bjh review

Hormones and pregnancy: thromboembolic risks for women

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Summary

During their lifetimes, women face several unique situations with an increased risk of venous thromboembolism (VTE). Doctors in a variety of specialties must advise women on the risks of oral contraceptives (OC), hormone replacement or pregnancy. Modern 'low dose' OC are associated with a three to sixfold increased relative risk of VTE. Hormone replacement and selective oestrogen receptor modulators confer a similar two to fourfold increase in thrombotic risk. However, because the baseline incidence of thrombosis is higher in older postmenopausal women, the absolute risk is higher than in younger OC users. The risk of venous thrombosis is six to 10-fold higher during pregnancy than in non-pregnant women of similar age. Thrombophilic disorders increase the thrombotic risk of OC, hormone replacement and pregnancy, especially in women with homozygous or combined defects. This review focuses on recent data estimating the thrombotic risk of hormonal therapies and pregnancy in women with and without other thrombotic risk factors.

Keywords: thrombophilia, thromboembolism, pregnancy, hormone replacement therapy, factor V Leiden.

Oral contraceptives

An association between OC and VTE was first reported in 1961 when a nurse developed bilateral pulmonary emboli shortly after starting oestrogen for endometriosis (Jordan, 1961). Since OC were first approved for contraception in 1959, the specific types of oestrogen and progestin have changed, and their doses have been reduced. The gradual decrease in oestrogen dose has not resulted in a consistent reduction in thrombotic risk (Bloemenkamp *et al*, 1995; Rosendaal *et al*, 2002a). Multiple studies in the 1990s showed that modern 'low dose' OC (<50 μg ethinyl oestradiol) are associated with a three to sixfold increased relative risk of VTE (World Health Organization, 1995). The risk is highest during the first year of use, but persists with prolonged use (Herings *et al*, 1999; Bloemenkamp *et al*, 2000). However, because the baseline risk of VTE is low in young healthy women (an estimated one VTE per 10 000 women per year), the absolute risk remains low (three to four VTE per 10 000 women per year using OC) (Vandenbroucke *et al*, 1994, 2001). Nevertheless, because OC are so widely used, they contribute to a large proportion of VTE in this age group.

Although the prothrombotic effects of oestrogen have been recognized for decades, the progestin component in OC was not thought to affect thrombotic risk. However, since 1995, the majority of a large number of studies showed that OC containing one of the so-called third-generation progestins, desogestrel or gestodene, have a significantly higher risk of VTE than second-generation preparations containing levonorgestrel with the same dose of oestrogen (Bloemenkamp *et al*, 1995; Jick *et al*, 1995, 2000; Herings *et al*, 1999) A meta-analysis found an overall 1·7-fold increase in risk, and a threefold higher risk among first-time users (Kemmeren *et al*, 2001). Despite initial controversy, most experts now agree that women using third-generation OC have a twofold higher thrombotic risk than those using second-generation preparations, and a six to ninefold higher risk than non-users (World Health Organization, 1998a). The risk is highest during the first year of use, with an incidence as high as one in 1000 women (Herings *et al*, 1999). In support of these clinical observations, multiple biochemical studies comparing OC that differed only in the progestin component showed that formulations containing desogestrel or gestodene have significantly more pronounced effects on procoagulant, anticoagulant and fibrinolytic pathways (Rosing *et al*, 1997, 1999; Tans *et al*, 2000; Mackie *et al*, 2001). Prothrombotic effects on anticoagulant pathways include the development of a greater acquired resistance to activated protein C and a more pronounced decrease in protein S levels than seen with second-generation formulations. Plasma from women using third-generation OC shows an acquired resistance to activated protein C comparable with that found in women with factor V Leiden (FV Leiden) (Rosing *et al*, 1997). The observation that resistance to activated protein C in the absence of FV Leiden is an independent risk factor for VTE suggests it may contribute to thrombosis in OC users (Rodeghiero & Tosetto, 1999; de Visser *et al*, 1999). However, whether or not the prothrombotic haemostatic effects of third-generation progestins explain the increased clinical risk is unknown. The thrombotic risk of

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OC containing the newer progestins, cyproterone and drospirenone is less well-defined, although one study found a three to fourfold higher risk than those containing levonorgestrel (Vasilakis-Scaramozza & Jick, 2001).

A progestin alone is a popular alternative contraceptive for high-risk women, despite only limited observational data on thrombotic risk. Two case–control studies found no significant increase in risk when an unopposed progestin was used for contraception, although there was a non-significant trend in one study (World Health Organization, 1998b; Vasilakis *et al*, 1999). In contrast, two studies found a five- to sixfold increased risk when higher doses of progestin were used for other therapeutic indications, primarily menstrual disorders (Poulter *et al*, 1999; Vasilakis *et al*, 1999). All three studies excluded women with a prior history of VTE or other known risk factors. Thus, although unopposed progestin contraception has a much lower thrombotic risk than oestrogen-containing formulations, the risk in women with thrombophilia and/or prior thrombosis is unknown.

A variety of acquired and inherited risk factors interact with OC to increase the risk of VTE. For example, the combination of obesity and OC is associated with an overall 10-fold increase in thrombotic risk (Abdollahi *et al*, 2003). A recent case–control study found that the combination of OC and air travel conferred an approximately 14-fold increased risk of VTE, suggesting a multiplicative interaction between these two risk factors (Martinelli *et al*, 2003a). Thrombophilic defects are now identified in >50% of patients presenting with an oestrogen-related VTE (Table I). A case–control study found a 20–30-fold higher risk of a first VTE in women with inherited thrombophilia who used second or third-generation OC [odds ratio (OR) = 63·3 and 52·5, respectively] than in thrombophilic non-users (OR = 2·6), although the confidence intervals were wide for these risk estimates (Andersen *et al*, 1998).

Factor V Leiden is a genetic disorder characterized by an impaired anticoagulant response to activated protein C. It is due to a point mutation in the factor V gene, which results in a single amino acid change that destroys a cleavage site for activated protein C. The mutant FV Leiden protein is inactivated at a 10-fold slower rate than normal, and persists longer in the circulation, resulting in increased thrombin generation and a prothrombotic state (Press *et al*, 2002). A heterozygous mutation is found in 5–8% of the general population, and is associated with a four to eightfold increase in relative venous thrombotic risk. Homozygous FV Leiden occurs in one in 1600 individuals and confers an 80-fold increase in risk. The mutation is found primarily in Caucasians of European descent, and occurs only rarely in minority Americans. FV Leiden is found in 20–35% of women who develop VTE on OC (Hellgren *et al*, 1995; Hirsch *et al*, 1996; Schambeck *et al*, 1997). The combination of OC and most thrombophilic disorders has a supra-additive effect on overall thrombotic risk. In the Leiden Thrombophilia study, OC use was associated with a fourfold increased risk of VTE. A heterozygous FV Leiden mutation conferred a sevenfold increase in risk. The risk was increased 35-fold in women with both risk factors, indicating a multiplicative, rather than an additive, effect on overall thrombotic risk (Vandenbroucke *et al*, 1994). Heterozygous FV Leiden carriers using OC containing a third-generation progestin had a 50-fold higher risk of VTE than unaffected non-users (Bloemenkamp *et al*, 1995). The overall thrombotic risk is increased more than 100-fold in homozygous carriers who use OC (Vandenbroucke *et al*, 1994). The adverse interaction between FV Leiden and

Table I. Prevalence of thrombophilic disorders and thrombotic risk of OC.

Thrombophilic disorder	Prevalence in general population (%)	Prevalence in women with VTE on OC (%)	Risk of OC-associated VTE (OR)*	References
FVL	5–8	20–35	20–41	Hirsch *et al* (1996), Legnani *et al* (2002a), Schambeck *et al* (1997), Martinelli *et al* (1999)
PGM	3	14	16–59	Martinelli *et al* (1999), Legnani *et al* (2002b), Cosmi *et al* (2003)
FVL/PGM (double heterozygotes)	0·1	6	17–86	Emmerich *et al* (2001), Legnani *et al* (2002a), Cosmi *et al* (2003)
AT deficiency	0·04	1–2	NA	Santamaria *et al* (2001), Cosmi *et al* (2003)
PC deficiency	0·3	4	NA	Santamaria *et al* (2001), Cosmi *et al* (2003)
PS deficiency	0·1	2	NA	Santamaria *et al* (2001), Cosmi *et al* (2003)
High FVIII levels†	10	NA	10	Bloemenkamp *et al* (1999)
High prothrombin levels‡ (without PGM)	17–20	NA	3–10	Legnani *et al* (2002b), Poort *et al* (1996), van Hylckama Vlieg and Rosendaal (2003)

OC, oral contraceptives; VTE, venous thromboembolism; FVL, factor V Leiden; PGM, prothrombin gene mutation; AT, antithrombin; PC, protein C; PS, protein S; FVIII, factor VIII; NA, not available.

*Risks relative to non-users of OC without thrombophilia.

†>150% of normal activity.

‡>115–121% of normal activity.

OC was confirmed in other studies with OR ranging from 10 to 41 for the combination of both risk factors (Rintelen *et al*, 1996; Martinelli *et al*, 1999; Spannagl *et al*, 2000; Legnani *et al*, 2002a). The synergistic interaction between FV Leiden and OC probably reflects the fact that both risk factors result in resistance to activated protein C. Plasma from heterozygous FV Leiden carriers using OC showed profoundly reduced sensitivity to activated protein C, in the range of that of homozygous mutation carriers (Rosing *et al*, 1997).

A single nucleotide substitution (G20210A) in the 3′ untranslated region of the prothrombin gene is associated with elevated plasma prothrombin levels and a two to fourfold increased risk of VTE. The mutation increases the efficiency and accuracy of processing of the 3′ end of the mRNA, resulting in an accumulation of mRNA and increased prothrombin protein synthesis (Gehring *et al*, 2001). The prothrombin gene mutation, found in 2–3% of the general population, occurs primarily in Caucasians, and is rare in individuals of African, Asian or native American descent. Several studies suggested the combination of OC and the prothrombin gene mutation has a multiplicative effect on overall thrombotic risk, with OR ranging from 16 to 59 (Martinelli *et al*, 1999; Legnani *et al*, 2002a). In another study, the prothrombin gene mutation and OC increased the risk of cerebral vein thrombosis by 10- and 20-fold, respectively. The combination of both risk factors increased the risk of this rare but potentially life-threatening complication by 150-fold, consistent with a supra-additive effect on thrombotic risk (Martinelli *et al*, 1998). The biochemical basis of this interaction may involve the increase in prothrombin levels with both OC and the prothrombin gene mutation (Poort *et al*, 1996; Kluft & Lansink, 1997). Elevated prothrombin levels increase the risk of VTE independently of the mutation and also potentiate the thrombotic risk of OC (Poort *et al*, 1996; Legnani *et al*, 2002b). Because of the relatively high prevalence of FV Leiden and the prothrombin gene mutation in the general population, heterozygosity for both mutations affects approximately one in 1000 individuals. Double heterozygous carriers who use OC have an estimated 17–86-fold increase in overall thrombotic risk, based on the limited available data. (Emmerich *et al*, 2001; Legnani *et al*, 2002a).

Deficiencies of the natural anticoagulant proteins C and S and antithrombin are much less common, with a combined prevalence of <1–2% of the population. Because of their rarity and the tendency to avoid hormonal therapy in affected women, their interaction with OC is not well defined. Women with antithrombin, protein C or protein S deficiency had a five to sixfold higher thrombotic risk during OC use than non-deficient relatives in retrospective family studies (van Boven *et al*, 1999; Simioni *et al*, 1999). The incidence of VTE in antithrombin deficient women who used OC was as high as 28%/year, compared with only 3·4%/year for deficient non-users (Pabinger & Schneider, 1994). In a study of 52 women from a single kindred, 42% of protein C-deficient women using OC developed VTE, compared with none of the unaffected women (Trauscht-Van Horn *et al*, 1992).

A high factor VIII (FVIII) level is a common risk factor for VTE, conferring a four to fivefold increase in risk in several studies (Koster *et al*, 1995). Women with a history of OC-associated VTE had significantly higher baseline FVIII levels than controls, suggesting that high FVIII levels define a population at increased risk (Bloemenkamp *et al*, 1998). In the Leiden Thrombophilia Study, OC users with FVIII levels >150% of normal had a 10-fold higher risk of VTE than women without either risk factor, suggesting an additive effect on overall thrombotic risk (Bloemenkamp *et al*, 1999). In contrast, the combination of OC and high levels of prothrombin, FV or factor XI had a supra-additive effect on thrombotic risk with OR ranging from 10 to 13 (van Hylckama Vlieg & Rosendaal, 2003). OC users with hyperhomocysteinaemia had a 20-fold higher risk of cerebral vein thrombosis than women without these risk factors (Martinelli *et al*, 2003b).

Thrombophilic women develop thrombotic complications sooner, with the highest risk during the first year of OC use. In one study, the risk was 20-fold higher during the first 6 months, and 10-fold higher during the first year than during later years of use (Bloemenkamp *et al*, 2000). Despite the marked increase in relative risk, the absolute incidence may still be low, due to the rarity of VTE in healthy young women. For example, the combination of FV Leiden and OC is estimated to result in an additional 28 VTE events per 10 000 women/year (Vandenbroucke *et al*, 1994).

Conclusions

Oral contraceptives should be avoided in women with a history of VTE with or without thrombophilia as a prior history is the strongest risk factor for recurrence. Women with asymptomatic thrombophilia and no history of VTE should be counselled on the risks and encouraged to consider alternative forms of contraception. However, the risk of OC will vary in this group. For example, the risk is much higher in an antithrombin-deficient woman starting OC than in a long-time OC user incidentally discovered to have FV Leiden. If an asymptomatic woman with thrombophilia elects to use OC, third-generation formulations should be avoided, due to their higher thrombotic risk. Whether or not the newer transdermal preparation will have a lower risk of VTE is unknown. Unopposed progestin contraception has a much lower thrombotic risk than oestrogen-containing OC, but the risk in women with thrombophilia or a history of VTE is unknown, and is probably higher than in women without these risk factors.

Hormone replacement therapy

Until recently, indications for hormone replacement therapy (HRT) included relief of menopausal symptoms and primary and secondary prevention of cardiovascular disease and osteoporosis. With the recent evidence of a lack of cardiovascular

benefit, and alternative therapies for osteoporosis, HRT is no longer prescribed for the long-term prevention of disease. The dose of oestrogen in HRT is approximately one-fifth the dose found in low-dose OC, and increases postmenopausal oestradiol levels in the lower premenopausal range. These 'physiological' replacement doses of oestrogen were previously thought to have little or no effect on thrombotic risk. However, since 1996, a large number of observational studies consistently found a significant two to fourfold increased relative risk of VTE in current HRT users compared with non-users (Daly *et al*, 1996; Grodstein *et al*, 1996; Jick *et al*, 1996; Perez Gutthann *et al*, 1997; Varas-Lorenzo *et al*, 1998; Hoibraaten *et al*, 1999). Most studies found the highest risk during the first year of use, with OR ranging from 2 to 7 (Daly *et al*, 1996; Grodstein *et al*, 1996; Perez Gutthann *et al*, 1997; Varas-Lorenzo *et al*, 1998; Hoibraaten *et al*, 1999). There is no consistent evidence of a difference in the thrombotic risk of unopposed and combined oestrogen/progestin therapy.

Transdermal HRT preparations avoid the 'first pass' effect on hepatic protein synthesis, but their thrombotic risk has not been well studied. Accumulating biochemical data suggest transdermal oestrogen has minimal prothrombotic effects on procoagulant and anticoagulant pathways (Lowe *et al*, 2001; Post *et al*, 2003). Oral oestrogen replacement increases the levels of multiple clotting factors and markers of coagulation activation and results in an acquired resistance to activated protein C (Scarabin *et al*, 1997; Lowe *et al*, 2001; Oger *et al*, 2003). In contrast, transdermal HRT has little or no effect on these haemostatic parameters (Scarabin *et al*, 1997; Lowe *et al*, 2001; Oger *et al*, 2003; Post *et al*, 2003). The thrombotic risk of transdermal (OR 2·0–2·1) and oral HRT (OR 2·1–4·6) was similar in two case–control studies, although both were limited by the small number of women using the transdermal route (Daly *et al*, 1996; Perez Gutthann *et al*, 1997). Another study, in which 80% of HRT users used a transdermal preparation, found a similar overall twofold increase in thrombotic risk, but the risk of transdermal therapy was not specifically defined (Varas-Lorenzo *et al*, 1998). In a recent case–control study, oral HRT was associated with a fourfold higher risk of a first spontaneous VTE than transdermal preparations. Women using transdermal HRT had no increase in risk compared with non-users (Scarabin *et al*, 2003). The study excluded women with a previous thrombosis or other predisposing factors. Thus, the risk of transdermal HRT in women with a history of VTE and/or thrombophilia is unknown, and there have been no prospective randomized trials directly comparing the risks of oral and transdermal formulations.

In addition to the observational studies, three large randomized placebo controlled trials included VTE as a secondary outcome. In the Heart and Oestrogen/Progestin Replacement Study (HERS), 2763 postmenopausal women with coronary heart disease were randomized to combined oestrogen/progestin HRT or placebo. Although there was no significant difference in the rate of cardiovascular events, HRT users had a threefold higher risk of both deep venous thrombosis and pulmonary embolism, with the highest risk during the first 2 years of use (Hulley *et al*, 1998). In multivariate analysis, the risk was increased five to sixfold during the first 90 days after surgery or other hospitalization, and remained increased for at least 30 days after HRT was stopped (Grady *et al*, 2000). A subsequent analysis of the HERS data suggested the use of statins reduced the overall risk of VTE by >50%, and also attenuated the thrombotic risk of HRT (Herrington *et al*, 2002a). Women who used both HRT and statins had an overall risk only slightly higher than the baseline risk in women on placebo alone. The biochemical basis of the statin effect is unknown, although a variety of effects on haemostasis have been reported (Rosenson & Tangney, 1998).

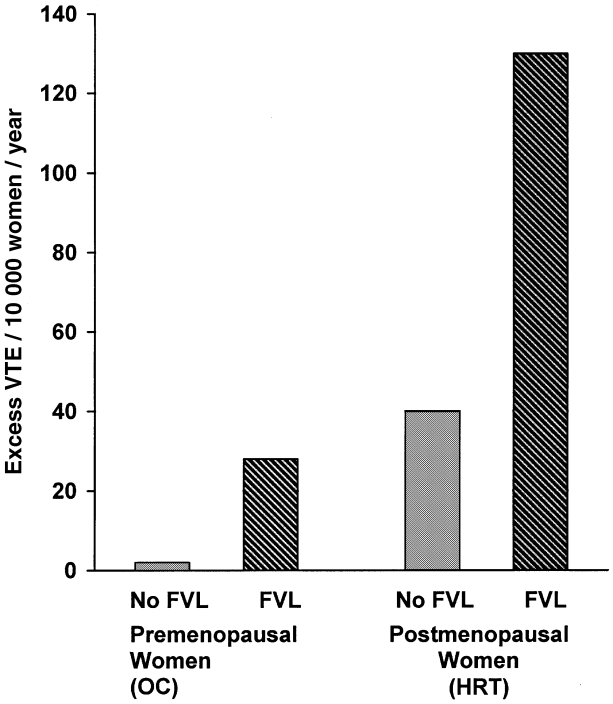

Fig 1. Estimated excess venous thromboembolism (VTE) events attributable to oral contraceptive (OC) use in premenopausal women with and without factor V Leiden (FVL) and to hormone replacement therapy (HRT) in postmenopausal women with coronary heart disease with and without FVL. Estimates of excess VTE events assume a baseline incidence of 1 VTE/10 000 women/year in premenopausal women and 23 VTE/10 000 women/year in postmenopausal women without either risk factor (Vandenbroucke *et al*, 1994; Grady *et al*, 2000; Herrington *et al*, 2002b).

The threefold increase in relative thrombotic risk with HRT is similar to the three to fourfold increased risk observed with OC. However, because of the higher baseline incidence of VTE in older postmenopausal women, the absolute risk in the HERS trial (40 extra VTE events/10 000 HRT users/year) was 20-fold higher than in younger premenopausal women using OC (two extra VTE/10 000 women/year) (Fig 1) (Vandenbroucke *et al*, 1994; Grady *et al*, 2000). Thus, despite the lower oestrogen dose, the excess number of thrombotic events attributable to HRT is much higher.

The Women's Health Initiative compared oestrogen/progestin replacement with placebo in 16 608 healthy postmenopausal women (Rossouw *et al*, 2002). The trial was stopped prematurely after an average 5 years follow-up due to an increased risk of invasive breast cancer and an unfavourable overall risk/benefit ratio. HRT users had a twofold higher relative risk of both deep venous thrombosis and pulmonary embolism, corresponding to an absolute risk of approximately 20 extra VTE/10 000 women using HRT/year. The risk was highest in the first year of use (risk ratio 3·6), but remained twofold higher during later years. A parallel trial compared unopposed oestrogen and placebo in 10 739 postmenopausal women with prior hysterectomy. Women randomized to oestrogen alone had an increased risk of deep venous thrombosis and pulmonary embolism, although the difference was statistically significant only for deep venous thrombosis (hazard ratio 1·47) (Anderson *et al*, 2004). A recent meta-analysis, which pooled the data from 12 studies, found that current HRT use was associated with a similar twofold increased thrombotic risk. The six studies that reported risk based on duration of HRT use found the highest risk in the first year (relative risk 3·49) compared with a relative risk of 1·91 after 12 months (Miller *et al*, 2002).

Most of the observational studies and the HERS trial excluded women with a history of VTE or other thrombotic risk factors. There is limited data estimating the risk of HRT in women with prior VTE and/or thrombophilia. A small, randomized trial comparing HRT and placebo in 140 women with a history of VTE was stopped early due to the higher recurrence rate with HRT (Hoibraaten *et al*, 2000). Recurrent VTE occurred in 10% of the HRT group (all within the first year), compared with 2·7% of women taking placebo. In the Women's Health Initiative, HRT was associated with a fivefold increased risk in the subgroup of 141 women with a history of VTE, compared with a twofold higher risk in women with no prior thrombotic history (Rossouw *et al*, 2002). Three recent case–control studies found that postmenopausal FV Leiden carriers who use HRT have a 13–16-fold higher risk of VTE than unaffected non-users, suggesting a supra-additive effect on overall thrombotic risk (Lowe *et al*, 2000; Herrington *et al*, 2002b; Rosendaal *et al*, 2002b). The estimated absolute incidence of VTE in women with coronary heart disease and FV Leiden who used HRT was 150 VTE events/10 000 women/year compared with 20 VTE/10 000 women/year for non-users with a normal genotype (Herrington *et al*, 2002b). (Fig 1) There are no data on the risk of HRT in women with other thrombophilic disorders, but based on their interaction with OC, the overall risk is likely to be high.

Selective oestrogen-receptor modulators

Selective oestrogen-receptor modulators (SERMs) are chemically diverse non-steroidal compounds which exert selective agonist or antagonist effects on various oestrogen target tissues (Riggs & Hartmann, 2003). The limited available data suggest the thrombotic risk of SERMs is similar to the risk of HRT. Tamoxifen treatment of breast cancer was associated with a sevenfold increased risk of idiopathic VTE (Meier & Jick, 1998). Several studies reported a higher incidence of VTE in women randomized to adjuvant tamoxifen compared with placebo (Fisher *et al*, 1989; McDonald *et al*, 1995). The risk is significantly higher when adjuvant tamoxifen is combined with chemotherapy than when used alone (Pritchard *et al*, 1996).

Tamoxifen was associated with a two to threefold increased risk of VTE in three of the four prospective randomized trials for breast cancer prevention, with VTE occurring more frequently in women over 50 years of age (Fisher *et al*, 1998; Veronesi *et al*, 1998; Cuzick *et al*, 2002). In one study, nearly 50% of the VTE events in the tamoxifen group (including three fatal events) occurred within 3 months of major surgery or other prolonged immobilization (Cuzick *et al*, 2002; Duggan *et al*, 2003). Women randomized to tamoxifen who required major surgery or immobilization had a 12-fold higher thrombotic risk than women without either risk factor (Duggan *et al*, 2003). The increased thrombotic risk in healthy women excludes the potential confounding effects of malignancy, chemotherapy and surgery as the cause of the risk observed in breast cancer treatment trials. In the Multiple Outcomes of Raloxifene Evaluation Study, postmenopausal women randomized to raloxifene had a threefold higher risk of VTE than those taking placebo, with an estimated absolute risk of one VTE/155 women using raloxifene for 3 years (Cummings *et al*, 1999). The risk of VTE in women with thrombophilia who use SERMs is unknown, but is likely to be higher (Weitz *et al*, 1997). In the International Breast Cancer Intervention Study, none of the women who developed VTE carried FV Leiden or the prothrombin gene mutation, although only one-third of cases had blood samples available for testing (Duggan *et al*, 2003).

Conclusions

Hormone replacement therapy and SERMs are associated with a two to fourfold increased relative risk of VTE in healthy postmenopausal women, but the risk is higher in women with other thrombotic risk factors. The recent evidence of a lack of cardiovascular benefit and an unfavourable overall risk/benefit profile strengthens the recommendation to avoid HRT in women with a history of VTE or thrombophilia. For women who require short-term HRT for severe menopausal symptoms, low-dose transdermal preparations may have a lower thrombotic risk. The preliminary evidence of a higher risk after surgery suggests HRT and SERMs should be stopped at the time of hospitalization or other prolonged immobilization, with consideration of prophylactic anticoagulation (Mosca *et al*, 2001). Prophylactic anticoagulation may also be considered for selected women with thrombophilia and/or a history of thrombosis who require tamoxifen for breast cancer treatment. The decision requires an assessment of the risks

and benefits of anticoagulation in each individual case. However, although warfarin is probably protective in high-risk women who use HRT or SERMs, this has not been confirmed in clinical trials.

Pregnancy and venous thromboembolism

Venous thromboembolism occurs in approximately one in 1000 pregnancies, and pulmonary embolism is a leading cause of maternal death (McColl *et al*, 1997; Lindqvist *et al*, 1999a). The risk of VTE is six to 10-fold higher during pregnancy than in non-pregnant women of similar age (Eldor, 2001; Martinelli, 2001). The frequency of VTE is similar in all three trimesters, but higher during the postpartum period (Ginsberg *et al*, 1992; Martinelli *et al*, 2002). In a retrospective study of 72,000 pregnancies, the incidence of VTE was three to eightfold higher postpartum than antepartum (McColl *et al*, 1997). A meta-analysis found that >50% of VTE during pregnancy occurred in the first two trimesters, with a 15-fold higher risk during the postpartum period (Ray & Chan, 1999).

Pregnancy is a prothrombotic state with all three components of Virchow's triad. Venous stasis results from both a hormonally induced decrease in venous tone and obstruction of venous flow by the enlarging uterus. Endothelial damage in pelvic veins can occur at the time of delivery or from venous hypertension. Normal pregnancy initiates a hypercoagulable state reflected by increased levels of several procoagulant factors, a progressive fall in protein S levels, an acquired resistance to activated protein C and impaired fibrinolysis (Comp *et al*, 1986; Bremme *et al*, 1992; Clark *et al*, 1998; Kjellberg *et al*, 1999). There is biochemical evidence of the activation of coagulation throughout normal pregnancy (Clark *et al*, 1998; Eichinger *et al*, 1999). All of these changes reflect the physiological preparation for the haemostatic challenge of delivery.

Risk factors for VTE during pregnancy include advanced maternal age, Caesarean section, obesity, immobilization, multiple gestations, prior thrombosis and thrombophilia. Women with a history of VTE have a higher risk of recurrence during pregnancy, but recurrence rates range from 0% to 15% in different studies, making it difficult to decide which women require prophylactic anticoagulation in subsequent pregnancies. A retrospective study of 109 women with a history of VTE found a threefold increased risk of recurrence during pregnancy (Pabinger *et al*, 2002). The risk is probably higher in women with a prior unprovoked event and/or other coexisting inherited or acquired thrombotic risk factors.

A recent prospective study evaluated the safety of withholding anticoagulation during pregnancy in a large group of women with a history of a single VTE (Brill-Edwards *et al*, 2000). Anticoagulation was not given during pregnancy, but all women received warfarin for 4–6 weeks postpartum. The overall rate of recurrent VTE during pregnancy was 2·6%. In a subgroup analysis, women with a prior unprovoked event and a thrombophilic disorder had the highest recurrence rate (20%). Women with either thrombophilia or a prior

Table II. Thrombophilic disorders and risk of pregnancy-associated VTE.

Thrombophilic disorder	Prevalence in women with pregnancy-associated VTE (%)	Risk of pregnancy-associated VTE (OR)*	Probability of pregnancy-associated VTE† (VTE/1000 pregnancies)	References
FVL (heterozygous)	20–46	5–16	2–3	Bokarewa *et al* (1996), Hirsch *et al* (1996), Hallak *et al* (1997), Gerhardt *et al* (2000, 2003), Lensen *et al* (2000a), McColl *et al* (1997), Meglic *et al* (2003)
FVL (homozygous)	2–4	20–40	40	Gerhardt *et al* (2000, 2003), Martinelli *et al* (2001)
PGM	6–26	3–15	3–5	Gerhardt *et al* (2000, 2003), Martinelli *et al* (2002), Meglic *et al* (2003)
FVL/PGM (double heterozygotes)	7–9	9–107	10–50	Gerhardt *et al* (2000, 2003), Martinelli *et al* (2001)
AT deficiency‡	1–19	7–64	4–333	McColl *et al* (1997), Gerhardt *et al* (2000, 2003)
PC deficiency§	2–14	4–7	1–9	McColl *et al* (1997), Gerhardt *et al* (2000, 2003)
PS deficiency¶	1–12	2–3	1–3	Gerhardt *et al* (2000, 2003)
High FVIII levels**	18	4–5	2–3	Gerhardt *et al* (2003)

VTE, venous thromboembolism; FVL, factor V Leiden; PGM, prothrombin gene mutation; AT, antithrombin; PC, protein C; PS, protein S; FVIII, factor VIII.

*Risks relative to non-pregnant women without thrombophilia.

†Assuming baseline incidence of one VTE/1000–1500 pregnancies.

‡Variably defined as <60% or <80% of normal activity.

§Variably defined as <50% or <70% of normal activity.

¶<53–55% of normal activity.

**>170% of normal activity.

unprovoked VTE (but not both) had recurrence rates of 13% and 7·7%, respectively. In contrast, there were no recurrences in women with a prior VTE provoked by a temporary risk factor, and no thrombophilic defects, suggesting this may define a low-risk group (Brill-Edwards *et al*, 2000).

Women with thrombophilia have a higher risk of VTE during pregnancy (Table II). The FV Leiden mutation was found in 20–46% of women with pregnancy-associated VTE in retrospective studies (Bokarewa *et al*, 1996; Hirsch *et al*, 1996; Hallak *et al*, 1997; Grandone *et al*, 1998; Gerhardt *et al*, 2000). The available data suggests that FV Leiden is associated with a five to 16-fold increased thrombotic risk during pregnancy and the puerperium (Gerhardt *et al*, 2000, 2003; Lensen *et al*, 2000a; Martinelli *et al*, 2002; Meglic *et al*, 2003). In one study, the mutation was found in 44% of women with a history of pregnancy-associated VTE, compared with 8% of matched control women, suggesting a ninefold increase in risk (Gerhardt *et al*, 2000). The prothrombin gene mutation is found in 6–26% of unselected women with a history of VTE during pregnancy or the puerperium. Heterozygous carriers have a three to 15-fold higher risk of pregnancy-associated VTE than unaffected women (Gerhardt *et al*, 2000, 2003; Martinelli *et al*, 2002; Meglic *et al*, 2003). At least 50–75% of thrombotic episodes in carriers of FV Leiden or the prothrombin gene mutation are provoked by additional predisposing factors, with pregnancy the most common circumstantial risk factor in several studies (Gerhardt *et al*, 2000; Lensen *et al*, 2000b).

Deficiencies of antithrombin, protein C or protein S are found in 8–25% of women with a history of pregnancy-related VTE and are associated with an estimated eight to 64-fold increase in risk (Simioni *et al*, 1999; Gerhardt *et al*, 2000, 2003; Martinelli *et al*, 2002). The widely varying prevalences and relative risks reported may reflect the relatively small sample sizes and different cut-off levels used to define a deficiency. In studies of thrombophilic families, 4% of pregnancies in antithrombin, protein C or protein S-deficient women were complicated by VTE compared with 0·5% in non-deficient relatives (Friederich *et al*, 1996; Simioni *et al*, 1999). In another family study, antithrombin-deficient women had a nearly 50-fold higher risk of VTE during pregnancy and the puerperium than in non-pregnant periods, with the highest risk postpartum. In the absence of prophylactic anticoagulation, postpartum VTE occurred in 15% of previously asymptomatic-deficient women, and 50% of those with a prior history of VTE (van Boven *et al*, 1999).

Pregnancy and OC are assumed to markedly increase the risk of VTE in patients with antiphospholipid antibodies, but there is surprisingly little data estimating the risk. The assumption is based on the marked increase in overall thrombotic risk when multiple predisposing factors are combined. Pregnancy increased the risk of thrombosis in women with the antiphospholipid antibody syndrome in a cross-sectional study which was not designed to estimate the relative risk (Erkan *et al*, 2002). A case–control study found antiphospholipid antibodies in 27% of women with pregnancy-associated VTE compared with 3% of control women with uneventful pregnancies (OR 8), although the confidence intervals were wide, probably due to the small number of cases (Ogunyemi *et al*, 2003). Hyperhomocysteinaemia and high levels of several clotting factors are independent thrombotic risk factors, but their contributions to VTE during pregnancy are also not well defined. High FVIII levels (>170% of normal) were found in 18% of women with a history of pregnancy-associated VTE, compared with 4·7% of controls, suggesting a four to fivefold increase in thrombotic risk (Gerhardt *et al*, 2003).

Women with multiple or homozygous thrombophilic defects have the highest risk of pregnancy-associated VTE. The risk is increased 20–40-fold in homozygous FV Leiden carriers (Martinelli *et al*, 2001; Gerhardt *et al*, 2003). The prevalence of pregnancy-related VTE was 9% in a series of unselected homozygous carriers (Pabinger *et al*, 2000). In another study, the risk of pregnancy-associated VTE was increased ninefold in FV Leiden carriers and 15-fold in women with the prothrombin gene mutation. In contrast, the risk was increased >100-fold in women with both mutations, illustrating the dramatic increase in overall risk when thrombophilic defects are combined (Gerhardt *et al*, 2000). In a retrospective study, VTE occurred in 17·8% of pregnancies in double heterozygous carriers of FV Leiden and the prothrombin gene mutation, compared with 6·2% of those in women with only the prothrombin gene mutation, suggesting the combination of both mutations confers a nearly threefold greater risk than the prothrombin gene mutation alone (Samama *et al*, 2003). In studies of thrombophilic families, VTE complicated 4% of pregnancies in double heterozygous carriers, and 16% of pregnancies in women with homozygous FV Leiden, compared with 0·5% of those in unaffected relatives (Martinelli *et al*, 2000, 2001; Middeldorp *et al*, 2001).

Although thrombophilia increases the relative risk of pregnancy-associated VTE, the absolute risk in asymptomatic carriers is unknown. Retrospective observational data and studies of thrombophilic families probably overestimate the risk in unselected asymptomatic thrombophilic women. In a prospective study of unselected pregnant women screened for FV Leiden, 1·1% of heterozygous carriers developed VTE, compared with 0·14% of unaffected women (Lindqvist *et al*, 1999b). Several retrospective studies estimated the probability of VTE in FV Leiden carriers in the range of one in 300–400 pregnancies (McColl *et al*, 1997; Gerhardt *et al*, 2000, 2003). The risk in women with the prothrombin gene mutation is approximately one in 200–300 pregnancies (Gerhardt *et al*, 2000, 2003). These estimates suggest asymptomatic women with a single thrombophilic defect and no other predisposing factors have a relatively low absolute risk. In contrast, women with homozygous or combined thrombophilia have a much higher probability of VTE, in the range of one in 20 to one in 100 pregnancies (Martinelli *et al*, 2001; Gerhardt *et al*, 2003). Women with antithrombin deficiency also have a higher risk, although estimates range from one in three to one in 250

pregnancies, depending on the type and severity of deficiency (McColl *et al*, 1997; Gerhardt *et al*, 2000).

Conclusions

The available data suggest that women with a history of a single VTE provoked by a temporary risk factor and no thrombophilia have a low rate of recurrence during pregnancy. These low-risk women may not require anticoagulation during pregnancy, but should be offered a 4–6-week course of warfarin postpartum, as thrombotic risk is highest during this period. Antepartum prophylactic anticoagulation is reasonable in women with a prior oestrogen-related thrombosis, although there is no data defining the risk of recurrence in this group. There is currently no consensus on the optimal management of thrombophilic women during pregnancy, although accepted guidelines are similar to those for non-pregnant patients(Ginsberg *et al*, 2001). Thrombophilia increases the risk of pregnancy-associated VTE, especially in women with combined or homozygous defects. However, anticoagulation during pregnancy is not routinely recommended for asymptomatic women with a single defect and no history of VTE (Ginsberg *et al*, 2001). The available evidence, suggesting carriers of FV Leiden or the prothrombin gene mutation have a low absolute risk of VTE during pregnancy, does not support routine screening for these mutations. Prophylactic anticoagulation may be justified in women with homozygous or combined thrombophilic defects, especially in those with other risk factors. Until more specific guidelines are defined by prospective trials, decisions about anticoagulation should be individualized based on thrombophilic defects, coexisting risk factors, and personal and family history of thrombosis.

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