gate was then placed across the middle third of the vessel lumen, and a spectral Doppler recording of the flow wave form was made over a period of 15 seconds of quiet respiration. In order to minimise velocity calculation errors from the Doppler shift, the angle of insonance was electronically steered to subtend an angle less than 60^{o} to the axis of flow and the velocities measured were angle corrected by aligning the cursor to the direction of flow. The wave form recording was then analysed for maximum and minimum flow velocities, time averaged maximum velocity (TAMV) over 15 seconds, and for the presence of respiratory and cardiac fluctuation. The degree of flow fluctuation with respiration was calculated by dividing the difference between maximum and minimum velocity by the TAMV, giving the Venous Variation Index (VVI).

These measurements were repeated at the superficial femoral vein proximal to its exit from the adductor canal, and at the popliteal vein, distal to its junction with the short

saphenous tributary. On completion of this protocol, the subject turned to the left lateral and after a 5 minute period to enable haemodynamic stabilisation, the measurements were repeated at the common femoral and popliteal vein. The subject was then invited to adopt the upright position for 5 minutes before the same measurements were again performed.
Liberal application of sonic gel enabled good imaging through the stockings at the superficial femoral and popliteal levels without the need for cutting holes which might have affected the function of the stocking (Mayberry et al 1991).

All the scans were recorded onto video. On screen measurements of vessel diameter and TAMV were later carried out by an observer who was blinded to which, if any, stocking was being assessed. The statistical analysis was performed using analysis of variance with post hoc comparisons using Fishers Protected LSD test. The VVI data was log transformed prior to analysis.

11.3 Results

The application of elasticated stockings had no significant effect on the diameter of the common femoral, or superficial femoral vein. At the popliteal vein, the thigh length T.E.D and Brevet stockings were associated with a significant reduction in vessel diameter in both the supine and left lateral positions (**Table 11.1**). However, no significant increase in flow velocities was demonstrated at this or more proximal points by the T.E.D., Brevet or Seton stocking (**Table 11.2**).

In contrast, altering posture was found to affect both the diameter and flow velocity at the common femoral vein and the popliteal vein. With no stocking applied, adoption of the left lateral position resulted in a decrease in right common femoral vein diameter from 8.9±0.9mm to 5.6±0.6mm ($p<0.05$) and an increase in time averaged maximum flow velocity at the right common femoral vein from 16±4cm/s to 25±4cm/s ($p<0.05$). This effect was reproduced on the application of all three stocking types (**Tables 11.1 and 11.2**) and two factor analysis of variance demonstrated no stocking dependent effect . No significant effects of the adoption of the left lateral position were recorded at the right popliteal vein. As expected, adoption of an upright posture resulted in a significant increase in the diameter of the right common femoral vein and right popliteal vein (8.9±0.9mm to 13.3±0.9mm and 5.9±0.5mm to 8.6±0.5mm respectively ($p<0.05$)). A corresponding fall in time

averaged maximum flow velocity was recorded at both the common femoral and popliteal veins (16±4cm/s to 6±2cm/s and 6±1cm/s to 4±1cm/s respectively ($p<0.05$)). Again, no significant additional effects were noted on the application of stockings **(Tables 11.1 and 11.2)**. **Figure 11a** illustrates the combined data relating posture to right common femoral vein diameter and time averaged maximum flow velocity.

The amplitude of respiratory variation in flow velocity, expressed as the VVI, was not altered by posture in the observed limb. However, the application of stockings was found to alter the VVI at both the common femoral and popliteal vein. In the supine position, the TED stocking produced a significant reduction in VVI at the popliteal vein. On adopting the left lateral position this effect was also produced by the Brevet stocking. Paradoxically, the application of stockings in the left lateral position produced the opposite effect at the common femoral vein, increasing the VVI **(Table 11.3)**.

11.4 Discussion

Although the efficacy of graduated stockings in preventing DVT has been clearly demonstrated, uncertainty remains over their mode of action. Early studies on compression stockings suggested that they acted by increasing the velocity of flow in the venous system of the leg (Makin et al 1969). Later, Sigel, using continuous wave Doppler techniques, demonstrated an increased flow velocity proximal to applied compression stockings (although no measurements were made of flow directly beneath the stocking) and showed compression to reduce the fluctuation effect of respiration on venous flow (Sigel et al 1973). Although these reports suggested the effects were observed at the femoral vein, the techniques employed made distinction between the femoral vein and adjacent vessels (such as the long saphenous vein) difficult.

More recent studies have employed photoplethysmography, a technique which has been shown to yield measurements which correlate with ambulatory venous pressures (Abramowitz et al, 1979), to assess the effects of graduated compression on venous refilling time in subjects with venous incompetence. Many stockings appear not to be effective in improving this parameter of venous function (Cornwall et al, 1987). Duplex Doppler ultrasound, which enables observation of flow characteristics in

individual vessels, has become established as an important tool for investigating venous flow velocity. Recent studies employing duplex ultrasound suggest that graduated compression does not have a significant effect on peak venous flow velocity. Keith et al (1992) used duplex ultrasound to assess whether intermittent pneumatic compression (IPC) and elasticated stockings have additive effects on peak venous flow velocity showed no independent or additional effect of graduated compression stockings on flow velocity, which was increased by intermittent pneumatic compression. Mayberry et al (1991) carrying out a more comprehensive assessment of the effect of elastic compression stockings on deep venous haemodynamics, were unable to demonstrate any significant effect of either 30 to 40 or 40 to 50 torr stockings on ambulatory venous pressure, venous refill time, maximum venous pressure with exercise or amplitude of venous pressure excursion. Further, no significant effects were observed on duplex derived CFV and popliteal vein diameter or peak flow velocities, either in normal healthy subjects, or in patients with chronic deep venous insufficiency. These findings are consistent with our own , as we found no significant increase in flow velocity at either the common femoral, superficial femoral or popliteal levels by the application of any of three stockings investigated. Only the graduated thigh-length stockings (Kendall and Brevet) appeared to reduce vessel diameter but this effect reached statistical significance only at the popliteal vein.

If stockings do not act by increasing peak flow velocity and hence prevent venous stasis then the proven clinical efficacy of compression stockings and the possible synergistic thromboprophylactic effect of using both compression stockings and calf muscle flexion (Scurr et al 1987) demand some other explanation for their effect. Recent studies have shed light on other possible mechanisms. Passive venous dilatation has been shown to occur during operative surgery (Camerota et al, 1989), and may extend to the point where the media can no longer provide support for the endothelial layer. Tears may occur, ultimately exposing thrombogenic subendothelial collagen (Stewart et al 1980). Prevention of venous dilatation may be an important effect of compression, and would explain the adjuvent effect seen when both compression and calf muscle flexion are applied together as post-operative DVT prophylaxis (Scurr et al 1987).

Compression stockings may also act at a molecular level to influence thrombogenesis. Arcleus et al (1995) have shown that application of compression stockings can cause an increase in circulating levels of tissue factor pathway inhibitor (TFPI). This factor,

which has been shown to increase up to 4-fold after heparin administration, plays a key role in the regulation of the extrinsic pathway. Increased activation of the fibrinolytic system has been demonstrated when intermittent pneumatic compression is applied (Guyton et al 1985) although no data relating to compression stockings is available.

Venous valvular incompetence can exacerbate venous stasis and cause venous dilatation with possible endothelial damage. Sarin et al (1992) using real-time ultrasound demonstrated that compression stockings can correct valvular dysfunction possible by allowing coaptation of valvular cusps. However, this effect would not explain the efficacy of compression stockings in postoperative patients who have no demonstrable valve incompetence. It may however, be an important mechanism in pregnancy, since the vessel dilatation which occurs in pregnancy may act to prevent coaptation of the valve cusps, producing valvular incompetence which might be corrected by elastic stockings. This possible effect warrants further study.

The data presented here, while consistent with recent studies, may also be compatible with the seminal studies of Sigel described above. We like other recent workers, have measured peak flow velocities whereas earlier studies reported effects on mean flow velocities. Keith et al (1992) have shown significant compressive pressures to be exerted by elastic stockings on superficial tissues, which may act to divert superficial blood to deeper vessels. This may cause an increase in mean flow velocity without necessarily effecting peak velocity values. The fact that recent data indicates no major effect of compression stockings on peak venous blood flow velocities, however, indicates that other mechanisms of action are likely to be important in the thromboprophylactic function of elastic compression stockings.

Posture may also offer an important adjuvent in prophylaxis. Our results show that adoption of a lateral recumbent position increases flow velocity at the common femoral vein in the non-dependent limb. Although recognised as an important means of increasing venous return in late pregnancy (Ueland & Hansen 1969), this phenomenon has not been previously described in non-pregnant healthy subjects and may offer a potential additional means of thromboprophylaxis.

11.5 Conclusion

The presented data are consistent with recent publications which question the previously held view that compression stockings act to prevent thromboembolism by increasing flow velocity. In addition the evidence for stasis as a cause of thrombosis which relates to the proven efficacy of anti-'stasis' stockings needs to be reviewed. In contrast, flow velocity is shown to be significantly altered by adoption of the lateral recumbent position. This study has also demonstrated the additional effects of graduated support stockings on these postural changes in venous flow, suggesting a potential synergistic role in thromboprophylaxis.

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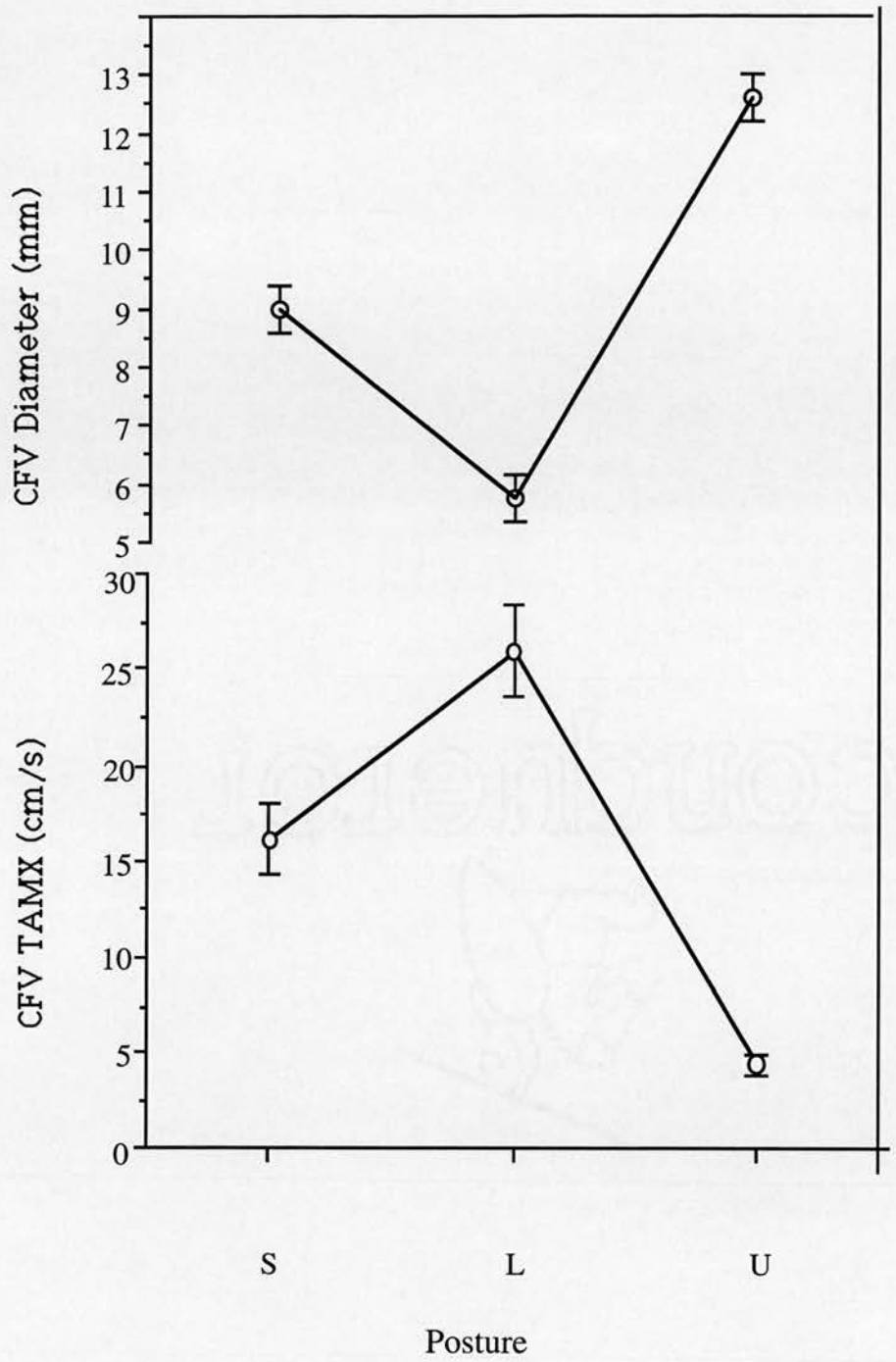

Figure 11a
The mean diameter of the CFV and the mean time average maximum velocity at the CFV are shown in the supine (S), left lateral (L) and the upright (U) positions (bars: SEM). Values are derived from all stocking and 'no stocking' data - see text.
(p = 0 .0001)

Table 11.1 Mean (SEM) vein diameters recorded with varying posture and stocking.

*p<0.05 compared to 'No Stocking'.
†p<0.05 compared to Supine position.

	STOCKING			
DIAMETER (mm)	**No Stocking**	**TED**	**Brevet**	**Tubigrip**
CFV (Supine)	8.9 (±0.9)	8.7 (±0.8)	9.7 (0.±9)	9.3 (±0.8)
CFV (Left Lat.)	5.6 (±0.6)†	6.3 (±0.7)†	5.1 (±0.5)	6.4 (±0.4)†
CFV (Upright)	13.3 (±0.6)†	13.3 (±0.5)†	12.5 (±0.4)†	12.6 (±0.5)†
SFV (Supine)	7.9 (±0.5)	6.8 (±0.5)	7.6 (±0.4)	7.9 (±0.5)
POP (Supine)	5.9 (±0.5)	4.4 (±0.5)*	4.4 (±0.3)*	4.8 (±0.5)
POP (Left Lat.)	5.4 (±0.4)	4.3 (±0.3)*	4.2 (±0.4)*	5.4 (±0.5)
POP (Upright)	8.6 (±0.5)†	8.2 (±0.6)†	9.8 (±0.7)†	7.6 (±0.6)†

Table 11.2 Mean (SEM) venous Time Averaged Mean Velocities (TAMV) recorded with varying posture and stocking.

*p<0.05 compared to supine position.

	STOCKING			
TAMV (cm/s)	**No Stocking**	**TED**	**Brevet**	**Tubigrip**
CFV (Supine)	16(±4)	15 (±2)	23 (±6)	11 (±2)
CFV (Left Lat.)	25 (±4)*	21(±4)*	37 (±6)*	25 (±5)*
CFV (Upright)	6 (±2)*	4 (±1)*	4 (±1)*	4 (±<1)*
SFV (Supine)	6 (±1)	9 (±2)	6 (±1)	6 (± 1)
POP (Supine)	6 (±1)	9 (±2)	6 (±1)	7 (±1)
POP (Left Lat.)	7 (±1)	9 (±1)	8 (±1)	16 (±9)
POP (Upright)	4 (±<1)*	4 (±1)*	3 (±<1)*	4 (±<1)

Table 11.3 Mean (SEM) Venous Variation Index (VVI) recorded with varying posture and stocking.

*p<0.05 compared to 'No Stocking' measurements.

	STOCKING			
DIAMETER (mm)	**No Stocking**	**TED**	**Brevet**	**Tubigrip**
CFV (Supine)	1.24 (±0.09)	1.20 (±0.10)	1.13 (±0.05)	1.42 (±0.24)
CFV (Left Lat.)	0.82 (±0.09)	1.00 (±0.03)*	1.10 (±0.05)*	1.12 (±0.10)*
SFV (Supine)	1.04 (±0.11)	1.51 (±0.12)	1.21 (±0.08)	1.1 (±0.07)
POP (Supine)	1.72 (±0.27)	0.65 (±0.21)*	0.80 (±0.11)	0.96 (±0.07)
POP (Left Lat.)	0.77 (±0.16)	0.34 (±0.08)*	0.32 (±0.10)*	0.86(±0.27)

Plate 11.1 The stockings studied were (from left to right), The Brevet thigh length graduated stocking, the Seton knee length non-graduated stocking and the Kendal Thromboembolic Deterrent (T.E.D) graduated thigh length stocking.

Chapter 12

Conclusions and future research

Summary

In this final chapter the principle findings of the presented work are summarised and their implications for thromboprophylaxis and the diagnosis of pulmonary thromboembolism in pregnancy are discussed. Directions for further related research are then suggested.

12.1 Introduction

While maternal mortality from all causes has fallen dramatically over the past fifty years, death from thromboembolism has shown a slower reduction, and as a result, is now a major contributor to maternal mortality statistics. Its increasing importance in this regard has generated new research interest in the field in relation to pregnancy after a period of some neglect. Since the early 1960s, little new data on the physiology of the deep venous circulation of the legs in pregnancy has been published. Developments in duplex ultrasound technology have offered a non-invasive means to further knowledge in this field. Given the now widespread use of ultrasound as a diagnostic tool for DVT in pregnancy, contemporary information on the normal deep venous anatomy and blood flow characteristics in pregnancy and the puerperium as observed with ultrasound imaging is essential to aid not only our diagnostic ability but also with regard to the physiology and pathology of the deep venous system. The data presented in this thesis go somewhere to addressing this, and may aid duplex and colour Doppler ultrasound diagnostic tools for suspected DVT in pregnancy to move closer to becoming the true 'gold standard' test in pregnancy.

12.2 Summary of Results

A retrospective study of DVT and PTE complicating pregnancy indicated that age over 35 and emergency caesarean section were major risk factors, together increasing the risk of postnatal DVT ten fold. A prospective screening study for as asymptomatic DVT in the puerperium suggested a low incidence in women at low to moderate risk. Ultrasound studies of deep venous flow in the leg showed spontaneous respiratory fluctuation to be maintained throughout pregnancy, while venous flow velocity fell markedly, particularly at the CFV. A corresponding gestational increase in vessel diameter was observed. Adoption of the left lateral position resulted in a marked increase in flow velocity in both the left and right CFV. On the right, this effect was

not confined to late pregnancy. An increase in the amplitude of respiratory fluctuation of flow was noted in the left lateral position. Significant differences in flow velocity between the right and left leg were demonstrated. These persisted in the puerperium. Between the 4th and 42nd postnatal day, the CFV diameter was observed to fall and the flow velocity to increase. Delivery by caesarean section was associated with a lower postnatal flow velocity than vaginal delivery. The application of three types of support stocking in non-pregnant subjects were found to have little detectable effect on flow velocity within the deep venous system of the leg. Adoption of the left lateral position resulted in a marked increase in flow velocity in the right CFV in the same subjects. The above findings have implications for both thromboprophylaxis and diagnosis of DVT, and these are outlined below.

12.3 Implications for Thromboprophylaxis

In addition to stimulating research, recognition of the importance of thromboembolic disease as a cause of maternal death has resulted in the means of treatment and, more importantly, prevention coming under review. The Royal College of Obstetricians and Gynaecologists has recently published guidelines for the prevention of thromboembolism in obseterics and gynaecology (RCOG 1995). This and several other publications have recently come to the attention of practicing obstetricians. Assuming these guidelines are widely instituted, a fall in maternal mortality and long-term morbidity might be hoped for in the coming years. The survey of obstetricians and gynaecologists attitudes to thromboprophylaxis published by Greer and de Swiet (1993) should be repeated in the coming years in order to test what impact recent highlighting of the problem and its methods of prevention might have in the future.

Part of the problem in attempting to influence practice with regard to thromboprophylaxis is the rarity of severe thromboembolic complications as perceived by individual clinicians. This was highlighted as a reason for many obstetricians not using thromboprophylaxis in their practice by Greer and de Swiet (1993). The data presented in chapters 6 and 10 would appear to support this perception as the incidence as a fraction of the total obstetric population appears low. However, if the data from chapter 6 are accepted as indicative of the true incidence of thromboembolic complications in pregnancy and the puerperium, most obstetricians will expect to encounter at least 3 cases of PTE each year. For these individuals, their potentially preventable complication may result in death, or more commonly, years of

pain and discomfort arising from chronic venous insufficiency. Although thromboprophylaxis is not entirely without risk and discomfort, its judicious use may prevent many of these lifethreatening complications arising. While some clinicians adopt thromboprophylactic regimens on all their patients, this approach is unusual, and the data presented in this thesis would tend to support the direction of thromboprophylaxis to women with recognised risk factors.

The data presented in chapter 6 illustrates the importance of certain risk factors. The eliciting of such simple information as age and mode of delivery can alone indicate a ten fold increase in risk of postnatal DVT. The importance demonstrated in chapter 6 of age over 35 as a risk factor for antenatal DVT may help guide the often difficult clinical decision as to when antenatal thromboprophylaxis should be commenced in women who have suffered a previous thromboembolic event. The rise in proportion of women over the age of 35 also demonstrated in chapter 6 might be expected to impact negatively on mortality statistics from thromboembolism unless appropriate thromboprophylactic regimens are widely instituted.

Prevention of pathology requires a knowledge of the relevant physiology. While studies of venous flow in relation to the respiratory and cardiac cycle have been performed before, the situation in the pregnant subject has not been addressed. The pregnant uterus has been shown to affect venous flow from the lower extremities. The data presented in chapter 10 suggest that in addition to reducing venous flow velocity, the gravid uterus can act to alter the waveform characteristics of venous flow when the subject lies supine. This observation may have implications for the initiation of thrombus formation since marked fluctuations in venous flow may serve to dislodge early thrombi and prevent thrombosis occurring. It was therefore interesting to note that in the supine position, advancing gestational age and uterine weight was not associated with either a qualitative or quantitative change (chapter 7) in respiratory fluctuation of flow.

The adoption of the lateral (decubitus) position is recommended in late pregnancy to prevent the 'caval syndrome' as the compressive effect of the gravid uterus in late pregnancy can be removed if the patient adopts a decubitus or left lateral posture. Chapter 11 presents data which indicate that this effect, the increase in flow velocity in the deep veins of the leg on adoption of the decubitus posture, is not confined to late pregnancy. Indeed, a marked effect is demonstrated in non-pregnant women. The studies presented in chapter 7 show marked increases in flow velocity in both the

right and left CFV when the left lateral position is adopted, although this effect appears to occur only after 25 weeks gestation in the left leg. Prior to this, and after delivery, adoption of the left lateral posture appears to result in a slowing in left CFV blood flow velocity. It would therefore appear that the gravid uterus has an important but not a solitary role in producing postural changes in venous flow velocity. The liver lies on the ascending vena cava and is likely to cause a degree of compression which may be reduced on adoption of the left lateral position. The influence of abdominal organs on venous return is likely to be complex, and will vary between individuals. However, the data presented here provides a clear indication that the left lateral position results in increased venous flow velocity in the left and right CFV in mid-late pregnancy, and may therefore prevent DVT forming. A beneficial effect is also likely to result from adoption of the right lateral position although this was not investigated. To demonstrate that adopting the decubitus posture when lying down actually prevents thrombus formation however, would require a very large study (given the incidence of DVT in pregnancy suggested by the data in chapter 6), controlled for other means of thromboprophylaxis. The practical difficulties such a study would present makes it unlikely that it would ever be carried out. However, the data presented in this thesis provides evidence of the likely benefits of the left lateral position as a painless, safe and cheap means of thromboprophylaxis.

The findings relating to differences in venous flow velocity and fluctuation between the left and right leg were consistent with the clinically observed preponderance of left sided DVT. These data, when considered with the postural effects discussed above may suggest that any thromboprophylactic effect of the decubitus position might be enhanced if the right lateral position was adopted as the increase in venous flow velocity would be more marked in the left CFV, the more common site of thrombus formation. However, further studies are required to address this.

The puerperium is a period of particular risk. Operative delivery is associated with a higher incidence of DVT (chapter 8) and this has been thought to be primarily due to prolonged inactivity and trauma to the vessels. The data presented in chapter 7 suggests that flow velocity may also be reduced after caesarean section. The reason for this is not clear, but may it may be associated with the lack of muscle pump activity in women recovering from caesarean delivery. Early mobilisation and the use of calf compression boots would therefore seem an appropriate way of preventing DVT in this group. The data presented in chapter 8 has implications for the period for which postnatal thromboprophylaxis should be used. It would seem that by the 42nd

day most of the alterations in the deep venous system of the leg observed in pregnancy have returned to resemble these observations made in early pregnancy. The current tendency to maintain postpartum thromboprophylaxis for 6 weeks would appear appropriate.

The work presented in chapter 11 relates to the most important current method of physical thromboprophylaxis, graduated compression stockings. This study was limited to non-ambulant, but fit and healthy subjects, and therefore did not assess the function of stockings within the normal clinical context of their use. Nevertheless, their moderate effects on venous flow was in marked contrast to those observed on the adoption of the decubitus posture. As discussed in chapter 11, their mode of action may relate more to the support they provide to the vessels resulting in an enhanced muscle pump action during ambulation ore calf muscle exercises in non-ambulant patients. This hypothesis could be studied by repeating the presented study during controlled flexion and extension of the foot as can be achieved with passive calf muscle flexion apparatus normally employed as a means of physical thromboprophylaxis.

12.4 Implications for Diagnosis

The data relating to gestational changes in vessel diameter presented in chapter 7 may provide some explanation for the observed tendency in pregnancy for DVT to originate in the ileofemoral region rather than in the soleal sinuses of the calf, as is believed to occur outwith pregnancy. The marked increase in CFV diameter, greater than that observed in more distal vessels has implications for ultrasound diagnosis of DVT. Duplex Doppler ultrasound is of reduced sensitivity in small vessels such as the calf veins. While colour Doppler ultrasound makes examination of the calf veins possible (Baxter et al 1990) the procedure is time consuming and technically difficult. In practice ultrasound examination is normally confined distally to the popliteal vein. Even in relatively inexperienced hands, the identification of the CFV is possible with simple real-time ultrasound alone. The marked enlargement of the CFV demonstrated with advancing gestation serves to make such an examination easier. However, since marked dilatation of the CFV is in itself suggestive of acute DVT within, knowledge of the normal appearances of the vessel in pregnancy is required. Occlusion of vessel upon application of gentle compression can easily clarify the situation. This simple technique requires no special expertise. Since many maternity units remain on separate sites from full radiological services, those training in or practising obstetric

ultrasound should learn these basic techniques, as particularly out of hours, the decision to withhold or commence anticoagulation in a pregnant woman need not be deferred unnecessarily.

When doubt remains over the diagnosis, other ultrasound measures such as augmentation may clarify whether or not occlusion of the vessel is present as discussed in chapter 1. The presence of respiratory fluctuation in flow can indicate proximal patency of the vessel, and this may be of particular value when proximal segments of the ileofemoral system and vena cava are masked by the gravid uterus. The presented data showing that respiratory fluctuation barely alters through pregnancy is important in this regard and may aid the accurate diagnosis or exclusion of DVT in late pregnancy. The enhancing of the amplitude of respiratory fluctuation demonstrated on adoption of the left lateral position may also be utilised when doubt remains over the patency of vessels proximal to the segment under scrutiny.

The role of ultrasound in screening for DVT in asymptomatic patients remains unclear. As discussed in chapter 10, ultrasound is potentially a useful means of screening because of its safety and noninvasiveness but its accuracy in non-pregnant subjects is not certain. The screening study presented represents the first such study of the puerperium to be published. However, in terms of the probable incidence of postnatal DVT (chapter 6) it is too small to assess the true incidence of subclinical DVT in women at high risk. A large screening study of high risk subjects may impact on thromboprophylaxis guidelines if the true incidence of objectively diagnosed DVT was observed to differ from that derived from the data presented in chapter 6. A full ultrasound examination is time-consuming and requires a certain degree of expertise, and the resources required to offer screening to all high risk women are unlikely to become available.

12.5 Future Research

In addition to those areas already highlighted as meriting further research, certain other questions should be addressed. The recognition of activated protein C resistance as a form of thrombophilia has led to the study of its prevalence in subjects who have sustained a thromboembolic complication. Both in this group and the general population, it would appear to be the most common inherited thrombophilia. Studies are now required to assess the incidence of activated protein C resistance in the

pregnant population. Screening studies may identify women at particular risk, and enable the direction of thromboprophylaxis to a previously unrecognised risk group. Those screening positive for APC resistance could be offered duplex Doppler ultrasound screening for DVT in the antenatal and postnatal period, and the incidence of subclinical DVT in group determined. This study should be carried out as part of a larger ultrasound screening study of high risk women in the puerperium, as already described.

The ultrasound studies of venous physiology presented would have benefited from assessing a larger subject group. Information might be considered lacking as to the true state of the deep veins of the leg outwith pregnancy, as the presented studies used subject measurements at 6 postnatal weeks as their own non-pregnant controls. However, further resolution in the observed changes in the deep venous system may continue beyond 6 weeks. There is scope therefore, for a repeat of the serial ultrasound study of pregnancy, with larger numbers, a larger subgroup of patients with a previous history of DVT, and measurements made at a longer interval after pregnancy to indicate more clearly the non-pregnant state.

The non-invasive nature of ultrasound studies offer the scope for intrapartum examination of the deep venous system. Intraoperative venous dilatation is a well described phenomenon (Camerota et al 1991), and may be demonstrable to varying degrees in women undergoing spontaneous vaginal, forceps or caesarean delivery. Intrapartum studies may shed further light on the reasons behind the observed increase in DVT and PTE in those undergoing operative delivery.

The ultrasound techniques described lend themselves to studies outwith pregnancy. The development of laparoscopic surgery has been hailed as beneficial to patients in many ways, not least because they are found to mobilise earlier, with a presumed reduced risk of postoperative thrombosis. Laparoscopic surgery requires the use of high intra-abdominal pressures as CO_2 is used to lift the anterior abdominal wall off the organs of surgical interest. These pressures may act to compress the intrabdominal veins, and thereby impede the velocity of venous flow in the deep leg veins. On the other hand the moderate elevation of the legs required for laparoscopic surgery may have a beneficial effect on flow velocity. Ultrasound techniques could readily be employed to ascertain whether laparoscopic surgery might result in a greater intra-operative thrombotic risk than conventional surgery.

At present, ultrasound techniques for diagnosing DVT continue to be used more widely in pregnancy. The data presented in this thesis may serve to enhance its utility in this important aspect of pregnancy care.

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