

Venous thromboembolism in women: a specific reproductive health risk

ESHRE Capri Workshop Group^{†*}

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BACKGROUND: Venous thromboembolism (VTE) is a specific reproductive health risk for women.

METHODS: Searches were performed in Medline and other databases. The selection criteria were high-quality studies and studies relevant to clinical reproductive medicine. Summaries were presented and discussed by the European Society of Human Reproduction and Embryology Workshop Group.

RESULTS: VTE is a multifactorial disease with a baseline annual incidence around 50 per 100 000 at 25 years and 120 per 100 000 at age 50. Its major complication is pulmonary embolism, causing death in 1–2% of patients. Higher VTE risk is associated with an inherited thrombophilia in men and women. Changes in the coagulation system and in the risk of clinical VTE in women also occur during pregnancy, with the use of reproductive hormones and as a consequence of ovarian stimulation when hyperstimulation syndrome and conception occur together. In pregnancy, the risk of VTE is increased ~5-fold, while the use of combined hormonal contraception (CHC) doubles the risk and this relative risk is higher with the more recent pills containing desogestrel, gestodene and drospirenone when compared with those with levonorgestrel. Similarly, hormone replacement therapy (HRT) increases the VTE risk 2- to 4-fold. There is a synergistic effect between thrombophilia and the various reproductive risks. Prevention of VTE during pregnancy should be offered to women with specific risk factors. In women who are at high risk, CHC and HRT should be avoided.

CONCLUSIONS: Clinicians managing pregnancy or treating women for infertility or prescribing CHC and HRT should be aware of the increased risks of VTE and the need to take a careful medical history to identify additional co-existing risks, and should be able to diagnose VTE and know how to approach its prevention.

Key words: venous thromboembolism / pregnancy / hormonal contraception / ovarian hyperstimulation / hormone replacement therapy

[†] Participants of the ESHRE Capri Workshop Group are given in Appendix.

Introduction

Venous thromboembolism (VTE) is defined as a condition in which a blood clot (thrombus) forms in a vein, most commonly in the deep veins of the legs or pelvis [deep vein thrombosis (DVT)] while pulmonary embolism (PE) occurs when the thrombus dislodges to the pulmonary arteries (NICE, 2013).

VTE is a major cause of morbidity and mortality and one of the leading causes of maternal mortality in the western world. While the incidence of VTE over recent time has remained unchanged, survival after VTE is worse than expected, especially after PE for which one-quarter of patients present with sudden death. Of those patients who survive VTE, some 30% will develop a recurrence of VTE within 10 years with a case-fatality rate of 4–12% and 30% will develop a disabling post-thrombotic syndrome (Heit, 2006).

The estimated overall annual incidence of VTE is 117 per 100 000 persons (48/100 000 for DVT and 69/100 000 for PE) (Silverstein *et al.*, 1998). Major complications of VTE are a disabling post-thrombotic syndrome and acute death from PE occurring in 1–2% of patients (Rosendaal, 1999). Specifically, VTE is a reproductive health risk for women. In pregnancy, the relative risk (RR) of VTE is increased ~5-fold and in the puerperium (defined as the 6 weeks following childbirth), the risk is increased by as much as 60-fold (Pomp *et al.*, 2008). Additionally, large numbers of women worldwide are exposed to an increased RR of VTE as a result of using combined hormonal contraception (CHC) or hormone replacement therapy (HRT). Even women undergoing infertility treatment may be exposed to situations associated with a significantly increased risk of VTE. This review considers VTE as a specific reproductive health risk for women and summarizes our current knowledge of the subject for reproductive medicine practitioners.

Methods

Searches were performed in Medline and other databases by individual participants in the workshop. The selection criteria were high-quality studies and studies relevant to clinical reproductive medicine. Each subject summary was presented at a meeting of the European Society of Human Reproduction and Embryology (ESHRE) Workshop Group and omissions or disagreements were resolved by discussion.

Results

Age and gender differences for VTE

The incidence of VTE among white men and women of European origin exceeds 1 per 1000; the incidence among persons of African and Asian origin may be higher and lower, respectively (Heit, 2006). The incidence of VTE increases with age: in women it is 51 per 100 000 per year in 25 year olds but it doubles to 123 by the age of 50, increasing to 207 at age 60, to 351 at age 70 and to 703/100 000 per year at age 80. A similar pattern is seen in men, and in both sexes there is a strong age gradient. Table I summarizes the incidence rates of the first DVT alone or complicated with PE, for women and men according to their age group (Naess *et al.*, 2007).

Although VTE is a specific reproductive health risk for women, there is also firm evidence that male gender *per se* is an important risk factor for VTE. In a population-based study of the hospital incidence and case-

fatality rates, the incidence rates for DVT, PE or both were significantly higher in men than in women with a RR for male versus female patients of 1.4 (Anderson *et al.*, 1991). The difference in the incidence rates between men and women was particularly striking at an older age (>60 years). In a similar study from Sweden, the incidence rates of DVT were higher in women during the child-bearing years. With advancing age, however, rates were much higher in men than in women (3.3 per 1000 per year in men aged between 60 and 69 years versus 2.2 per 1000 per year in women in the same age group) (Nordström *et al.*, 1992). Importantly, male sex is a major determinant of the risk of recurrent VTE (Kyrle *et al.*, 2004).

Despite this, there is a suggestion of differences between men and women (who are not pregnant and not using exogenous estrogen) with regard to coagulation factor and coagulation inhibitor activities, which push women towards a hypercoagulable state (as suggested by the increase in coagulation activation markers F1 + 2, thrombin–antithrombin complexes and D-dimer in women and not in men) but the data are not robust (Lowe *et al.*, 1997).

Risk factors for VTE

Rudolf Virchow in 1856 proposed changes in blood coagulability as one of the mechanisms that predispose to thrombosis (Bagot and Arya, 2008). These changes in blood coagulability, i.e. thrombophilia, indicate the presence of a hypercoagulable state, a feature of a number of conditions which, when combined with circulatory stasis and/or vascular wall injury, leads to venous thrombosis. Coagulability is determined by the balance between coagulation factors which are procoagulant and anticoagulant.

Risk factors for venous thrombosis can be genetic or acquired, permanent or transient, and are listed in Table II (Jaffer, 2008).

Inherited risk factors

The most well-known genetic or biochemical risk factors leading to a thrombotic tendency are deficiencies of the natural anticoagulant proteins, i.e. antithrombin, protein C and protein S, the presence of procoagulant factors such as factor V Leiden (FVL), the prothrombin 20210A mutations and elevated levels of prothrombin, factor VIII, IX and XI. The prevalence of these conditions and the increased RR of VTE are shown in Table III.

The presence of hereditary thrombophilia strongly increases the risk of venous thrombosis associated with pregnancy or the use of CHCs or HRT. Compared with women who are not using CHCs and do not carry the FVL mutation, the risk of VTE is increased 35-fold in heterozygous carriers using oral contraceptives (Van Vlijmen *et al.*, 2011). This risk is considerably higher than would be expected based on the effects of FVL and oral contraceptive use separately. A similar but less striking synergistic effect has also been reported between oral contraceptive use and the prothrombin 20210A mutation (Van Vlijmen *et al.*, 2011).

Weight

At all ages, arguably, the commonest risk factor for women (and men) is overweight and obesity (Table IV). In the UK Confidential Enquiry into maternal deaths, 18 women died from VTE in the triennium 2006–2008. Obesity was identified as the most important risk factor. Fourteen women were overweight (BMI ≥ 25 kg/m²), of whom 11 had a BMI ≥ 30 , including 3 who had a BMI of ≥ 40 (CMACE, 2011). Obesity predisposes to venous stasis, increases prothrombotic factors and impairs

Table I Incidence rates (IRs) per 100 000 person-years and 95% CIs for first DVT alone and PE with or without DVT (PE ± DVT) in Nord-Trøndelag County (n = 93 857) in 1995–2001 (Naess et al., 2007, adapted).

Age groups (years)	Women		Men	
	DVT alone IR (95% CI)	PE ± DVT IR (95% CI)	DVT alone IR (95% CI)	PE ± DVT IR (95% CI)
20–24	21 (7–66)	14 (4–57)	0 (—)	13 (3–53)
25–29	8 (2–32)	16 (6–43)	4 (1–25)	0
30–34	25 (11–56)	21 (9–50)	15 (6–41)	4 (1–27)
35–39	39 (20–74)	13 (4–40)	16 (6–43)	12 (4–37)
40–44	17 (6–44)	21 (9–50)	20 (8–47)	24 (11–52)
45–49	82 (53–127)	0 (—)	50 (29–86)	15 (6–41)
50–54	72 (44–115)	46 (26–84)	72 (45–111)	16 (6–42)
55–59	91 (56–146)	37 (18–78)	89 (55–142)	36 (17–76)
60–64	93 (55–157)	40 (18–89)	114 (71–184)	74 (41–133)
65–69	113 (70–182)	100 (60–166)	162 (108–244)	85 (48–149)
70–74	145 (96–218)	69 (38–125)	185 (126–272)	157 (103–238)
75–79	294 (219–395)	167 (113–247)	353 (260–479)	146 (91–235)
80–84	384 (287–514)	205 (137–305)	373 (256–544)	249 (157–394)
≥ 85	473 (354–631)	267 (182–393)	405 (259–636)	149 (71–313)
Total	103 (91–116)	55 (47–65)	84 (73–96)	44 (37–53)

DVT, deep vein thrombosis; PE, pulmonary embolism.

Table II Risk factors for VTE.

Surgery	Heart failure
Trauma	Respiratory failure
Immobility	Inflammatory bowel disease
Malignancy	Nephrotic syndrome
Cancer-related therapy (chemotherapy)	Myeloproliferative neoplasms
Previous VTE	Obesity
Advanced age	Smoking
Pregnancy/puerperium	Varicose veins
Hormone use (CHC and HRT)	Thrombophilia abnormalities
Infection	Long-haul travel

VTE, venous thromboembolism.

Table III Coagulation abnormalities causing inherited thrombophilia and associated RR of VTE in family studies (Vossen et al., 2004, adapted).

Causes	Prevalence (%)	Relative risk of first venous thrombosis
Antithrombin deficiency	0.02	5–10
Protein C deficiency	0.2	4–6.5
Protein S deficiency	0.03–0.13	1–10
Factor V Leiden	3.0–7.0	3–5
Prothrombin G20210A	0.7–4.0	2–3
High factor VIII	10	5
High factor IX	10	2
High factor XI	10	2

VTE, venous thromboembolism.

fibrinolytic activity (Allman-Farinelli, 2011). However, obese men and women often have other risk factors for VTE such as immobility and it has taken some time to establish that obesity is an independent risk factor for VTE. With this aim in mind, Stein et al. (2005) used a US database of the National Hospital Discharge Survey. Comparing obese with non-obese patients, the RR of both DVT and PE were more than doubled, 2.50 (95% confidence interval (CI) = 2.49–2.51) and 2.21 (95% CI = 2.20–2.23), respectively. Obese women had a greater RR for DVT than obese men, 2.75 (95% CI = 2.74–2.76) versus 2.02 (95% CI = 2.01–2.04) (Stein et al., 2005). A Danish study considered the distribution of body fat assessing the association between anthropometric variables and VTE. All measurements of obesity were found to be predictors of the risk for VTE. Positive associations were found between VTE and

body weight, body mass index, waist circumference, hip circumference and total body fat mass (Severinsen et al., 2009). Obesity appears to confer a greater risk than other cardiovascular risk factors (Ageno et al., 2008). A meta-analysis to assess the association between cardiovascular risk factors and VTE included 21 case-control and cohort studies with a total of 63 552 patients. Compared with control subjects, the risk of VTE was 2.33-fold for obesity (95% CI: 1.68–3.24), which was higher than the RR associated with hypertension (1.51 95% CI: 1.23–1.85), diabetes mellitus (1.42 95% CI: 1.12–1.77), smoking (1.18 95% CI: 0.95–1.46) and hypercholesterolemia (1.16 95% CI: 0.67–2.02).

Table IV RRs of deep venous thrombosis in obese women according to age categories (Stein et al., 2005, adapted).

Obese versus non-obese women		
Age group	RR	95% CI
<40	5.20	5.15–5.25
40–49	2.13	2.11–2.15
50–59	1.67	1.65–1.68
60–69	1.88	1.87–1.90
70–79	1.89	1.87–1.91
≥80	2.16	2.12–2.20
All ages	2.50	2.49–2.51

VTE, venous thromboembolism.

Reproductive risks in women

Women are subject to specific hormonal changes (either naturally occurring or induced by common hormone treatments) which influence factors relevant to thrombosis and put them at a temporary increased risk of VTE. During the reproductive years contraceptive use, pregnancy and pro-fertility ovarian stimulation may alter the levels of pro- and anticoagulants as well the fibrinolytic system, while after menopause age-related aspects contribute to the changes in the hemostatic system. Thus, for periods of a woman's life, the risk of VTE is significantly increased above baseline and for those women who are more predisposed towards thrombosis, the threshold for clinical VTE will be crossed (Rosendaal, 1999).

Contraception. The use of CHCs is associated with changes in the levels of coagulation factors, levels of anticoagulant proteins, such as protein S and tissue factor pathway inhibitor, as well as fibrinolytic parameters (van Hylckama Vlieg and Middeldorp, 2011). This potentially thrombophilic condition differs between types of CHCs and is dependent on the dose of estrogen and the type of progestogen in the pill.

Pregnancy. Normal pregnancy is associated with alterations of the hemostatic system towards a hypercoagulable state. Elevated markers, throughout pregnancy, of coagulation and fibrinolytic system activation, such as D-dimer and prothrombin fragment F1 + 2, indicate increased thrombin generation and increased fibrinolysis following fibrin formation (Eichinger et al., 1999). The overall balance between pro- and anticoagulant forces during pregnancy seems to be altered in favor of a prothrombotic state, most likely in preparation for the inevitable substantial bleeding which occurs during childbirth. While the levels of factors V, VII, VIII, IX, X, XII and von Willebrand antigen increase, protein S, factor XI and platelets tend to decrease throughout pregnancy (Hellgren, 2003), along with acquired resistance to protein C.

Ovarian stimulation. Women undergoing infertility treatment, which involves the use of CHC for down-regulation or estrogen for preparation of the endometrium for embryo transfer, should be advised of the increased risk of VTE associated with these hormones. Of course since the aim of infertility treatment is pregnancy with its attendant

risks of VTE, the risks associated with treatment can be put into perspective.

End of reproductive age. Menopause is accompanied by processes of physiological aging which are associated with increased plasma levels of many proteins of blood coagulation, alterations of platelets and fibrinolysis impairment (Bucciarelli and Mannucci, 2009).

Signs and symptoms

Between 38 and 58% of patients presenting with a DVT also have PE and in 80% of PE multiple perfusion defects occur in both lungs (Mostbeck, 1999). Pelvic vein thrombosis leads to PE in 77% of cases, proximal leg thrombosis leads to PE in 67% of cases and lower limb DVT leads to PE in 47% of cases, i.e. the smaller the vessels in which the thrombosis occurs, the less likely they are to lead to PE (Mostbeck, 1999).

Deep vein thrombosis

DVT is often asymptomatic and in some cases may be found following diagnosis of a PE. The presenting features of DVT include swelling of the leg, redness, pain, leg fatigue and dilatation of the superficial veins. Clinical examination may demonstrate calf tenderness, pitting edema, warmth and discoloration of the affected extremity. Most of the time it will be the pelvic vessels or those of the lower extremities that are affected; however, the upper extremities may be involved especially in patients with ovarian hyperstimulation syndrome (OHSS) (see below).

Pulmonary embolism

Likewise the signs and symptoms of PE overlap with other (mostly cardiac and pulmonary) disorders. They include sudden sharp chest pain, a rapid pulse, shortness of breath, anxiety, sweating and coughing and sometimes hemoptysis. The patient may collapse. Of every 100 patients who develop DVT, one dies due to PE. The overall mortality of PE (30%) can be reduced to < 10% with appropriate early intervention (Ramzi and Leeper, 2004).

Diagnostic work up

Many signs and symptoms similar to those of VTE may occur in other disorders. Making a correct diagnosis may be difficult. Yet, given the life-threatening complications, especially of PE, it is critical not to miss the diagnosis. In the UK Confidential Enquiry into Maternal Deaths 2006–2008 (CMACE, 2011), risk factors for thromboembolism were present in 16 of the 18 women who died. Substandard care was present for 56% of women and included inadequate risk assessment and failure to investigate chest symptoms in at-risk women. While a false-negative diagnosis risks death and disability, a false-positive result leads to unnecessary treatment of the acute condition and later unnecessary thromboprophylaxis.

Women presenting with symptoms or signs of DVT/PE should have a full medical history taken, including the assessment of known risk factors and a physical examination. Clinical probability algorithms may help in deciding which patients to subject to further testing. The most commonly used, and best evaluated, is that developed by Wells et al., (1997). Scores are assigned according to the medical history and findings at physical examination. The overall score allows for categorization into low (3%), intermediate (17%) or high risk (75%) for DVT. Although a useful tool for initial triage of patients with suspected DVT, the accuracy of the score is not sufficient to allow for its use as the only means of

establishing a diagnosis and starting treatment. While a high Wells score is found more often in patients with DVT than in patients without, a low Wells score is less discriminating with respect to excluding DVT. The Institute for Clinical Systems Improvement has published a much used algorithm for the diagnosis of DVT, based on the Wells score, the D-dimer test and venous ultrasound examination (ICSI, 2012). A similar algorithm is available for the diagnosis of PE (ICSI, 2012). A Wells clinical probability rule can be used to diagnose PE (Wells et al., 1998). The risk score interpretation is 78% for patients with a high score, 28% for an intermediate score and 3% for patients with a low Wells score (Wells et al., 1998). In prospective studies in which the diagnosis of PE was confirmed by ventilation-perfusion scans or pulmonary artery angiography, the diagnosis was confirmed in 3–28% of patients with a low Wells score, in 16–46% of patients with an intermediate score and in 38–98% of patients with a high Wells score (Chunilal et al., 2003). Additional testing to confirm the diagnosis should include D-dimer testing and compression ultrasound of the lower extremities. If these are negative, computed tomography (CT), pulmonary angiography and ventilation–perfusion scanning should be performed.

DVT in pregnancy is sometimes difficult to diagnose since leg swelling, dyspnea and chest pain due to non-thrombotic causes are common. Furthermore, D-dimer concentrations are not diagnostic as they are physiologically raised in pregnancy and increase with gestational age (Jeremiah et al., 2012). However, given the serious consequences, the index of suspicion should be high. Clinical diagnosis of DVT is inaccurate and objective examinations are needed to confirm DVT and establish the extension of the thrombus. Compression ultrasound examination is an easy, non-invasive and widely used objective diagnostic method with an accuracy close to 100% in symptomatic patients (Goodacre et al., 2005). Hence, compression ultrasound is the test of choice for femoral vein thrombosis (at the inguinal ligament) and/or popliteal vein thrombosis (at the popliteal fossa). If compression ultrasound is equivocal, or isolated iliac vein thrombosis is suspected, helical CT scanning should be considered. The potential risks of teratogenesis associated with the radiologic tests used when VTE is suspected are minimal when compared with the consequences of misdiagnosis (Chen et al., 2008).

Specific risks for thromboembolism in women

Risks associated with hormonal contraception

It has been recognized for over 40 years that the use of CHC is associated with an excess risk of thromboembolic disease, and specifically of VTE. In the 1960s, on the basis of UK, Danish and Swedish data, such an excess risk was attributed to the estrogen dose of various CHCs, and this led to the reduction of estrogen doses in the late 1960s and early 1970s (Inman et al., 1970).

Among users of CHC, obese women, smokers and those with an inherited thrombophilia are the individuals at highest risk (Table V).

Numerous reports have been published on the increase in thrombotic risk, with CHCs, indicating a 2-fold to 6-fold increased risk of DVT associated with current use (van Hylckama Vlieg et al., 2009; Lidegaard et al., 2009). While the increased risk is related to the dose of estrogen, it is also influenced by the type of progestogen, with the second generation progestogens [levonorgestrel (LNG) and norethisterone] regarded as being safer than the newer progestogens. This difference has been the subject of an ongoing debate.

The European Active Surveillance study was a multinational, prospective, cohort study of new users of drospirenone (DRSP), LNG and other progestin-containing pills, in which 58 674 women were followed for 142 475 women-years of observation (Dinger et al., 2007). Hazard ratios for DRSP-containing versus LNG-containing or other oral preparations were only 1.0 and 0.8 (upper 95% confidence limits, 1.8 and 1.3), respectively, for VTE.

However, the most recently published data from a large data set come from a Danish national cohort study which reviewed data from 3.3 million woman years of CHCs use including 4213 venous thrombotic events among 2045 current users of CHCs. The overall absolute risk of venous thrombosis per 100 000 woman years in non-users of combined contraception was 30.1, but in current CHC users this risk was 62.9. Compared with CHC-containing LNG and with the same dose of estrogen and duration of use, the rate ratio for CHCs with norethisterone was 0.98 (0.71–1.37), with norgestimate 1.19 (0.96–1.47), with desogestrel (DSG) 1.82 (1.49–2.22), with gestodene 1.86 (1.59–2.18), with DRSP 1.64 (1.27–2.10) and with cyproterone 1.88 (1.47–2.42) (Lidegaard et al., 2009). The Food and Drug Administration (FDA) introduced specific warnings on the labels of DRSP-containing preparations in 2011 (FDA, 2011), and very recently the French medicines agency has suspended marketing authorization for Diane 35 (cyproterone acetate 2 mg, ethinylestradiol 35 mcg Bayer) and its generics (European Medicines Agency, 2013). Although licensed only for the treatment of acne in France and other countries, Diane 35 is widely used by women with acne or hirsutism who require contraception. The UK Committee for the Safety of Medicines and the Medicines Control Agency (UK) in 2002 similarly restricted its use to women with symptoms of androgen excess and advised that it ‘should be withdrawn three–four cycles after the treated condition has completely resolved’ (CSM, 2002). Various experts give different advice about which oral contraceptive pills to prescribe. In general, most agree that pills containing a second generation progestogen should be the first choice for most women (Lidegaard et al., 2012a). Recently, an increased risk of VTE has been associated with the PCOS conditions (Okoroh et al., 2012; Bird et al., 2013). Since many women will start using Diane 35 because of acne and hirsutism, and since many of these will have PCO, this is an important confounder. It may be that the increased tendency to develop

Table V RR of VTE in combined oral contraceptive users in association with thrombophilia, obesity and smoking (Pabinger and Schneider, 1994; Vandenbroucke et al., 1994; Simioni et al., 1999; Legnani et al., 2002; Abdollahi et al., 2003).

Associated factor	RR
PC/PS/AT deficiency	High
Factor V Leiden mutation	20–30
Prothrombin G20210A mutation	10–20
High levels of procoagulant factors	5–10
Obesity	24
Smoking	9

PC, protein C; PS, protein S; AT, antithrombin.

thromboembolism in these patients is due to their PCO and not (or to a lesser extent) to Diane 35.

Non-oral hormonal contraceptives are also associated with an increased risk of VTE, including the transdermal patch (containing norgestimate) and the contraceptive vaginal ring (containing etonorgestrel) with a 7.9- and 6.5-fold increased risk of VTE, respectively (Lidegaard *et al.*, 2012b). Several studies have reported that the RR of VTE is highest during the first year and perhaps during the first 3 months of use, probably due to VTE among women with undiagnosed inherited thrombophilias (Suisa *et al.*, 1997; Jick *et al.*, 2000; Lidegaard *et al.*, 2009).

In contrast, progestogen-only contraception (POC) has been considered as generally safe with respect to the risk of cardiovascular disease including VTE. Studies of coagulation factors and other metabolic indices during use of POC have not found clinically meaningful changes for pills (McCann and Potter, 1994; Winkler *et al.*, 1998), POC implants containing either LNG (Norplant®) (Egberg *et al.*, 1998; Dorflinger, 2002) or DSG (Implanon®) (Egberg *et al.*, 1998; Viera *et al.*, 2007) or the injectable depot-medroxyprogesterone acetate (DMPA) (Goldstein *et al.*, 2007). Normal (or even increased) sensitivity to activated protein C was reported 3 months after the insertion of a levonorgestrel-releasing intrauterine system (LNG-IUS, Mirena®) also indicating that this contraceptive does not have a prothrombotic effect (van Vliet *et al.*, 2009).

Epidemiologic evidence regarding the cardiovascular safety of progestogen-only methods of contraception is limited. In most countries POC amounts for only a very small proportion of contraceptive methods and in those countries where POC use is common (e.g. Depo Provera® in South Africa), routine epidemiological data collection at a national level is rare or incomplete and so record linkage studies are not possible. In addition, since POC are the obvious alternative for women with contraindications to estrogen-containing contraceptives, it is likely that cohorts of POC users will contain a proportion of women with known risk factors for VTE such as obesity or a family history of thrombosis and so the data need to be regarded with caution. In the Transnational Study, there was a clear distinction between users of POC and those women who were using CHCs (Heinemann *et al.*, 1999).

Using data from four national registries in Denmark, Lidegaard *et al.* (2011) demonstrated that the risk of VTE was not increased with use of pills containing norethisterone [adjusted RR 0.56 (95% CI: 0.29–1.07)] or DSG [adjusted RR 0.64 (95% CI: 0.29–1.42)]. Data from the same cohort of women demonstrated a reduced RR of VTE compared with non-users among women using the LNG-IUS [RR 0.57 (95% CI: 0.41–0.81)] and an RR of 1.4 (95% CI: 0.58–3.38) among women using the DSG-containing implant (Implanon®; Lidegaard *et al.*, 2012b).

In a population-based case-control study on risk factors for venous thrombosis, injectable DMPA was associated with a statistically significant 3.6-fold (95% CI: 1.8- to 7.1-fold) increased risk of venous thrombosis compared with non-users of hormonal contraceptives, but the number of women was small (20 cases and 15 controls) (Van Hylckama Vlieg *et al.*, 2010). A very recent systematic review and meta-analysis of all the published data concluded that the use of POC was not associated with an increased risk of VTE compared with non-users of hormonal contraception. However, the potential association between injectable progestogens and thrombosis requires further study (Mantha *et al.*, 2012).

In the light of the available evidence, the widely used WHO Medical Eligibility Criteria for Contraceptive Use (WHO, 2011) rate known risk factors for VTE as either category 1 (use method in any

circumstances) or category 2 (generally use the method) or category 3 (use of method not recommended) conditions (Table VI).

Risks during pregnancy and the puerperium

The RR of VTE is increased ~5-fold in pregnancy, and in the puerperium, defined as the 6 weeks period after childbirth, it is as high as 60-fold (Pomp *et al.*, 2008). Hence, VTE occurs in 1–2 per 1000 pregnant women every year. The incidence of pregnancy associated DVT is about three times higher than that of pregnancy-associated PE (Bourjeily *et al.*, 2010). Major determinants are advanced age, mode of delivery and systemic risk factors (such as co-morbidities or inherited thrombophilia) (Heit *et al.*, 2005; James *et al.*, 2006). Based on the above figures, PE is considered the main cause of maternal mortality in Western countries and pregnancy-related DVT is one of the main causes of maternal morbidity (Rosfors *et al.*, 2001; Heit *et al.*, 2005; James *et al.*, 2006). DVT occurring during pregnancy accounts for two-thirds of cases, involves mainly the left leg because of the anatomic course of iliac vessels and is equally distributed in the three trimesters (Martinelli *et al.*, 2002). In contrast, PE is more prevalent in the puerperium (Heit *et al.*, 2005). Examples of known determinants of the high risk of VTE during the puerperium are hemoconcentration, dissemination of tissue factor in the bloodstream after placenta removal and Cesarean section.

Risks associated with ovarian stimulation

A particular relationship between OHSS and thromboembolic disorders has been recognized for a long time. The first case was reported in 1965 (Mozes *et al.*, 1965). Since then, a plethora of case reports has been published. Reviews of the various case reports demonstrate that both the arterial and the venous systems may be affected (even if the latter prevails), that thromboses can occur up to several weeks after embryo-transfer (at least for VTE), that these events are more common in women who conceive in the presence of OHSS (Chan, 2009; Nelson, 2009) and that the events tend to occur in unusual locations (the upper extremities and the neck for venous thrombosis and intra-cranially for the arterial events). This peculiar localization of venous thrombosis is intriguing and two possible explanations have been provided. (Bauersachs *et al.* (2007) attributed this feature to the increased drainage of peritoneal fluid with prothrombotic properties through the thoracic duct into the subclavian veins. Salomon *et al.* (2009) suggested that rudimental brachial cysts may cause mechanical obstruction of the veins of the upper extremities veins when filling with fluid during OHSS. Overall, albeit interesting, evidence emerging from case reports must be interpreted with caution. A causal relationship cannot necessarily be inferred, publication bias in particular may distort reality (e.g. papers reporting thrombosis in the upper limb may be more likely to be published than those reporting lower limb DVT) and the magnitude of the association cannot be estimated.

There is however some biological plausibility. Several studies have evaluated coagulation changes during ovarian stimulation. Taken together, they indicate that the supra-physiological levels of estrogens exert direct effects on hemostatic variables and may induce a procoagulable state due to an increase in coagulation factors, such as von Willebrand factor, factor VIII, factor V and fibrinogen and a reduction in anticoagulation factors, such as antithrombin, protein C and protein S (Chan and Dixon, 2008; Nelson, 2009; Westerlund *et al.*, 2012). Most reported biological changes however are modest and the variables tend to remain within the normal range. Thus, the clinical relevance of these modifications warrants confirmation in population-based studies.

Table VI World Health Organization medical eligibility criteria.

Condition	Category			Clarifications/evidence
	POP	D/NE	LNG/ETG	
DVT/PE				
(a) History of DVT/PE	2	2	2	
(b) Acute DVT/PE	3	3	3	Evidence: there is no direct evidence on the use of POCs among women with DVT/PE on anticoagulant therapy. Although evidence on the risk of venous thrombosis with the use of POCs is inconsistent in otherwise healthy women, any small increased risk is substantially less than that with CHCs.
(c) DVT/PE and established on anticoagulant therapy	2	2	2	Evidence: there is no direct evidence on the use of POCs among women with DVT/PE on anticoagulant therapy. Although evidence on the risk of venous thrombosis with the use of POCs is inconsistent in otherwise healthy women, any small increased risk is substantially less than that with CHCs. Limited evidence indicates that intramuscular injections of DMPA in women on chronic anticoagulation therapy does not pose a significant risk of hematoma at the injection site or increase the risk of heavy or irregular vaginal bleeding
(d) Family history (first-degree relatives)	1	1	1	
(e) Major surgery	2	2	2	
With prolonged immobilization	1	1	1	
Without prolonged immobilization	1	1	1	
(f) Minor surgery without immobilization				
Known thrombogenic mutations (e.g. factor V Leiden, prothrombin mutation, protein S, protein C and antithrombin deficiencies)	2	2	2	Clarification: routine screening is not appropriate because of the rarity of the conditions and the high-cost screening

POP, progestogen-only pills; LNG/ETG, levonorgestrel and etonogestrel implants; D/NE, depot medroxyprogesterone acetate (DMPA)/norethisterone enantate (NET-EN). WHO Medical Eligibility Criteria for Contraceptive Use (WHO, 2011) rates known risk factors for VTE as category 1 (use method in any circumstances), category 2 (generally use the method) or category 3 (use of method not recommended) conditions. Use of progestogen-only contraceptives by women with known risk factors for venous thrombosis (WHO, 2011, adapted). DVT, deep vein thrombosis; PE, pulmonary embolism; CHC, combined hormonal contraception.

However, very recently, four pivotal investigations have been published. *Jacobsen et al. (2008)* identified 268 cases of VTE in pregnancy among 18 Norwegian hospitals and compared them to 1229 pregnant unaffected controls from the general pregnant population. There were 20 cases which occurred in women achieving pregnancy through ART. The corresponding adjusted odds ratio (OR) was 4.3 (95% CI: 2.0–9.4) (*Jacobsen et al., 2008*). *Rova et al. (2012)* matched information from relevant inpatient registries in Sweden. They observed that women conceiving through IVF had a 10 times higher risk of being admitted for VTE during the first trimester of pregnancy compared with women conceiving spontaneously (OR = 9.8, 95% CI: 6.7–14.3). This increased risk disappeared during the second and third trimester and during the puerperium. Importantly, women conceiving through IVF and developing OHSS were at a 100 times higher risk of VTE during the first trimester (OR = 99.7, 95% CI: 61.8–161.1). In contrast, women conceiving through IVF using frozen embryos (thus not requiring ovarian stimulation) were not exposed to an enhanced risk (*Rova et al., 2012*). Very recently, the Swedish registers were used by independent authors who performed a partly different and somehow more subtle analysis (*Henriksson et al., 2013*). They included also outpatient cases, they controlled for several confounders and they retrieved data also on PE that represents the most frightening complication of VTE. The overall results were in line with the previous Swedish evidence even if

the magnitude of the associations was less striking. The adjusted hazard ratio of VTE in women achieving pregnancy through IVF was 1.8 (95% CI: 1.4–2.2) and it peaked in the first trimester (hazard ratio = 4.0, 95% CI: 2.5–6.5). Considering PE, the hazard ratio during pregnancy and during the first trimester were 1.8 (95% CI: 0.9–3.7) and 7.0 (95% CI: 2.2–22.0), respectively. Unfortunately, these authors did not provide independent data for OHSS. Finally, the fourth available study reported results that are apparently in contrast (*Hansen et al., 2012*). These authors used data from the national IVF registry and the national patient registry of Denmark and failed to document any significant association. The incidence rate ratio of venous and arterial thrombosis in the first 6 months following the procedure was 0.95 (95% CI: 0.38–1.95) and 0.36 (0.04–1.30), respectively. However, it has to be underlined that pregnant women were excluded from the analysis (*Hansen et al., 2012*).

Based on the available evidence, it can be reasonably concluded that ovarian stimulation does increase the risk of thrombo-embolic disorders. However, this risk peaks dramatically in pregnant women with OHSS requiring hospital admission. In this latter group, the incidence has been estimated to reach ~2% (*Rova et al., 2012*).

Risks associated with HRT

After menopause, HRT poses a specific thrombotic risk to women, being associated with a 2- to 4-fold increased risk of DVT (*Rosendaal et al.,*

2003). There is emerging evidence that the thrombotic risk may depend on the route of estrogen administration. In a French study, the odds ratio for VTE in current users of oral and transdermal estrogens compared with non-users was 3.5 (95% CI: 1.8–6.8) and 0.9 (95% CI: 0.5–1.6), respectively. The estimated RR for VTE in current users of oral, compared with transdermal, estrogens was 4.0 (95% CI: 1.9–8.3) (Scarabin *et al.*, 2003).

As with CHC, the risk of thromboembolic events among women using HRT may also depend on the type and dose of the progestogen. In a study using data from the UK General Practice Research Database, pregnane derivatives were associated with a slightly higher RR (1.72; 95% CI: 1.52–1.94) than nortestosterone derivatives (RR 1.48; 95% CI: 1.37–1.60) (Renoux *et al.*, 2010). In a population based study using the data set of ~1 million women, a higher risk for venous thrombosis was again seen in women using oral compared with transdermal HRT and the risk was greatest in users of oral formulations containing medroxyprogesterone acetate (Sweetland *et al.*, 2012).

HRT also confers an increased risk of recurrent venous thrombosis (Hoibraaten *et al.*, 2000; Olié *et al.*, 2011; Goldhaber and Bounameaux, 2012). As with the risk of a first thrombosis, risk of recurrence seems dependent on the route of estrogen administration. In a French hospital-based case–control study, transdermal estrogens were not associated with an increased risk of recurrent VTE compared with non-use (1.0; 95% CI: 0.4–2.4; Olié *et al.*, 2011). In the Austrian Study on Recurrent Venous Thromboembolism, the risk of recurrence was 1.8-fold higher (95% CI: 0.9–4.0) among women who had their first thrombosis without taking HRT compared with those whose first thrombosis was during HRT use (Eischer *et al.*, 2012). The probability of recurrence 5 years after discontinuation of anticoagulation was 15% (95% CI: 5.4–24.6%) among women who had their first thrombosis during HRT compared with 4% (95% CI: 1.3–6.7%) among women who had their thrombosis associated with hormonal contraceptive use.

Prevention of VTE in women

The management of women who present with VTE should be undertaken by a specialist physician or hematologist and is beyond the scope of this review. In contrast, prevention of the disease is the province of gynecologists, family planning providers and menopause and infertility specialists since all should be aware that women under their care may be at increased risk of VTE.

Women requiring contraception

A wide range of contraceptives is available in most countries including non-hormonal methods that carry no increased risk of VTE (male and female barrier methods and the highly effective copper intrauterine device). Women with known serious risk factors for VTE requiring contraception should be advised to use a non-hormonal method (RCOG, 2010). The World Health Organization Medical Eligibility Criteria for Contraceptive Use (WHO, 2011) is a useful source of evidence-based guidance on who can use different methods of contraception. The highly increased risk of VTE associated with CHC use in carriers of the FVL mutation has led commentators to question whether young women should be screened for FVL prior to CHC prescription. However, in the absence of a clear family history of venous thrombosis, i.e. in the general population, where some 5% of women carry FVL, the number needed to be tested to withhold CHCs in carriers

and to prevent one death from PE would be more than half a million (RCOG, 2010; Favaloro and McDonald, 2012). Since the combined oral contraceptive pill is the most commonly used contraceptive method in much of Europe even when women are eligible to use others methods it is worth prescribing the 'safest' CHC given the increased risk of VTE. Thus, at the end of 2001, the Committee for Proprietary Medicinal Products of the European Medicine Agency (Garattini and Bertele, 2001) advised that there was no urgency to modify the pattern of CHC prescription for current users, but that oral contraceptives containing LNG should be preferred to pills with newer progestogen when an CHC is used by a woman for the first time. More recently in December 2011, the FDA decided to add warnings on labels of two DRSP-containing preparations (Lenzer, 2011). Even in the presence of an RR of 2–3, the absolute risk of VTE is low, and modern CHCs, including patches and vaginal rings, remain an extremely safe drug with risks of VTE much lower than those incurred during pregnancy (Hannaford, 2011).

Pregnant women

Prevention of pregnancy-related VTE has not been systematically addressed and physicians do not have a consistent approach between hospitals and countries. Anticoagulant prophylaxis of VTE in pregnancy is prescribed with analogy to prophylaxis outside pregnancy and is not standardized. With this limitation, a low-molecular-weight heparin (LMWH) given subcutaneously once daily is the drug of choice for preventing pregnancy-related VTE, whereas in the puerperium the oral anti-coagulant vitamin-K antagonists can be alternatively used (Bates *et al.*, 2012). The optimal dose of LMWH for VTE prophylaxis in pregnancy is not established and ranges from ~2000 to 4000 UI or more (Lindqvist and Hellgren, 2011; Roeters van Lennepe *et al.*, 2011). LMWH is safe for the fetus because it does not cross the placenta, while vitamin-K antagonists are associated with fetal abnormalities throughout the whole gestational period. Antithrombotic prophylaxis is defined as primary when is aimed to prevent the first VTE in women considered at risk, or as secondary when is aimed to prevent VTE recurrence.

Women who should receive primary antithrombotic prophylaxis are those with known inherited or acquired thrombophilia and usually a positive family history of VTE. However, which type of thrombophilia does increase significantly the risk of VTE during pregnancy, suggesting the appropriateness of LMWH prophylaxis, is a matter of debate. Women with severe thrombophilia due to antithrombin, protein C or protein S deficiencies, homozygous factor V Leiden or prothrombin mutation, antiphospholipid antibodies and combined abnormalities do deserve primary prophylaxis (Martinelli *et al.*, 2002). Women with the most common heterozygous FVL or prothrombin mutations have a small increased risk of pregnancy-related VTE and should simply be counselled about signs and symptom of VTE without prescribing LMWH through the gestational period. Other risk factors to be taken into account when deciding the appropriateness of antithrombotic prophylaxis during pregnancy are family history of VTE, the presence of co-morbidities, obesity and maternal age. In the puerperium women with any type of thrombophilia should receive LMWH prophylaxis.

Secondary prophylaxis is given to women who had already had an episode of VTE and received an anticoagulant therapy for a limited period. The choice of prescribing LMWH for secondary prophylaxis is independent of the presence of thrombophilia and may depend on the triggering factors present at the time of previous event. If the

thromboembolism was idiopathic, pregnancy-related or occurred during CHC use, the risk of recurrence in pregnancy is higher than if the VTE was surgery- or trauma related. Although the evidence is limited, women with previous VTE occurring after surgery, leg fracture or immobilization (e.g. plaster cast) may avoid LMWH prophylaxis in pregnancy. In the puerperium, all women with previous VTE should receive LMWH prophylaxis (De Stefano *et al.*, 2006; Bates *et al.*, 2012).

It is important to note that being on LMWH prophylaxis does not indicate induction of labor nor operative delivery. The only caution is for spinal anesthesia that can be done at least 12 h after the last LMWH injection.

Women undergoing ovarian stimulation

All women undergoing IVF should be individually assessed for their risk of thromboembolic disorders, taking into account previous VTE, a family history of VTE, concurrent medical conditions, age, obesity and laboratory data on thrombophilia if available. Pragmatically, women with previous VTE should receive thromboprophylaxis (Nelson, 2009). Thromboprophylaxis with LMWH until the 13th week of gestation is suitable for women conceiving in the presence of OHSS. Alternatively, and arguably, a safer approach is to consider postponing embryo transfer in women at consistent risk of developing OHSS (D'Angelo, 2010). Cryopreserved oocytes or embryos can be safely used in a subsequent unstimulated cycle. Screening for thrombophilia is unlikely to be cost-effective.

Women using HRT

VTE risk rises in postmenopausal women with age and the use of estrogen either alone or combined with progestogen further increases the risk.

Following the publication of the WHI studies (The Writing Group for the Women's Health Initiative, 2002), many drug regulatory authorities (Medicines and Healthcare products Regulatory Agency, 2007) and professional societies issued advice about HRT prescribing. Most agree that women should be advised of the risks and HRT should only be prescribed for the relief of serious menopausal symptoms. Transdermal treatments seem safer than oral administration (Olié *et al.*, 2010). As with contraception, alternative therapies for the management of menopausal symptoms are available but, unlike contraception, they are often not all that effective (Sassarini and Lumsden, 2010). Once again, screening all women considering the risk for inherited thrombophilias is unlikely to be cost-effective (RCOG, 2011).

Conclusions

VTE is a serious health problem for both men and women but, because of pregnancy and common hormonal treatments, it is a specific health risk for women. Clinicians managing pregnant women or treating them for infertility or with oral contraceptives or HRT should be aware of the associated risks of VTE and of the need to take a careful medical history to identify additional co-existing risks. Clinicians should be able to suggest appropriate objective testing to diagnose VTE and to approach its prevention.

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Conflict of interest

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Appendix

A meeting was organized by ESHRE [August 26–27, 2012] to discuss VTE as a reproductive health risk. The contributors included: S. Eichinger (Klinische Abteilung für Hämatologie und Hämostaseologie, Universitätsklinik für Innere Medizin I, Medizinische Universität Wien, Wien, Österreich), J.L.H. Evers (Dept. Obstet. Gynecol., Maastricht University Medical Centre, Maastricht, The Netherlands), A. Glasier (Centre for Reproductive Biology, University of Edinburgh, UK), C. La Vecchia (Department of Epidemiology, IRCCS, Istituto di Ricerche Farmacologiche 'Mario Negri' and Department of Clinical Sciences and Community Health, Università degli Studi di Milano, Milano, Italy), I. Martinelli (A. Bianchi Bonomi Hemophilia and Thrombosis Center, Department of Internal Medicine and Medical Specialties, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milano, Italy), S. Skouby (Director of Endocrinological and Reproductive Unit, Dep. Ob/Gyn. Herlev Hospital, Faculty of Health and Medical Sciences

University of Copenhagen and Department of Thrombosis Research, Esbjerg, University of Southern Denmark, Copenhagen, Denmark), E. Somigliana (Department of Clinical Sciences and Community Health, Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, Milano, Italy). The discussants included: D.T. Baird (Simpson Centre for Reproductive Health, University of Edinburgh, UK), G. Benagiano (Dipartimento di Scienze Ginecologiche, Ostetriche ed Urologiche,

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