Biological effects of progestins: focus on deep venous thrombosis risk

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ABSTRACT

Combined hormonal contraception containing estrogen and progestin and menopausal hormone therapy with estrogen plus progestins or estrogen alone are consistently reported risk factors for deep venous thrombosis (DVT) and, with less certainty, arterial thrombosis. The DVT risk associated with combined hormonal contraceptives (CHCs) appears to vary by route of administration, estrogen dose and type of progestin. CHCs containing low-dose estrogen (< 35 microgram ethinyl estradiol) combined with "newer generations" of progestins (e.g., desogestrel, gestodene and drospironone) may have a higher DVT risk than those containing low-dose estrogen combined with the older (second) generation progestin types (e.g., levonorgestrel). Among postmenopausal women, DVT risk also varies by estrogen type and mode of delivery. Among combined oral contraception (COC) users, the variation in DVT risk can be at least partially explained by differences in resistance to activated protein C (APC) as measured by thrombin generation based on the APC resistance test and quantified by means of a normalized APC sensitivity ratio. The net estrogenicity of COC may also serve as a risk marker for DVT as several studies have shown an association between clinical risk and levels of sex hormone-binding globulin during COC use. Similar findings have been obtained using measurements of factor VII-activating protease. Limited evidence suggests increased odds of DVT with the use of injectables and oral use of progestin-only contraception. Of note, however, even with the most expressed DVT risk demonstrated during COC use, any increase in relative risk translates to a small increase in absolute numbers of thrombotic events.

KEYWORDS

Deep venous thrombosis, hemostasis risk markers, estrogens, progestins, combined estrogen/progestin application, progestin-only contraception.

Introduction

Deep venous thrombosis (DVT) is a specific reproductive health risk for women. In pregnancy the relative risk of DVT is increased approximately 5-fold, and in the puerperium it is increased by as much as 60-fold. Additionally, large numbers of women worldwide are exposed to an increased relative risk of DVT as a result of using combined hormonal contraceptives (CHCs) or hormone therapy after the menopause (MHT). Even women undergoing infertility treatment may be exposed to situations of significantly increased risk of DVT [1]. Several studies have established a 2- to 4-fold increased risk of DVT for users of MHT compared with non-users [2], comparable to the relative risk of CHCs.

The risk of DVT induced by MHT is, however, higher in absolute figures because of the age factor per se, but also dependent on the composition of the MHT used, since users of estrogen-only preparations have a lower risk of DVT than women receiving combined estrogen-progestin preparations [3]. Also, the dose and route of administration seems to play an important role, as women treated with transdermal MHT have a lower risk of DVT than women receiving orally administered MHT, as consistently demonstrated in clinical studies [4]. Moreover, epidemiological and pharmacological factors may contribute to the precipitation of DVT among exogenous sex steroid users.

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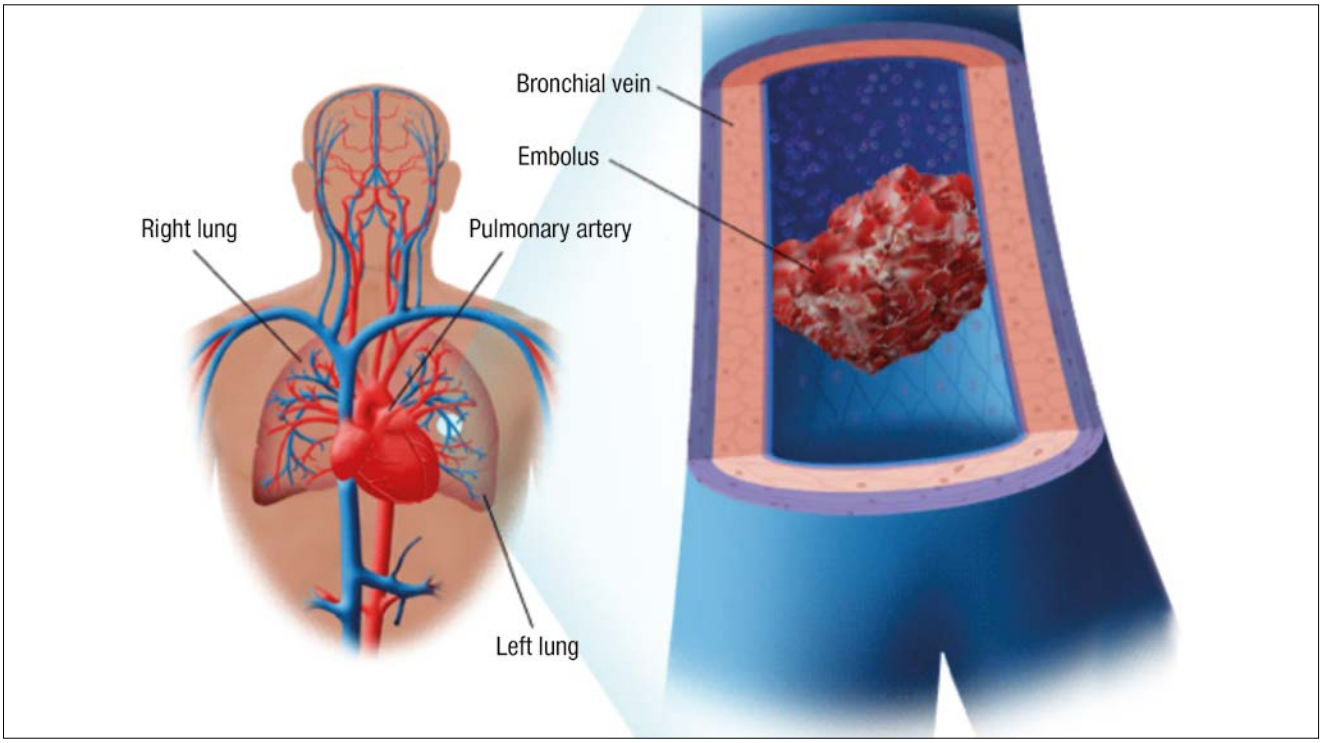
The pharmacological alterations induced by MHT and CHCs on the hemostatic system may be of particular interest [4], because both hormonal therapies significantly change the inhibitory potential of coagulation, as well as the activation of fibrinolysis. Consequently, the choice of estrogen and progestin may translate into clinical manifestations in both normal and thrombosis-prone individuals.

DVT mostly manifests in the deep veins of the leg, but may also occur in other sites, such as the upper extremities, cerebral sinus, liver and portal veins or retinal veins. Venous thrombi are composed predominantly of red blood cells but also platelets and leukocytes bound together by fibrin. Embolization occurs when parts of the clot dislodge and are transported by the blood flow, usually through the heart to the vasculature of the lungs (Figure 1). Major complications of DVT are a disabling post-thrombotic syndrome or acute death from a pulmonary embolus that occurs in 1-2% of patients [5].

Figure 1 Pulmonary embolism with blockage in one of the pulmonary arteries.



Biological mechanism of sex steroid-induced thrombosis risk

Oral MHT has very similar effects on coagulation and fibrinolysis variables as the use of COCs. Estrogens have many different effects on hemostasis, lipids, and inflammatory risk markers. The changes in the coagulation system include increases in the levels of procoagulant factors VII, X, XII, and XIII, and reductions in the anticoagulant factors protein S and antithrombin.

These changes predict a change toward a more procoagulant state, which is confirmed in studies examining global tests, such as activated protein C resistance or global coagulation capacity measured with the thrombin generation test. With increased levels of coagulation factors VII, IX, X, XII, and XIII and reduced levels of the natural anticoagulants protein S and antithrombin, the overall effect is a prothrombotic shift in the hemostatic balance (Fig. 2). Epidemiological studies have shown that high levels of many of these factors are thrombotic risk factors. It is currently unclear how these effects are brought about at the molecular level of the steroid receptors. It is likely that these effects at the cellular level are also under genetic control, which translates to the thrombophilia conditions described above, and therefore some women appear to be more sensitive to the effects of hormones than other women. The changes in fibrinolysis induced by hormones, especially progestins, are less straightforward. Estrogen use enhances the fibrinolytic activity in plasma. The main enzyme in fibrinolysis is plasmin, which dissolves the fibrin clot, producing fibrin degradation products such as D-dimers (Fig. 2). Levels of plasminogen activator inhibitor-1 (PAI-1) are decreased while tissue plasminogen activator (tPA) increases. However, the decreased concentration and activity of PAI-1 and the increased plasma levels of tPA and plasminogen during estrogen use are at least partially counteracted by elevated thrombin-activatable fibrinolysis inhibitor (TAFI). But it is not clear whether the effects of estrogens or the combined effect of estrogen/progestin on fibrinolysis variables have clinical implications, since there is no firm evidence that changes in the fibrinolytic system affect the risk of venous thrombosis.

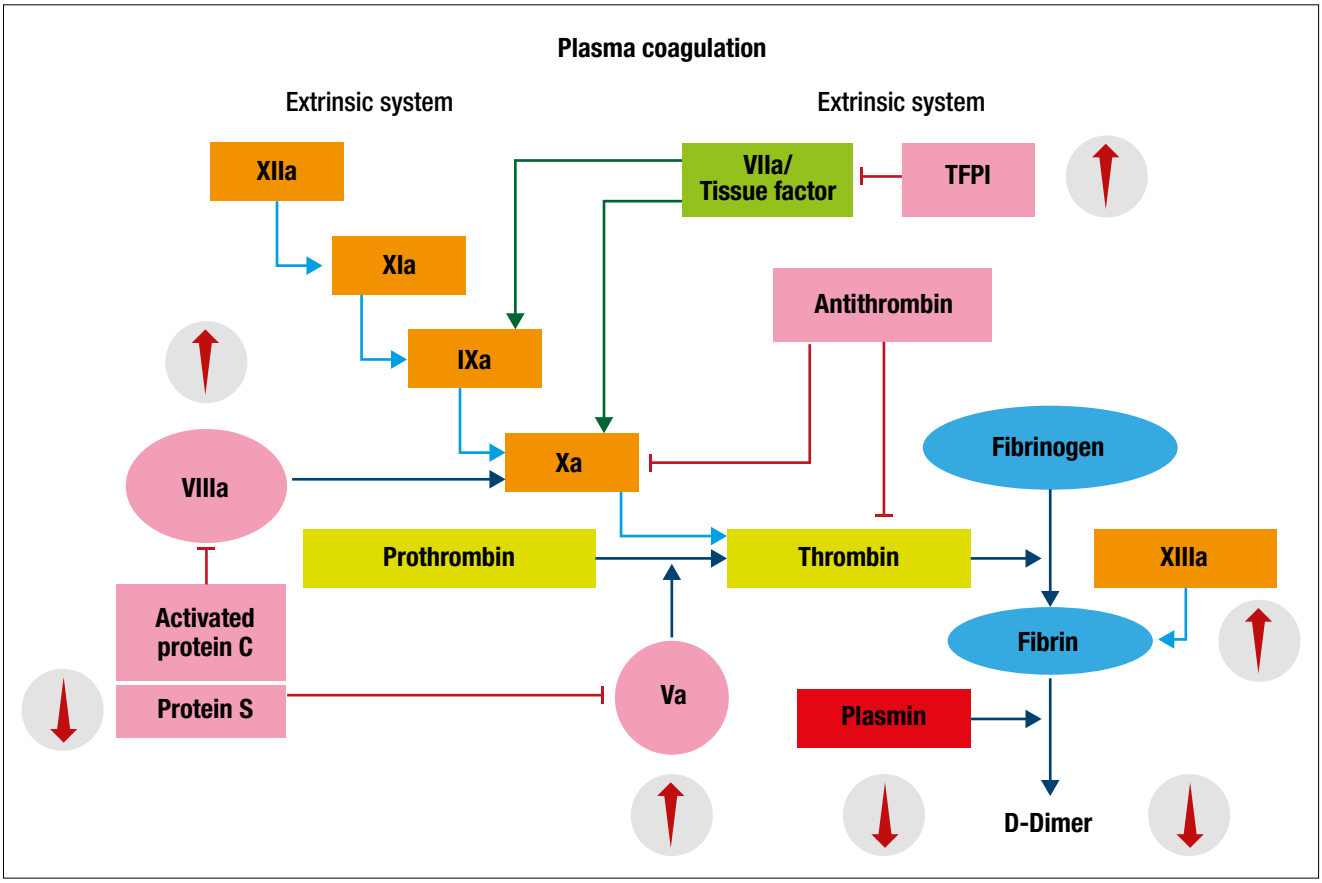
The hemostatic effects of estrogen/progestin are due to the impact on liver synthesis of the proteins involved in coagulation/fibrinolysis. In contrast to COCs, where there is a direct chemical action on the liver, for MHT it is rather a first-pass effect that is seen. Although existing data indicate that combined oral estrogen/progestin carries a greater risk of venous thromboembolism (VTE) compared with unopposed estrogen, at present the available data are inconclusive, especially in relation to the different types and doses of progestins [6]. The ESTHER study was the first to establish a differential association of DVT risk with the different progestin subgroups irrespective of the route of estrogen administration in MHT [7].

The specific roles of progestins

1. In combination therapy

Ethinyl estradiol (EE) has a strong impact on liver proteins and seems to be responsible for slight changes observed in the procoagulation and fibrinolytic balance irrespective of the route of administration [8]. The more androgenic progestins are able to counteract the potent EE-induced stimulation of liver proteins and coagulation factors, but in contrast, non- or antiandrogenic progestins seem to exert a limited counteraction

Figure 2 Thrombophilic effect of combined EE/progestin treatment.



against the action of EE, as measured by sex hormone-binding globulin (SHBG) changes [9]. Because 17-beta estradiol (E2) or E2 valerate (E2V) are weaker estrogens than EE, they do not stimulate SHBG production [10,11]. Due to this difference in counteracting the EE effect, progestins have been suggested as an additional factor possibly related to an increased incidence of VTEs [12,13].

The first progestins synthesized in the 1960s were structurally related to testosterone and include levonorgestrel (LNG), the most androgenic of the progestins used in contraception [14]. To improve the safety profile of OCs, progestins with less androgenic properties, such as desogestrel (DSG), gestodene (GSD), and norgestimate, were developed in the 1970s, and their combination with lower doses of EE were named third-generation OCs. More recently, progestins derived from 19-norprogesterone, or from spironolactone, have been developed. It was found that, in addition to binding specifically to the progesterone receptor (PR) with differing binding affinities, most progestins, according to their chemical structure, could also interact with the androgen receptor (AR), estrogen receptor, glucocorticoid receptor (GR), or mineralocorticoid receptor, which in turn may lead to agonistic or antagonistic actions, according to the coactivators or corepressors involved in the specific receptor interaction [15].

Most progestins that transactivate the PR also transactivate the AR or the GR, and therefore may induce effects other than progestin ones [16]. The progestins derived from the 19-norprogesterone exhibit a higher specificity for the PR and do not transactivate other steroid receptors or induce androgenic side effects. Drospirenone (DRSP) and dienogest (DNG) exhibit antiandrogenic properties, a potential medical benefit for some women [8,14]. When associated with E2, nonandrogenic or antiandrogenic progestins exert minimal influence on the lipid profile and carbohydrate metabolism, properties that in theory may lessen the risk of developing coronary heart disease [17,18]. Progestins when given alone as hormonal contraception do not increase VTE risk. However, when combined with EE, an androgenic progestin such as LNG decreases the impact of EE on liver protein synthesis, while the anti-androgenic progestins have minimal counteracting and even a synergistic EE effect on hemostatic liver factors. Accordingly, the most recent COCs containing DSG, GSD, or DRSP have been reported to show similar changes in most procoagulant variables and with a simultaneous decrease in the anticoagulatory protein C and protein S antigen activity. Of note, statistically significant, less pronounced changes were observed for fibrinogen and protein S activity with DRSP 3 mg/20 µg EE versus DSG 3mg/30 µg EE. No statistically significant differences were found in changes in antifibrinolytic variables, global clotting tests, and D-dimer levels, but it was concluded that changes in hemostasis for DRSP 3 mg/20 µg EE were less pronounced [19].

These EE/progestin findings contrasts with findings for COCs containing 17-beta estradiol or the placenta derived estriol which have been reported to show no or less impact on hemostatic variables even compared with EE/LNG products [20]. In concordance, it has consistently, although not unanimously,

been reported that there is a COC differential effect on the clinical risk of VTE with these varied estrogen/progestin combinations [21-23]. So, in summary, when looking at the progestin effect on hemostasis when a combined estrogen/progestin treatment is employed, the specific progestin effect will depend on a) the type of progestin; b) the dose of progestin; c) the route of application; and the type and dose of estrogen with which it is combined. This concept has been underscored by Stanczyk, who stressed the existence of major differences in the chemical structures, structure-function relationships, metabolism, pharmacokinetics, pharmacodynamics, and potencies of progestins and concluded that no class effect exists [24].

2. Progestin-only treatment.

In reviewing this topic, Schindler [25] noted that no negative effects on hemostasis were observed following oral or parenteral administration of progesterone/progestins (progestin-only contraceptives, POCs) either in cyclic or in continuous regimens. He also concluded that no negative effects were found for progestin-only pills (POPs), independent of the type and dose of progestin. At the same time, at high doses (such as those utilized in oncology), an increased activation of the hemostatic system has been observed.

A review by Blanco-Molina *et al*. [26] found that, as a general rule, progestins, chlormadinone acetate, megestrol acetate, LNG, racemic norgestrel, norethisterone acetate, and ethynodiol diacetate do not adversely affect the coagulation cascade, i.e. have no negative effects on fibrinogen, factors II, V, VII, VIII, and IX, antithrombin III, clotting time, activated partial prothrombin time, platelet aggregation, plasminogen, α2-microglobulin, α1-antitrypsin, or fibrinolytic activity. At the same time, it seems that DSG and LNG produce a reduction in factor VII, and prothrombin fragments 1+2, with a possible decrease in procoagulant activity.

In a recent systematic review, the majority of evidence did not suggest an increase in odds for venous or arterial events with the use of most POCs. Limited evidence suggested increased odds of VTE with the use of injectables (three studies) and the use of POCs for therapeutic indications (two studies, one with POCs unspecified and the other with POPs). And of note: any increase in risk likely translates to a small increase in absolute numbers of thrombotic events at the population level [27].

Thrombophilia

Thrombophilia is a term used to describe a group of conditions in which there is an increased tendency, often repeated and manifested over an extended period of time, for excessive clotting. These include inherited conditions, based on a demonstrated genetic mutation such as factor V Leiden, protein C and S deficiencies, antithrombin deficiency, and prothrombin 20210A mutations (which may be suspected on the basis of family history); or an acquired condition such as lupus anticoagulant or antiphospholipid antibody syndrome, which can occur alone as a manifestation of an autoimmune disorder, or as part of a syndrome such as systemic lupus erythematosus. The presence of an inherited thrombophilia is a major modifier of thrombosis risk in users of COCs.

Therefore, the World Health Organization (WHO) recommendations state COC use in women with thrombophilic mutations as associated with an unacceptable health risk. These recommendations are mainly based on case-control studies reporting increased relative risks of venous thrombosis during COC use in women with hereditary thrombophilic defects [28]. However, to qualify all hereditary thrombophilic defects as similarly strong risk factors might be questioned. The absolute risk of venous thrombosis in factor V Leiden heterozygous carriers is estimated as being 0.15 per 100 person-years, whereas in antithrombin-, protein C-, or protein S-deficient persons these estimates range from 0.7 to 1.7 per 100 person-years, indicating a considerably higher degree of risk. The overall risk seems to be unchanged during use of POCs [29].

Conclusion

The estrogen EE contained in most COCs appears to be the major factor of risk for VTE. While most progestins when administered alone do not induce changes in clotting factors, EE modifies several hemostatic factors whatever its route of administration, and the role of the progestin in COCs relates to its ability to counteract or modulate the EE effects. Selecting androgenic progestins that oppose the EE action or combining natural estrogens with nonandrogenic progestins similarly result in a neutral effect on the hemostatic system.

Systematic reviews report that most of the available evidence demonstrates no significantly increased risk of VTE in users of POCs. Women with thrombophilic disorders are at increased risk of VTE, and estrogen exposure, either in pregnancy or through CHCs, is associated with further significantly increased risk. However, POCs are not associated with increased risk of VTE in these patients, thus providing a safe option to reliably avoid unwanted pregnancy.

The WHO eligibility criteria for POCs highlight that while a history of VTE is classified as Category 4 (a condition which represents an unacceptable health risk if the contraceptive method is used) for COCs, it is Category 2 (a condition where the advantages of using the method generally outweigh the theoretical or proven risks) for POCs.

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