Venous Thromboembolism Issues in Women

Birgit Linnemann[1] Hannelore Rott[2] Rainer Zotz[3] Christina Hart[4]

[1] Division of Angiology, University Center of Vascular Medicine, University Hospital Regensburg, Regensburg, Germany
[2] Gerinnungszentrum Rhein-Ruhr, Duisburg, Germany
[3] Centrum für Blutgerinnungsstörungen und Transfusionsmedizin, Düsseldorf, Germany
[4] Department of Haematology and Oncology, Internal Medicine III, University Hospital Regensburg, Regensburg, Germany

Address for correspondence Birgit Linnemann, Prof. Dr. med., Bereich Angiologie - Universitäres Gefäßzentrum Ostbayern, Universitätsklinikum Regensburg, Franz-Josef-Strauss-Allee 11, 93053 Regensburg, Germany (e-mail: Birgit.Linnemann@klinik.uni-regensburg.de).

Hamostaseologie 2022;42:290–299.

Abstract

The lifetime risk of venous thromboembolism (VTE) is slightly higher in women than in men. There are several issues related to VTE that are unique to women. Combined hormonal contraceptives and pregnancy increase the risk of VTE in women of childbearing age, whereas hormone replacement therapy increases the VTE risk of postmenopausal women. Hereditary thrombophilia and risk factors such as older age, obesity, or smoking contribute to the risk increase. In women diagnosed with acute hormone-related VTE who are treated with oral anticoagulants, adequate contraception is mandatory to avoid unwanted pregnancies. According to current knowledge, hormonal contraception may be continued during anticoagulant therapy but must be switched to an estrogen-free contraception method at least 6 weeks before the termination of anticoagulation. VTE is also a major cause of maternal morbidity and mortality during pregnancy and the postpartum period. Currently, assisted reproduction technologies such as in vitro fertilization are widely used to treat couples affected by infertility. Complications of fertility treatment comprise VTE cases, especially in women with ovarian hyperstimulation syndrome. With this review, we intended to focus on VTE issues in women and summarize current evidence and guideline recommendations.

Keywords

- venous thromboembolism
- contraception
- hormone replacement therapy
- thrombophilia
- women

Introduction

Venous thromboembolism (VTE) is a common disease with an average incidence of 1 to 2 per 1,000 per year. The annual total burden of VTE has been estimated by modeling country-specific data from six European countries (i.e., France, Germany, Italy, Spain, Sweden, and the United Kingdom) with an overall population of 310.4 million inhabitants.[1] The extrapolation of data from these countries revealed approximately 760,000 patients per year with nonfatal VTE and 370,000 patients per year with VTE-related death, of which only 7% were diagnosed antemortem. In a meta-analysis of 18 studies involving 7,515 patients with a first unprovoked VTE who had completed at least 3 months of anticoagulant therapy, the long-term risk for recurrent VTE was substantial.[2] The cumulative risk of recurrent VTE at 10 years after discontinuation of anticoagulation was 41% in men and 29% in women. For recurrent VTE, a case fatality rate of 4% (95% confidence interval [CI]: 2–6%) was reported. Moreover, within 5 years after the discontinuation of anticoagulant therapy a substantial number of patients will develop long-term sequelae after VTE such as postthrombotic syndrome (≈28%) or chronic thromboembolic pulmonary hypertension (≈2%).[1]

Data from the Danish National Patient Registry covering all Danish hospitals indicate that the lifetime risk of VTE is

received
February 6, 2022
accepted after revision
July 26, 2022

Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/a-1919-9558.
ISSN 0720-9355.

slightly higher in women than in men and that reproductive factors contribute modestly to the risk increase in women.[3] In particular, women of childbearing age are at increased risk of VTE when compared to men of the same age, which is mainly attributed to combined hormonal contraceptive (CHC) use and pregnancy. Moreover, when compared to men, VTE manifests more often with symptoms of pulmonary embolism (PE) in women.[4]

In this comprehensive review, specific issues of VTE in women will be highlighted.

Combined Hormonal Contraception and Risk of VTE

Traditionally, estrogens are considered as sex hormones that mainly affect the development and regulation of the female reproductive system. However, estrogens are ubiquitous and have impact on almost all physiological organs and tissues including the cardiovascular system. In humans, there are four natural estrogens that exert differential effects throughout lifetime[5] (►Table 1). The natural estrogens estrone (E1), estradiol (E2), and estriol (E3) as well as synthetic estrogens have been introduced for therapeutic use more than 80 years ago. Ethinyl estradiol (EE) was the first synthetic estrogen that has been applied for the treatment of dysmenorrhea. Conjugated equine estrogens (CEE), a mixture of estrogen conjugates found in the urine of mares, were approved for the relief of climacteric symptoms such as hot flushes in the early 1940s. Approximately 20 years later, the first combined oral contraceptive pill containing an estrogen in combination with a gestagen component was introduced in the United States and has been available in Germany since 1961.

The association of VTE and the use of CHCs became evident shortly after the introduction of CHCs.[6] The extent of the risk increase mainly depends on the content of estrogen (predominantly EE), the gestagen component, and the route of administration. Since then, the composition of CHCs has changed to include lower doses of estrogens and newer gestagen components, but this has not resolved the problem of thromboembolic complications. A review by the European Medicines Agency (EMA) in 2013 concluded that the risk of VTE was higher for recently developed gestagen components in CHCs such as desogestrel or drospirenone (DRSP) when compared to older gestagens such as levonorgestrel (LNG), norethisterone, or norgestimate.[7] Consequently, European authorities decided to update the product information of CHCs and to provide information to women regarding the risk of VTE related to CHC use and to health care professionals regarding the types of CHC with the lowest VTE risk. Khialani et al analyzed the CHC prescription pattern in three European countries (the Netherlands, Denmark, United Kingdom) before and after the European Commission mandated changes in product information.[8] Among new CHC users in these three countries, the proportion of women initiating a CHC classified by the EMA as the safest option increased over time. Before the EMA decision, ≈76% of new users received a CHC containing LNG, norethisterone, or norgestimate; since 2014 this proportion has increased to ≈84%. In Germany, the proportion of women receiving a low-risk CHC is substantially lower. A recent data analysis of the largest public health insurance company (AOK) revealed that the proportion of women with low-risk CHCs was 28% in 2009 and increased only moderately to 47% in 2019.[9]

Only recently, the "Bundesinstitut für Arzneimittel und Medizinprodukte" (BfArM) revised its warning ("Rote-Hand-Brief") concerning the use of CHCs, which is still the most common method to avoid unwanted pregnancies in Germany.[10] Of note, the term CHC refers to oral as well as nonoral preparations (e.g., transdermal patches, vaginal ring).

Table 1 Natural and synthetic estrogens

Estrogen	Synthesis and function
Natural human estrogens	
Estrone (E1)	Present throughout life, primary estrogen in menopause
Estradiol (E2)	Produced by the ovaries, primary estrogen during reproductive years
Estriol (E3)	Produced by the placenta, major estrogen during pregnancy
Estetrol (E4)	Produced by the human fetal liver after the 9th week of gestation, present only during pregnancy with high levels in the fetus and lower levels in the maternal circulation
Synthetic estrogens	
Ethinyl estradiol (EE)	First synthetic estrogen, introduced for the treatment of dysmenorrhea
Conjugated equine estrogens (CEE)	Estrogen conjugates found in the urine of mares, introduced for the treatment of hot flushes in postmenopausal women

Oral Combined Hormonal Contraceptives

Modern oral preparations usually contain low-dose estrogen (e.g., 20–35 µg of EE) and a synthetic gestagen (progestin). These "pills" increase the risk of VTE two- to sixfold in females using hormonal contraceptives when compared to females not using hormonal contraceptives. However, the absolute risk of VTE in young women without additional risk factors remains low. In the general population, the overall VTE incidence of women without hormonal contraception is approximately 2 per 10,000 per year (►Table 2).[10]

Estrogens bind to classic estrogen receptors (e.g., Erα, ERβ) that act as transcription factors and regulate the transcription and expression of procoagulant, anticoagulant, and fibrinolytic factors, leading to a state of hypercoagulability.[11,12] The use of CHCs is accompanied by increased activities of prothrombotic factors (e.g., fibrinogen, prothrombin, and factors VII, VIII, and X) and reduced activities of natural coagulation inhibitors (e.g., antithrombin, protein S, and tissue factor pathway inhibitor). The extent of acquired resistance against activated protein C (APC resistance) has been shown to correlate with the risk of VTE.[13,14] These

Table 2 Incidence of VTE of the progestin component of traditional combined hormonal contraceptives (CHCs) according to the latest warning ("Rote-Hand-Brief") of the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM)[10]

Group	Brand name	Annual incidence of VTE
Women without hormonal contraception	–	2 per 10,000
CHC with levonorgestrel	e.g., Evaluna, Femigoa, Femikadin, Kleodina, Leios, Levomin, Microgynon, Minisiston, Miranova, Monostep, Triquilar	5–7 per 10,000
CHC with norethisterone	e.g., Eve	
CHC with norgestimate	–	
CHC with extended-cycle levonorgestrel	e.g., Seasonique	5–15 per 10,000
CHC with etonogestrel	e.g., Nuvaring (vaginal ring)	6–12 per 10,000
CHC with norelgestromin	e.g., Evra (transdermal patch)	
CHC with dienogest	e.g., Dienogenance, Dienovel, Finic, Maxim, Sillaba, Valette	8–11 per 10,000
CHC with drospirenone	e.g., Aida, Daylette, Drosfemine, Drospifem, Petibelle, Yasmin	9–12 per 10,000
CHC with gestodene	e.g., Femovan	
CHC with desogestrel	e.g., Desmin, Desofemine	
CHC with chlormadinon	e.g., Belara, Bellissima, Chariva, Enriqa, Madinette, Minette	Still unknown
CHC with nomegestrol[a]	e.g., Zoely	

Abbreviations: CHC, combined hormonal contraceptive; VTE, venous thromboembolism.
[a]Recent data suggest that CHCs containing estradiol/nomegestrol acetate (E2/NOMAC; brand name: Zoely), estradiol valerate/dienogest (E2V/DNG; brand name: Qlaira), or estetrol/drospirenone (E4/DRSP; brand name: Drovelis) are noninferior to CHCs containing levonorgestrel[16–18]

hormonal effects on the coagulation system are more pronounced in obese women and last up to 6 to 8 weeks after the cessation of CHC intake.[15]

The higher the estrogen dose is, the higher the risk of VTE. It has been suggested that the use of newer CHCs containing natural E2, estradiol valerate (E2V), or estetrol (E4) is associated with a lower risk of thromboembolic complications. In a large prospective observational study, E2/nomegestrol acetate (E2/NOMAC; brand name: Zoely) was shown to be noninferior to LNG-containing CHCs.[16] E2V has similar pharmacokinetic and pharmacodynamic properties to that of E2 as it is converted to E2 in the intestinal mucosa. To overcome inacceptable bleeding irregularities, E2V has been combined with dienogest (E2V/DNG; brand name: Qlaira). A large international active surveillance study demonstrated that VTE occurred less frequently with E2V/DNG in comparison to CHC containing LNG or other CHCs.[17]

Only recently, E4—in combination with DRSP (E4/DRSP; brand name: Drovelis)—has been introduced as a new estrogen component in CHCs.[18,19] E4 is a natural estrogen that is produced in the fetal liver and—due to both agonist and antagonist estrogenic properties—acts differentially on human tissues and has only minimal impact on liver gene expression. Phase 2 trials revealed only minimal impact on hemostasis biomarkers.[20,21] The changes of hemostatic parameters (e.g., endogenous thrombin potential, resistance to APC, prothrombin fragment 1 + 2, sex hormone binding protein) related to the use of E4/DRSP were at least similar or even less than that of EE/LNG and more pronounced than that of an EE/DRSP combination. Moreover, E4/DRSP administered in a 24/4 regimen completely inhibited ovulation and was associated with a favorable bleeding pattern and good body weight control resulting in high user satisfaction.[18]

Among CHCs, formulations containing LNG, norethisterone, or norgestimate are associated with the lowest risk of VTE,[22,23] whereas combinations with third- or fourth-generation progestins (e.g., DRSP, gestodene, or desogestrel) exert a higher risk increase (►**Table 2**). The risk of VTE is highest within the first year of prescription but remains elevated even thereafter. In one study, the risk was fivefold increased even after more than 60 months of use compared to nonusers of hormonal contraception (odds ratio [OR]: 5.2; 95% CI: 4.3–6.2),[24] whereas another study reported ORs ranging from 2.4 to 4.6 depending on the progestin component after at least 4 years of exposure.[25] Of note, the risk is temporarily increased again if CHC intake is resumed after a period of interruption of several weeks or months.

In general, the absolute risk of VTE in young and healthy women of childbearing age is rather low (annual incidence of VTE: 2 per 10,000). However, there may be a significant risk increase if additional VTE risk factors are present (e.g., hereditary thrombophilia, a positive family history of VTE, aged >35 years, obesity, smoking). Therefore, gynecologists, hemostaseologists, and experts of vascular medicine, as well as the BfArM, call to prescribe CHCs with the lowest risk increase and to choose or switch to an estrogen-free

Table 3 VTE risk factors, clinical relevance, and recommended consequences from the Association of Scientific Medical Societies in Germany (AWMF)[26]

VTE risk factor	Risk increase	Recommendation
Age > 35 y	Low to moderate	Thorough risk assessment and counseling. Generally, all contraceptive methods are applicable (provided that no additional risk factors are present)
BMI > 35 kg/m^2	Low to moderate	Thorough risk assessment and counseling. If possible, avoid CHCs (especially if aged >35 years and/or smokes >15 cigarettes per day)
Smoking	Low to moderate	Thorough risk assessment and counseling. If possible, avoid CHCs (especially if aged >35 years and/or has a BMI >35 kg/m^2)
Prolonged immobility, major surgery	Moderate to high	Thorough risk assessment and counseling. No new CHC prescription. Risk-adapted VTE prophylaxis measures.
Prior VTE	Moderate (after VTE related to a nonhormonal risk factor) to high (after unprovoked or hormone-related VTE)	Avoid CHCs. Consider consultation with a hemostaseologist. Consider testing for thrombophilia.
Family history of VTE	Moderate (after VTE related to a nonhormonal risk factor) to high (after unprovoked or hormone-related VTE)	Avoid CHCs. Consider consultation with a hemostaseologist. Consider testing for thrombophilia
Asymptomatic thrombophilia or known thrombophilia in a first-degree relative	Low to high (dependent on the thrombophilic defect and VTE manifestation in family members)	Reluctant indication of screening for thrombophilia in asymptomatic individuals, in case of thrombophilia consultation with a hemostaseologist before the prescription of CHCs.

Abbreviations: BMI, body mass index; CHC, combined hormonal contraceptive; VTE, venous thromboembolism.

contraceptive method for women with prior VTE, those with comorbidities predisposing them to VTE (e.g., inflammatory bowel disease), or those with additional VTE risk factors.[26] The relevant clinical risk factors and recommended consequences are shown in ►Table 3.

The recently updated AWMF-S3 guideline states that an individual risk assessment should be mandatory in each case in which a CHC prescription is planned.[26] The woman must be informed about the increased risk of VTE and alternative contraception methods, and the woman's preference should be included in decision-making. Moreover, if the woman decides to use a CHC, she should be informed about the leading symptoms of deep vein thrombosis (DVT) and PE and advised to contact an emergency physician or her general practitioner as soon as symptoms occur. In Germany, specific patient information materials can be downloaded from the BfArM website.[10]

Nonoral CHC Formulations

Attention should be given to the fact that transdermal and transvaginal CHCs have also been related to an increased risk of VTE and therefore provide no benefit in terms of VTE risk.[27–30] Analyzing data from four national registries in Denmark, Lidegaard et al calculated an eightfold increased relative risk of VTE in users of transdermal CHC patches (95% CI: 3.5–17.7) when compared to nonusers of hormonal contraceptives.[28] The relative risk of a CHC-releasing vaginal ring was 6.5 (95% CI: 4.7–8.9). Thus, the corresponding incidence rates are 9.7 and 7.8 per 10,000 years of exposure.

Estrogen-Free Contraception Methods

Progestin-only pills (POPs) do not contain any estrogen and, based on the current state of scientific knowledge, do not increase the risk of VTE.[26,31] Common progestins used in POPs are LNG and desogestrel. In addition to the classical oral application, intrauterine devices (IUDs), injectables for intramuscular application, and subcutaneous implants that slowly release progestin have been approved. However, because CHCs have been related to better menstrual control and have desirable CHC side effects such as a decrease in acne and hirsutism, POPs are prescribed less frequently.[32] Only recently has a DRSP-only pill (brand name: Slinda) been approved by the EMA. This progestin mono-preparation containing 4 mg DRSP is similar in efficacy to CHCs and is a POP with a better bleeding profile than traditional POPs (i.e., lower rates of unscheduled intracyclic bleeding and spotting). Moreover, DRSP has antigonadotropic, antimineralocorticoidic, and antiandrogenic properties.[33] Whereas the intake of CHCs containing DRSP is associated with a sixfold increased incidence of VTE, no cases of VTE and no changes in hemostaseological factors (i.e., APC resistance, protein C, antithrombin, factor VII, factor VIII, D-dimer levels) were observed in more than 2,500 women and over 25,000 cycles in DRSP users.[34]

Because POPs do not increase the risk of VTE, they can be even used—among other estrogen-free contraception methods—by women with a substantially heightened risk of VTE (e.g., known thrombophilia or prior VTE).[35] Unfortunately, this is in contrast to the summary of the product characteristics of most POPs, which still consider acute VTE as a contraindication.[32]

The risk of VTE is also low in users of LNG-releasing IUDs.[28,36] Of note, users of injectable depot medroxyprogesterone acetate had a 1.9- to 3.6-fold increased risk of VTE when compared to nonusers of hormonal contraceptives.[36,37]

Alternative estrogen-free contraception methods include copper IUDs and barrier methods such as cervical caps, diaphragms, condoms and spermicidal foam, sponges, and films. These methods also do not increase the risk of VTE. However, barrier methods are not as effective as birth control pills or IUDs in preventing pregnancy.

Hereditary Thrombophilia and Hormonal Contraception

Whether CHCs should be avoided by women without prior VTE but with known thrombophilia or a positive family history of VTE is a controversial issue. Several studies revealed an increased risk of VTE in women with hereditary thrombophilia who used CHCs.[38,39] However, there is consensus that a general screening for hereditary thrombophilia before the prescription of CHCs is not advisable. Because factor V Leiden (FVL) and prothrombin G20210A mutations are common in the European population, at least syllabication? thrombophilia can be detected in 3 to 9% of healthy subjects (►Table 4). Despite the high prevalence in the general population, the absolute risk of VTE is low, provided that no other VTE risk factors are present. A recent French study that included 2,214 relatives from 651 families with known thrombophilia calculated an annual VTE incidence rate of 0.36% (hazard ratio [HR]: 1.91; 95% CI: 1.30–2.80) in patients with mild thrombophilia and 0.64% (HR: 3.78; 95% CI: 2.50–5.73) in patients with severe thrombophilia.[40]

Table 4 Classical hereditary thrombophilia: prevalence and relative risk of VTE[84–86]

	Prevalence in the general population	Relative risk of a first VTE
Low-risk thrombophilia		
FVL mutation, heterozygous	2–7%	4–6
PT mutation G20210A, heterozygous	1–2%	3–5
High-risk thrombophilia		
FVL mutation, homozygous	0.01–0.02%	4–41
PT mutation G20210A, homozygous	Very rare	2–4
FVL and PT mutation, double heterozygous	Very rare	2–7
Antithrombin deficiency	0.02–0.2%	13–59
Protein C deficiency	0.2–0.5%	13–42
Protein S deficiency	0.1–0.7%	26–56

Abbreviations: FVL, factor V Leiden; PT, prothrombin time; VTE, venous thromboembolism.

However, there is a remarkable risk increase in women with thrombophilia who use CHCs. The risk increase can be roughly estimated with multiplication of relative risks.[41] For example, assuming a basic annual risk of 2 per 10,000, the combined effect of FVL (fivefold risk increase) and a CHC containing DRSP (sixfold risk increase) results in an absolute annual risk of 60 per 10,000 or 0.6%. Only recently, a French study group analyzed the risk of VTE in women with a FVL mutation who were prescribed different CHCs. The authors demonstrated that the higher VTE risk associated with CHC containing DRSP or cyproterone acetate, compared with second generation or norgestimate, is even greater among FVL carriers.[42] A Dutch study analyzed the joint effects of common prothrombotic genetic factors and CHC use and found that the risk of VTE was highest when both risk factors were present.[43] The joint effect of FVL and CHCs containing LNG resulted in an OR of 17.4 (95% CI: 11.4–26.6), whereas the OR was 24.8 (95% CI: 12.3–50.0) when LNG-containing CHCs were used in women with the prothrombin mutation G20210A. The risk increase was even higher in women with a genetic factor using gestodene, desogestrel, and cyproterone.

Consequently, women with thrombophilia and a positive family history of VTE should be counseled to preferably use an estrogen-free method for contraception, especially if an index patient suffered unprovoked or hormone-related VTE at a younger age. If the prescription of CHCs seems to be inevitable due to comorbidities, a thorough hemostaseologic work-up is recommended, and the prescription of a CHC with LNG, norethisterone, or norgestimate may be considered.

Contraception in Women with Acute VTE

Women with acute CHC-related VTE often discontinue contraception use immediately after the diagnosis of VTE. Consequently, withdrawal bleeding occurs in the initial phase of anticoagulant therapy when higher doses of a factor-Xa inhibitor are required (e.g., 10 mg of apixaban or 15 mg of rivaroxaban twice daily) or vitamin K antagonist (VKA) therapy is given in addition to therapeutic-dose low-molecular-weight heparin (LMWH). Thus, the early discontinuation of a CHC may result in heavy menstrual bleeding. Moreover, the risk of unwanted pregnancies and oral anticoagulant exposure to a fetus will be increased. Of note, direct factor Xa or thrombin inhibitors as well as traditional VKAs cross the placental barrier and have the potential to harm a fetus. Beyer-Westendorf et al collected all available case reports of direct oral anticoagulant (DOAC) exposure in pregnancies and identified 614 unique cases.[44] Of the 336 pregnancies with available outcome data (55%), 74 (22%) resulted in miscarriage and 21 (6%) in fetal abnormalities, of

which 12 (4%) were adjudicated as major birth defects potentially related to DOAC exposure. Data from an observational cohort study including 1,642 pregnancies indicate that the risk for birth defects and fetal loss of phenprocoumon and other VKAs seems to be time-dependent and increases steeply after the 5th week of gestation.[45] The overall rate of major birth defects was 7.4% and spontaneous abortions occurred in 38% of pregnancies with exposure to phenprocoumon, which is the most commonly used VKA in Germany.

Therefore, the current AWMF-S3 guideline stipulates safe contraception for all women of childbearing age who require oral anticoagulant therapy.[26] However, there has been controversy regarding the continuation of hormonal therapy in women diagnosed with VTE. Whereas the World Health Organization (WHO) recommended the cessation of CHCs at VTE diagnosis, the International Society on Thrombosis and Haemostasis Scientific and Standardization Committee recommended discontinuing CHCs before stopping anticoagulant therapy.[46,47]

To the best of current knowledge, the prothrombotic effect of CHCs is compensated by full-therapeutic anticoagulation so that the continued intake of CHCs seems to be justifiable. In a post hoc subgroup analysis of the EINSTEIN-DVT/-PE studies that compared VTE recurrence among women with and without hormonal treatment before the age of 60, there was no risk increase among those who continued hormonal therapy (3.7 vs. 4.7%; HR 0.56; 95% CI: 0.23–1.39).[48] To minimize the risk of VTE under anticoagulant therapy, an estrogen-free contraception method, such as POPs, or a progestin, or copper IUD, should be preferred (►Table 5). If a woman and her attending physician decide to continue CHCs while she is being treated with oral anticoagulants, a switch to a combination containing a low-risk progestin (e.g., LNG) can be considered. Of note, the current AWMF-S3 guideline recommends switching to an estrogen-free contraception method at least 6 weeks before the discontinuation of anticoagulant therapy.[26]

Infertility Treatment

Infertility is common and affects approximately 10% of couples. The number of pregnancies achieved by fertility treatment (artificial reproduction technologies [ART]) has been increasing in recent decades. Complications of fertility treatment comprise VTE, ovarian hyperstimulation syndrome (OHSS), and implantation failure.

The risk of VTE after in vitro fertilization (IVF) was increased during the whole duration of pregnancy but was highest during the first trimester (HR: 4.22; 95% CI: 2.46–7.26). VTE incidence is significantly higher after successful ART cycles than after unsuccessful cycles (9.4 vs. 1.3 per 1,000 cycles; OR: 13.94; 95% CI: 1.41–137.4).[49]

In a Swedish population-based cohort study including 902,891 first pregnancies between 1992 and 2012, women who achieved pregnancy after IVF with fresh embryo transfer had a ninefold increased risk of VTE in the first trimester compared to that in women with spontaneous pregnancies (HR: 8.96; 95% CI: 6.33–12.67).[50] No significant risk increase was observed for pregnancies after frozen-thawed embryo transfer. The absolute incidence of VTE was 1.77 per 1,000 pregnancies after IVF with fresh embryo transfer as compared to 0.14 per 1,000 after natural conception and 0.61 per 1,000 after IVF with frozen-thawed embryo transfer.

Particular attention should be given to women with OHSS which is a recognized complication of ART after controlled ovarian hyperstimulation with exogenous gonadotropin administration. OHSS occurs in moderate or severe forms in 2 to 3% of all IVF patients[51,52] and is accompanied by high E2 concentrations. A substantially increased incidence of first-trimester VTE has been reported in women with moderate or severe OHSS (16.8 per 1,000 pregnancies; OR: 99.7; 95% CI: 61.6–161.1) as compared to women with natural pregnancies.[53] Thromboembolism is considered the most severe complication related to OHSS, and unusual site thrombosis involving the veins of the upper extremities and the internal jugular or cerebral veins has been reported.[54–56] In women

Table 5 AWMF-S3 guideline recommendation concerning contraception in women with VTE treated with oral anticoagulants and after the termination of therapy[26]

Contraception before VTE	Contraception during anticoagulant therapy	Contraception after the termination of anticoagulant therapy
None	Estrogen-free method (except DMPA); avoid CHCs (since not applicable after the termination of anticoagulation)	Estrogen-free method (except DMPA)
CHCs	Switch to an estrogen-free method or continue CHCs and switch to an estrogen-free method at latest 6 weeks before the termination of anticoagulant therapy	Estrogen-free method (except DMPA)
Progestin-only contraceptives (oral or IUD, except DMPA)	Continue progestin-only contraceptives	Estrogen-free method (except DMPA)
Barrier methods (e.g., condoms)	To increase contraceptive efficacy, consider switching to a preferably estrogen-free method (except DMPA)	Estrogen-free method (except DMPA)

Abbreviations: DMPA, depot medroxyprogesterone acetate; IUD, intrauterine device; VTE, venous thromboembolism.

with severe OHSS, a VTE incidence of 1 to 4% has been reported. Therefore, guidelines recommended thromboprophylaxis with LMWH for up to 3 months after the resolution of OHSS.[57]

Pregnancy-Associated VTE

VTE is one of the leading causes of maternal mortality in the Western world. According to a 2014 WHO systematic analysis, PE accounted for 14% of the maternal deaths in developed countries.[58] VTE complicates 1 to 2 per 1,000 pregnancies. Overall, the risk of VTE in pregnant women is four- to fivefold higher than that in age-matched nonpregnant women. VTE risk increases with gestational age and is highest around the time of delivery and immediately postpartum. A Danish population-based study revealed an ≈20-fold risk increase at term.[59] Approximately one-third of pregnancy-related DVT cases and half of pregnancy-related PE cases occur after delivery. Risk factors and VTE prevention strategies have been recently summarized in this journal by the working group "Women's Health" of the "Society of Thrombosis and Haemostasis" (GTH) and are not further discussed here.[60]

Hormonal Replacement Therapy

Estrogen therapy is the most effective treatment option for relieving climacteric symptoms such as hot flashes, sleep disturbances, depression, and urogenital complaints due to the atrophy of mucous membranes. Because estrogen monotherapy is associated with an elevated risk of endometrial cancer, estrogens are usually applied in combination with a progestin component. In this regard, estrogens are applied in the lowest effective dose and in the shortest time frame needed to provide the relief of symptoms.

The different estrogen types used for hormone replacement therapy (HRT)—mainly CEE or E2—are less potent than EE used in CHCs. Oral HRT preparations, in monotherapy as well as in combination with a progestin, increase the risk of VTE two- to threefold.[61,62] For women with prior VTE, an up to fourfold risk increase has been described.[63,64] Similar to CHCs, the risk of VTE increases with the estrogen dose and depends on the progestin compound. The risk is highest within the first year of application and remains elevated for the duration of therapy. A further risk increase is observed with the presence of additional VTE risk factors, such as older age, a higher body mass index, or the presence of thrombophilia. Because HRT patients are generally older, HRT populations have a higher absolute baseline risk than CHC populations. The overall annual incidence of DVT among Swedish women before the age of 40 was less than 20 per 100,000 per year but increased to more than 50 per 100,000 per year after the age of 50.[65] In contrast to CHCs, transdermal applications for HRT exert no influence on the risk of VTE.[66–68]

Sex-Specific Aspects of VTE Recurrence

VTE Recurrence in Women

In general, the risk of VTE recurrence depends on the site and manifestation of the initial VTE, the presence or absence of transient or persistent risk factors, and comorbidities. Several risk prediction scores have been validated in recent years with the objective of predicting the risk of VTE recurrence and individualizing the duration and intensity of therapy (e.g., DASH, HERDOO2, Vienna prediction model).[69–71] The sex aspect was included in each model.

Several studies have identified the male sex as an independent risk predictor of VTE recurrence.[72–74] A patient-level meta-analysis including 2,554 VTE patients who were followed for 2.5 years on average after stopping anticoagulant therapy revealed a 2.2-fold higher risk of recurrence after a first unprovoked VTE in men than in women.[75] Even after adjustment for women with hormone-related VTE, the recurrence risk in men remained significantly higher (HR: 1.8; 95% CI: 1.4–2.5).

In a multinational cohort management study (REVERSE-II), the HERDOO2 clinical decision rule was prospectively validated to identify women at low risk of recurrent VTE.[70] Women with none or one of the four HERDOO2 criteria (i.e., hyperpigmentation, oedema, or redness in either leg; a D-dimer level ≥250 µg/L while using anticoagulants; a body mass index ≥30 kg/m2; or an age ≥65 years) had a low risk of recurrence (3.0% per patient year; 95% CI: 1.8–4.8%) and therefore could safely discontinue anticoagulants after 5 to 12 months of treatment. In contrast, high-risk women (scores ≥ 2) and men who discontinued anticoagulant therapy had a substantially higher risk of VTE recurrence (8.1% per patient-year; 95% CI: 5.2–11.9%). Whether these high-risk women and men require indefinite anticoagulation remains controversial since the annual risk of recurrent VTE seems to decrease after the first 1 to 2 years.

Risk of Recurrence after Hormone-Related VTE

According to the current risk estimations, CHC use is generally considered to be a minor transient risk factor for VTE.[76] However, the continuation of CHC intake after the termination of anticoagulant therapy is supposed to put women at high risk for VTE recurrence. Therefore, CHCs should definitely be discontinued or switched to estrogen-free contraception at least 6 weeks before the cessation of anticoagulant therapy.

In general, women have a lower risk of recurrence than men of the same age after a first VTE. Among women with a first unprovoked VTE, the cumulative incidence for recurrent VTE was 8.9% in the first year, 13.6% at 2 years, 21.5% at 5 years, and 28.8% at 10 years.[2] The corresponding incidence rates for VTE recurrence in men were 11.9% in the first year, 18.3% at 2 years, 28.6% at 5 years, and 41.2% at 10 years. The risk of recurrence is also lower after hormone-related VTE than after unprovoked VTE.[75,77,78] In cohort studies, the absolute annual risk of recurrence was 1.1 to 2.5%.[79–81] This must be balanced against the risk of major bleeding under continued anticoagulant therapy. For example, phase 3 trials comparing DOACs with the traditional anticoagulation regimen of heparin followed by VKAs revealed an average major bleeding rate of 1.0% for patients taking DOACs and 1.7% for those taking VKA.[82] Some studies report an even higher bleeding risk for women than for men.[83] When

balancing the risks and benefits of anticoagulation after a CHC-related VTE, therapy—in the absence of additional or persistent risk factors—is often limited to 3 to 6 months.

Final Remarks

Because estrogens and estrogen–progestin combinations put women in jeopardy of thromboembolic events, an individual risk assessment and weighing of risks and benefits, including a woman's preferences, is mandatory before introducing any hormone therapy. The woman must be informed about the risk increase and the symptoms of DVT and PE and should be instructed to contact her general practitioner or an emergency physician as soon as symptoms occur. The same applies for women for whom ART or HRT due to climacteric symptoms is planned. As a matter of principle, a CHC composition with the lowest known risk of VTE should be chosen. Only recently, new formulations (e.g., combinations containing E4 and DRSP as well as DRSP-only pills) have been approved in Europe and many other countries and can be considered as an important step forward in terms of efficacy, better bleeding profile, and low risk of thromboembolic complications.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

1 Cohen AT, Agnelli G, Anderson FA, et al; VTE Impact Assessment Group in Europe (VITAE) Venous thromboembolism (VTE) in Europe. The number of VTE events and associated morbidity and mortality. Thromb Haemost 2007;98(04):756–764

2 Khan F, Rahman A, Carrier M, et al; MARVELOUS Collaborators. Long term risk of symptomatic recurrent venous thromboembolism after discontinuation of anticoagulant treatment for first unprovoked venous thromboembolism event: systematic review and meta-analysis. BMJ 2019;366:l4363

3 Arnesen CAL, Veres K, Horváth-Puhó E, Hansen JB, Sørensen HT, Brækkan SK. Estimated lifetime risk of venous thromboembolism in men and women in a Danish nationwide cohort: impact of competing risk of death. Eur J Epidemiol 2022;37(02): 195–203

4 Scheres LJJ, Brekelmans MPA, Beenen LFM, Büller HR, Cannegieter SC, Middeldorp S. Sex-specific differences in the presenting location of a first venous thromboembolism. J Thromb Haemost 2017;15(07):1344–1350

5 Gérard C, Arnal J-F, Jost M, et al. Profile of estetrol, a promising native estrogen for oral contraception and the relief of climacteric symptoms of menopause. Expert Rev Clin Pharmacol 2022;15 (02):121–137

6 TYLER ET. Oral contraception and venous thrombosis. JAMA 1963; 185:131–132

7 European Medicines Agency. Benefits of combined hormonal contraceptives (CHCs) continue to outweigh risks – CHMP endorses PRAC recommendation. Accessed June 16, 2022, at: https://www.ema.europa.eu/en/news/benefits-combined-hormonal-contraceptives-chcs-continue-outweigh-risks-chmp-endorses-prac

8 Khialani D, Jones ME, Szépligeti SK, et al. Combined hormonal contraceptive use in Europe before and after the European Commission mandated changes in product information. Contracept X 2020;2:100018

9 AOK-Bundesverband. Pille zur Verhütung: Verordnungsanteil risikoreicher Präparate nach wie vor hoch. Accessed August 5, 2022, at: https://aok-bv.de/presse/pressemitteilungen/2020/index_23804.html

10 Bundesinstitut für Arzneimittel und Medizinproduktesicherheit. Rote-Hand-Brief. Accessed January 23, 2022, at: https://www.bfarm.-de/SharedDocs/Risikoinformationen/Pharmakovigilanz/DE/RHB/2021/rhb-khk.html

11 Tchaikovski SN, Rosing J. Mechanisms of estrogen-induced venous thromboembolism. Thromb Res 2010;126(01):5–11

12 Oger E, Alhenc-Gelas M, Lacut K, et al; SARAH Investigators. Differential effects of oral and transdermal estrogen/progesterone regimens on sensitivity to activated protein C among postmenopausal women: a randomized trial. Arterioscler Thromb Vasc Biol 2003;23(09):1671–1676

13 Tans G, van Hylckama Vlieg A, Thomassen MCLGD, et al. Activated protein C resistance determined with a thrombin generation-based test predicts for venous thrombosis in men and women. Br J Haematol 2003;122(03):465–470

14 Tchaikovski SN, Thomassen MCLGD, Stickeler E, Bremme K, Rosing J. Resistance to activated protein C and impaired TFPI activity in women with previous hormone-induced venous thromboembolism. Thromb Res 2021;207:143–149

15 Abdollahi M, Cushman M, Rosendaal FR. Obesity: risk of venous thrombosis and the interaction with coagulation factor levels and oral contraceptive use. Thromb Haemost 2003;89(03):493–498

16 Reed S, Koro C, DiBello J, et al. Prospective controlled cohort study on the safety of a monophasic oral contraceptive containing nomegestrol acetate (2.5mg) and 17β-oestradiol (1.5mg) (PRO-E2 study): risk of venous and arterial thromboembolism. Eur J Contracept Reprod Health Care 2021;26(06):439–446

17 Dinger J, Do Minh T, Heinemann K. Impact of estrogen type on cardiovascular safety of combined oral contraceptives. Contraception 2016;94(04):328–339

18 Gemzell-Danielsson K, Apter D, Zatik J, et al. Estetrol-Drospirenone combination oral contraceptive: a clinical study of contraceptive efficacy, bleeding pattern and safety in Europe and Russia. BJOG 2022;129(01):63–71

19 Creinin MD, Westhoff CL, Bouchard C, et al. Estetrol-drospirenone combination oral contraceptive: North American phase 3 efficacy and safety results. Contraception 2021;104(03):222–228

20 Kluft C, Zimmerman Y, Mawet M, et al. Reduced hemostatic effects with drospirenone-based oral contraceptives containing estetrol vs. ethinyl estradiol. Contraception 2017;95(02): 140–147

21 Douxfils J, Klipping C, Duijkers I, et al. Evaluation of the effect of a new oral contraceptive containing estetrol and drospirenone on hemostasis parameters. Contraception 2020;102(06):396–402

22 de Bastos M, Stegeman BH, Rosendaal FR, et al. Combined oral contraceptives: venous thrombosis. Cochrane Database Syst Rev 2014;(03):CD010813

23 Weill A, Dalichampt M, Raguideau F, et al. Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study. BMJ 2016;353:i2002

24 van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJM, Rosendaal FR. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. BMJ 2009;339:b2921

25 Lidegaard Ø, Nielsen LH, Skovlund CW, Skjeldestad FE, Løkkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. BMJ 2011;343:d6423

26 AWMF-S3-Leitlinie Hormonelle Empfängnisverhütung. [AWMF Registry No. 015 - 015]. Published August 1, 2019. Accessed January 23, 2022, at: https://www.awmf.org/leitlinien/detail/ll/015-015.html

27 Dore DD, Norman H, Loughlin J, Seeger JD. Extended case-control study results on thromboembolic outcomes among transdermal contraceptive users. Contraception 2010;81(05):408–413
28 Lidegaard O, Nielsen LH, Skovlund CW, Løkkegaard E. Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001-10. BMJ 2012;344:e2990
29 Stocco B, Fumagalli HF, Franceschini SA, et al. Comparative study of the effects of combined oral contraceptives in hemostatic variables: an observational preliminary study. Medicine (Baltimore) 2015;94(04):e385
30 Westhoff CL, Eisenberger A, Tang R, Cremers S, Grossman LV, Pike MC. Clotting factor changes during the first cycle of oral contraceptive use. Contraception 2016;93(01):70–76
31 Tepper NK, Whiteman MK, Marchbanks PA, James AH, Curtis KM. Progestin-only contraception and thromboembolism: a systematic review. Contraception 2016;94(06):678–700
32 Rott H. Birth control pills and thrombotic risks: differences of contraception methods with and without estrogen. Hamostaseologie 2019;39(01):42–48
33 Römer T, Bitzer J, Egarter C, et al. Oral progestins in hormonal contraception: importance and future perspectives of a new progestin only-pill containing 4 mg drospirenone. Geburtshilfe Frauenheilkd 2021;81(09):1021–1030
34 Palacios S, Colli E, Regidor P-A. Efficacy and cardiovascular safety of the new estrogen-free contraceptive pill containing 4 mg drospirenone alone in a 24/4 regime. BMC Womens Health 2020;20(01):218
35 Klok FA, Barco S. Optimal management of hormonal contraceptives after an episode of venous thromboembolism. Thromb Res 2019;181(Suppl 1):S1–S5
36 van Hylckama Vlieg A, Helmerhorst FM, Rosendaal FR. The risk of deep venous thrombosis associated with injectable depot-medroxyprogesterone acetate contraceptives or a levonorgestrel intrauterine device. Arterioscler Thromb Vasc Biol 2010;30(11): 2297–2300
37 Tepper NK, Jeng G, Curtis KM, Boutot ME, Boulet SL, Whiteman MK. Venous thromboembolism among women initiating depot medroxyprogesterone acetate immediately postpartum. Obstet Gynecol 2019;133(03):533–540
38 van Vlijmen EFW, Wiewel-Verschueren S, Monster TBM, Meijer K. Combined oral contraceptives, thrombophilia and the risk of venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost 2016;14(07):1393–1403
39 Wu O, Robertson L, Langhorne P, et al. Oral contraceptives, hormone replacement therapy, thrombophilias and risk of venous thromboembolism: a systematic review. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study. Thromb Haemost 2005;94(01):17–25
40 Suchon P, Resseguier N, Ibrahim M, et al. Common risk factors add to inherited thrombophilia to predict venous thromboembolism risk in families. TH Open 2019;3(01):e28–e35
41 Rosendaal FR. Venous thrombosis: a multicausal disease. Lancet 1999;353(9159):1167–1173
42 Hugon-Rodin J, Horellou M-H, Conard J, Gompel A, Plu-Bureau G. Type of combined contraceptives, factor V Leiden mutation and risk of venous thromboembolism. Thromb Haemost 2018;118 (05):922–928
43 Khialani D, le Cessie S, Lijfering WM, Cannegieter SC, Rosendaal FR, van Hylckama Vlieg A. The joint effect of genetic risk factors and different types of combined oral contraceptives on venous thrombosis risk. Br J Haematol 2020;191(01):90–97
44 Beyer-Westendorf J, Tittl L, Bistervels I, et al. Safety of direct oral anticoagulant exposure during pregnancy: a retrospective cohort study. Lancet Haematol 2020;7(12):e884–e891
45 Hüttel E, Padberg S, Meister R, Beck E, Schaefer C. Pregnancy outcome of first trimester exposure to the vitamin K antagonist phenprocoumon depends on duration of treatment. Thromb Haemost 2017;117(05):870–879
46 Baglin T, Bauer K, Douketis J, Buller H, Srivastava A, Johnson G. Duration of anticoagulant therapy after a first episode of an unprovoked pulmonary embolus or deep vein thrombosis: guidance from the SSC of the ISTH. J Thromb Haemost 2012;10(04): 698–702
47 WHO. Medical Eligibility Criteria for Contraceptive Use. 5th ed. Geneva: World Health Organization; 2015
48 Martinelli I, Lensing AWA, Middeldorp S, et al. Recurrent venous thromboembolism and abnormal uterine bleeding with anticoagulant and hormone therapy use. Blood 2016;127(11): 1417–1425
49 Villani M, Favuzzi G, Totaro P, et al. Venous thromboembolism in assisted reproductive technologies: comparison between unsuccessful versus successful cycles in an Italian cohort. J Thromb Thrombolysis 2018;45(02):234–239
50 Olausson N, Discacciati A, Nyman AI, et al. Incidence of pulmonary and venous thromboembolism in pregnancies after in vitro fertilization with fresh respectively frozen-thawed embryo transfer: nationwide cohort study. J Thromb Haemost 2020;18(08): 1965–1973
51 Humaidan P, Nelson SM, Devroey P, et al. Ovarian hyperstimulation syndrome: review and new classification criteria for reporting in clinical trials. Hum Reprod 2016;31(09): 1997–2004
52 Nelson SM. Prevention and management of ovarian hyperstimulation syndrome. Thromb Res 2017;151(Suppl 1):S61–S64
53 Rova K, Passmark H, Lindqvist PG. Venous thromboembolism in relation to in vitro fertilization: an approach to determining the incidence and increase in risk in successful cycles. Fertil Steril 2012;97(01):95–100
54 Chan WS, Dixon ME. The "ART" of thromboembolism: a review of assisted reproductive technology and thromboembolic complications. Thromb Res 2008;121(06):713–726
55 Sachar P, Rajamani K. Young ischemic stroke in association with ovarian hyperstimulation syndrome. J Stroke Cerebrovasc Dis 2016;25(09):e134–e140
56 Lee SH, Park J-W, Han M, Bae JW, Cho YJ. Internal jugular vein thrombosis with OHSS. J Clin Ultrasound 2017;45(07):450–452
57 Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos A-M, Vandvik PO. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2, Suppl): e691S–e736S
58 Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health 2014;2(06): e323–e333
59 Virkus RA, Løkkegaard ECL, Bergholt T, Mogensen U, Langhoff-Roos J, Lidegaard Ø Venous thromboembolism in pregnant and puerperal women in Denmark 1995-2005. A national cohort study. Thromb Haemost 2011;106(02):304–309
60 Hart C, Bauersachs R, Scholz U, et al. Prevention of venous thromboembolism during pregnancy and the puerperium with a special focus on women with hereditary thrombophilia or prior VTE-position paper of the Working Group in Women's Health of the Society of Thrombosis and Haemostasis (GTH). Hamostaseologie 2020;40(05):572–590
61 Canonico M, Plu-Bureau G, Lowe GDO, Scarabin P-Y. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ 2008;336(7655):1227–1231
62 Rovinski D, Ramos RB, Fighera TM, Casanova GK, Spritzer PM. Risk of venous thromboembolism events in postmenopausal women using oral versus non-oral hormone therapy: a systematic review and meta-analysis. Thromb Res 2018;168:83–95
63 Cushman M, Kuller LH, Prentice R, et al; Women's Health Initiative Investigators. Estrogen plus progestin and risk of venous thrombosis. JAMA 2004;292(13):1573–1580

64 Høibraaten E, Qvigstad E, Arnesen H, Larsen S, Wickstrøm E, Sandset PM. Increased risk of recurrent venous thromboembolism during hormone replacement therapy–results of the randomized, double-blind, placebo-controlled estrogen in venous thromboembolism trial (EVTET). Thromb Haemost 2000;84(06): 961–967
65 Glise Sandblad K, Rosengren A, Sörbo J, Jern S, Hansson P-O. Pulmonary embolism and deep vein thrombosis-comorbidities and temporary provoking factors in a register-based study of 1.48 million people. Res Pract Thromb Haemost 2022;6(04):e12714
66 Roach REJ, Lijfering WM, Helmerhorst FM, Cannegieter SC, Rosendaal FR, van Hylckama Vlieg A. The risk of venous thrombosis in women over 50 years old using oral contraception or postmenopausal hormone therapy. J Thromb Haemost 2013;11(01):124–131
67 Renoux C, Dell'Aniello S, Suissa S. Hormone replacement therapy and the risk of venous thromboembolism: a population-based study. J Thromb Haemost 2010;8(05):979–986
68 Canonico M, Fournier A, Carcaillon L, et al. Postmenopausal hormone therapy and risk of idiopathic venous thromboembolism: results from the E3N cohort study. Arterioscler Thromb Vasc Biol 2010;30(02):340–345
69 Marcucci M, Iorio A, Douketis JD, et al. Risk of recurrence after a first unprovoked venous thromboembolism: external validation of the Vienna Prediction Model with pooled individual patient data. J Thromb Haemost 2015;13(05):775–781
70 Rodger MA, Le Gal G, Anderson DR, et al; REVERSE II Study Investigators. Validating the HERDOO2 rule to guide treatment duration for women with unprovoked venous thrombosis: multinational prospective cohort management study. BMJ 2017;356: j1065
71 Tosetto A, Iorio A, Marcucci M, et al. Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH). J Thromb Haemost 2012;10 (06):1019–1025
72 Baglin T, Luddington R, Brown K, Baglin C. High risk of recurrent venous thromboembolism in men. J Thromb Haemost 2004;2 (12):2152–2155
73 Kyrle PA, Minar E, Bialonczyk C, Hirschl M, Weltermann A, Eichinger S. The risk of recurrent venous thromboembolism in men and women. N Engl J Med 2004;350(25):2558–2563
74 Linnemann B, Zgouras D, Schindewolf M, Schwonberg J, Jarosch-Preusche M, Lindhoff-Last E. Impact of sex and traditional cardiovascular risk factors on the risk of recurrent venous thromboembolism: results from the German MAISTHRO Registry. Blood Coagul Fibrinolysis 2008;19(02):159–165
75 Douketis J, Tosetto A, Marcucci M, et al. Risk of recurrence after venous thromboembolism in men and women: patient level meta-analysis. BMJ 2011;342:d813
76 Kearon C, Ageno W, Cannegieter SC, Cosmi B, Geersing G-J, Kyrle PASubcommittees on Control of Anticoagulation, and Predictive and Diagnostic Variables in Thrombotic Disease. Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. J Thromb Haemost 2016; 14(07):1480–1483
77 Blanco-Molina Á, Trujillo-Santos J, Pesavento R, et al; RIETE Investigators. Outcome after discontinuing anticoagulant therapy in women with venous thromboembolism during hormonal use. Thromb Res 2017;151(Suppl 1):S6–S10
78 Kiconco S, Abdul Sultan A, Grainge MJ. Recurrence risk of venous thromboembolism and hormone use in women from England: a cohort study using clinical practice research datalink. Br J Haematol 2017;177(01):127–135
79 Christiansen SC, Lijfering WM, Helmerhorst FM, Rosendaal FR, Cannegieter SC. Sex difference in risk of recurrent venous thrombosis and the risk profile for a second event. J Thromb Haemost 2010;8(10):2159–2168
80 Vaillant-Roussel H, Ouchchane L, Dauphin C, Philippe P, Ruivard M. Risk factors for recurrence of venous thromboembolism associated with the use of oral contraceptives. Contraception 2011;84(05):e23–e30
81 Eischer L, Eichinger S, Kyrle PA. The risk of recurrence in women with venous thromboembolism while using estrogens: a prospective cohort study. J Thromb Haemost 2014;12(05):635–640
82 van Es N, Coppens M, Schulman S, Middeldorp S, Büller HR. Direct oral anticoagulants compared with vitamin K antagonists for acute venous thromboembolism: evidence from phase 3 trials. Blood 2014;124(12):1968–1975
83 Bistervels IM, Scheres LJJ, Hamulyák EN, Middeldorp S. Sex matters: practice 5P's when treating young women with venous thromboembolism. J Thromb Haemost 2019;17(09):1417–1429
84 Mannucci PM, Franchini M. Classic thrombophilic gene variants. Thromb Haemost 2015;114(05):885–889
85 Simone B, De Stefano V, Leoncini E, et al. Risk of venous thromboembolism associated with single and combined effects of Factor V Leiden, Prothrombin 20210A and Methylenetethraydrofolate reductase C677T: a meta-analysis involving over 11,000 cases and 21,000 controls. Eur J Epidemiol 2013;28 (08):621–647
86 Linnemann B, Hart C. Laboratory diagnostics in thrombophilia. Hamostaseologie 2019;39(01):49–61