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Review Article

# Optimal management of hormonal contraceptives after an episode of venous thromboembolism

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ABSTRACT

Optimal management of hormonal contraception in patients with venous thromboembolism (VTE) requires an individualized approach considering its potential benefits and complications during and after anticoagulant treatment. Potential benefits include prevention of pregnancy and mitigation of menstrual bleeding that is often worsened after start of anticoagulation therapy. Current evidence suggests that patients may opt for a continuation of (all forms of) hormonal contraception during anticoagulant treatment, provided that they are adequately informed by the treating physicians. Combined oral contraceptives should be stopped before anticoagulant therapy may be discontinued, preferably after the second last menstrual cycle of the intended anticoagulant treatment period. If hormonal contraceptive treatment needs to be initiated in patients with a history of VTE, oral prostagen-only therapy or intra-uterine devices are to be preferred: this may be independent of the anticoagulation status and in light of a negligible risk of (recurrent) VTE associated with their use.

## 1. Clinical case

A 19-year-old previously healthy woman was referred to the emergency ward because of acute-onset dyspnea. She had been well until approximately 4 days before this admission, when she noticed exertional dyspnea that had worsened since onset of symptoms. She had started to use combined contraceptives (Ethinylestradiol/Levonorgestrel) for alleviating menorrhagia four months before the current presentation. Upon examination, the blood pressure was 125/73 mmHg, the pulse 82 beats per minute, the respiratory rate 14 breaths per minute and the oxygen saturation 97% on breathing room air. Further physical examination revealed no signs of deep vein thrombosis or other abnormalities. Because of an elevated D-dimer level (>5000 ng/ml), a CT pulmonary angiography was ordered that showed bilateral segmental acute pulmonary embolism (PE). The attending physician discusses the management options with the patient, with particular attention to the current use of oral contraceptives. What would be, in your opinion, the best therapeutic and contraceptive strategy for this patient?

## 2. Introduction

The use of hormonal contraception is common among women of childbearing age and it is associated with a higher risk of acute deep vein thrombosis (DVT) and pulmonary embolism (PE), which represent the main clinical manifestation of venous thromboembolism (VTE) [1–5]. This well-known association has led to warnings concerning the use of hormonal contraception by patients characterized by an increased risk of VTE, e.g. the carriers of genetic thrombophilia or those who experienced a prior episode of VTE. As maximum caution is imperative, especially when managing an acute VTE event occurred in a young women without recognizable risk factors but hormonal contraception, a reflex of physicians is to instantly discontinue hormonal contraceptives when VTE diagnosis is confirmed [6,7]. However, the potential advantages of such a medical decision come at some costs. For instance, adequate contraception is of particular relevance during treatment with potentially teratogenic oral anticoagulants and may prevent or alleviate anticoagulant-associated abnormal menstrual bleeding [7]. Moreover, hormonal contraception is not only prescribed for birth control, but in some cases represents the preferred treatment option for dysmenorrhea, endometriosis, menstrual migraines, acne, and hirsutism [8]. Therefore, the presence and severity of these conditions should be taken into account when deciding on the optimal short-term, i.e. within weeks or months after the diagnosis of VTE, and long-term management of hormonal contraception. Here, we provide a state-of-the-art overview of the potential risks and benefits of continuing, switching, or even initiating hormonal contraceptives after a diagnosis of acute VTE.

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## 3. Hormonal contraceptives and risk of VTE

When compared with non-users, patients in the general population receiving hormonal contraception are at higher risk of VTE [1–4]. The main explanation for this association is the alteration in procoagulant factors and endogenous anticoagulant proteins related to the intake of hormonal contraception. The oestrogen components appear to be the main determinants of these changes, which include an increase in the procoagulants factors II, VII, FVIII, X and fibrinogen, and a decrease in antithrombin and tissue factor pathway inhibitor activity [9,10]. The magnitude of this increase in the VTE risk depends on the formulation of hormonal contraception, e.g. oral, transdermal, vaginal or intrauterine systems, the total dose as well as the type of hormones, notably the oestrogen dose and the subtype of progesterone in combined oral contraception. For instance, use of combined hormonal contraception containing ethinylestradiol plus levonorgestrel, norgestimate or norethisterone is associated with a 5- to 7-fold higher risk of VTE, whereas this risk is 9- to 12-fold increased during the exposure to ethinylestradiol plus gestodene, desogestrel or drospirenone [3,11–13]. A recent systematic review and meta-analysis of 22 studies evaluated the differential risk of VTE associated with the use of combined oral contraceptives classified according to the type of progestin versus combinations including levonorgestrel. It is important to highlight, however, that such relative risk, which had been estimated to be 1.5- to 2.0-fold for progestin compared with levonorgestrel users, corresponds to an absolute risk difference of only 5–10 events per 10,000 patient-years [14]. Preliminary results suggested that the differential risk of VTE carried by progestin type may be mediated by an interaction with the Factor V Leiden mutation with carriers exposed to drospirenone or cyproterone acetate being at a particularly elevated risk possibly due to the synergistic mechanisms of these two different risk factors [15].

The risk of VTE is highest in the four months following initiation of hormonal contraception or when restarting after a break of at least one month. The risk then reduces over the subsequent year and remains stable thereafter. Importantly, the levonorgestrel releasing intrauterine system does not seem to increase the risk of thrombosis, in contrast to transdermal contraceptive patches or contraceptive vaginal rings [16].

## 4. Thromboembolic risk associated with hormonal contraception during anticoagulation

Few studies have investigated the association between hormonal contraception during anticoagulation and the risk of (first or) recurrent VTE. In a post-hoc analysis of the EINSTEIN DVT and EINSTEIN PE studies, which had been limited to women aged 60 years or younger [17–19], a total of 7 recurrent VTE events occurred in 475 patients on hormonal contraception, whereas 38 events occurred during the period off hormonal contraception in 1413 patients, resulting in crude annualized rates of 3.7% and 4.7%, respectively (adjusted hazard ratio (HR) 0.56; 95% confidence interval (CI) 0.23–1.39). Most of recurrent VTE events occurred within the first 30 days after randomisation, and no differences were found in important subgroups, i.e. both treatment arms of the study, oestrogen containing oral contraceptives versus prostagen-only therapy, previous VTE versus no previous VTE, PE versus DVT as the presenting site of index VTE, and prior treatment with hormonal contraceptives versus treatment naïve patients. It must be noted, however, that most of the subgroups were too small to draw definitive conclusions. Of note, no recurrent VTE events were recorded over a total follow-up time of 15.3 patient-years in women using a levonorgestrel releasing intrauterine system [19].

A post-hoc analysis of the RE-COVER trials in 1264 women aged 18–50 years [20–22] confirmed these preliminary results and did not demonstrate an association between hormonal contraception, irrespectively of its onset and length, and recurrent VTE during active anticoagulant treatment in 270 patients (odds ratio 0.59; 95% CI 0.20–1.72). No data was available neither for the type of oral contraception nor for the use of levonorgestrel releasing intrauterine systems [22].

Although these observations suffer from confounding by indication because hormonal contraception was not randomly assigned, they suggest that continuation of hormonal contraception is safe as the prothrombotic effect of hormonal therapy is likely to be suppressed by therapeutic-intensity anticoagulation, provided that adequate compliance to anticoagulants is achieved. The same is true for starting hormonal contraception during anticoagulant treatment for VTE. In this perspective, physicians should put all efforts in instructing the patients about possible dangerous complications if only a single dose of oral anticoagulants with short half-life is missed during active use of hormonal contraception.

## 5. Thromboembolic risk associated with hormonal contraception after discontinuation of anticoagulant therapy

Several observational studies have evaluated the risk of recurrent VTE in patients with hormonal contraception-associated VTE after discontinuation of both the anticoagulant treatment and the contraception itself, but data on the risk of recurrent VTE if hormonal contraception is continued after anticoagulant cessation are scarce. Of the available observational studies, it seems that continuation or resumption of oral combined hormonal contraception was associated with a 3.5- to 13-fold higher risk of VTE recurrence than women who stopped contraceptive use, while no increased risk was reported for progestin-only therapy [23–25].

On the other hand, although available studies are contradicting, it seems that the risk of recurrent VTE is lower after discontinuation of oral hormonal therapy than after unprovoked VTE without exposure to hormonal contraception, suggesting that avoiding oral hormonal contraception in patients with prior VTE who discontinued anticoagulant treatment lowers the risk of recurrent VTE [26–28].

## 6. Benefits of hormonal contraceptives during anticoagulant therapy

### 6.1. Prevention of pregnancy associated VTE

As stated above, hormonal contraceptives increase the risk of developing VTE. Although the comparison may seem unconventional, this risk should be read in the perspective of the more pronounced increased risk of VTE during pregnancy and in the peripartum period, which could be avoided if unexpected pregnancies are prevented by hormonal contraception. Considering the latter, use of hormonal contraception may be preferred over possible pregnancy in exceptional cases, even despite a known higher baseline VTE risk [8,29]. In this perspective, it is known that both pregnancy and hormonal contraception are associated with a higher risk of developing DVT than PE [30]. In patients with isolated DVT, however, the localization of thrombi appeared more favourable (e.g. isolated distal DVT events) in women in whom DVT was triggered by hormonal contraceptives, whereas pregnancy was associated with proximal DVT events [31].

### 6.2. Teratogenicity of oral anticoagulants

A second reason why it is prudent to prevent pregnancy is that oral anticoagulants cross the placenta and may cause maternal and foetal complications. Vitamin K antagonists (VKA) have been associated with the so-called warfarin embryopathy, which involves bleeding complications, facial and skeletal anomalies, and occurs in 3.7% to 6.4% of exposed women during pregnancy [32,33]. Moreover, prematurity is more frequent in VKA exposed pregnant women, and mean gestational age at delivery as well as mean birth weight are lower than in unexposed pregnancies [34]. In these patients, oral

**Table 1**
Abnormal uterine bleeding in women treated for acute VTE with DOACs or VKAs from th elarge phase 3 DOAC trials.

| Study | *N* total | *N* on hormonal contraceptives | Definition of abnormal uterine bleeding | DOAC | VKA |
|---|---|---|---|---|---|
| RE-COVER and RE-MEDY [22] | 1280 | 270 (21.1%) | Uterine hemorrhage, hematoma, polymenorrhagia, metrorrhagia, menorrhagia, menometrorrhagia or dysfunctional uterine bleeding | Dabigatran: 38/643 (5.9% over 6–36 months) | Warfarin: 61/637 (9.6% over 6–36 months) |
| EINSTEIN DVT and PE [19] | 1737 | 463 (26.7%) | Investigator reported or leading to ≥1 unit of blood transfusion | Rivaroxaban and contraception: 29.8% per year | Warfarin and contraception: 15.5% per year |
| | | | | Rivaroxaban w/o contraception: 30.7% per year | Warfarin w/o contraception: 13.4% per year |
| HOKUSAI-VTE [53] | 1293 | 33.3% | Major abnormal vaginal bleeding (FIGO criteria) | Edoxaban: 8/628 (1.3% at 12 months) | Warfarin: 3/665 (0.9% at 12 months) |
| | | | Clinically relevant nonmajor abnormal vaginal bleeding | Edoxaban: 53/628 (8.4% at 12 months) | Warfarin: 37/665 (5.6% at 12 months) |
| AMPLIFY [54] | 2228 | 17.5% of patients with bleeding | Major abnormal vaginal bleeding (FIGO criteria) | Apixaban: 1/1122 (<0.1% at 6 months) | Warfarin: 0/1106 (0% at 6 months) |
| | | | Clinically relevant nonmajor abnormal vaginal bleeding | Apixaban: 28/1122 (2.5% at 6 months) | Warfarin: 24/1106 (2.1% at 6 months) |

anticoagulation with VKA is usually considered only in the presence of a mechanical heart valve, for which the efficacy of parenteral anticoagulation with heparins has not been proven.

Direct oral anticoagulants (DOACs) are an effective, safe, and convenient therapeutic alternative to VKAs in the treatment and prevention of VTE in non-pregnant patients [35–37], and are currently the treatment of choice for most patients with acute VTE. Notably, animal studies have demonstrated DOAC-associated embryopathy for dabigatran, edoxaban and rivaroxaban [38]. Since DOACs may freely cross the placenta, pregnant women were excluded from the large phase 3 trial programs. Experience with DOACs in pregnancy patients is therefore limited to small case series. While miscarriages and foetal abnormalities have been reported, available evidence does not indicate a high risk of embryopathy after DOAC exposure [39,40]. Even so, DOACs are strictly contra-indicated during pregnancy and lactation, and effective contraceptives measures should be advised to all women of fertile age in whom oral anticoagulants are prescribed [38,41].

Beyond the use of anticoagulants, a careful planning of pregnancies with the use of oral contraception is important also for avoiding the exposure to other potential teratogens. A recent analysis of more than 140,000 women with diabetes demonstrated that the absolute risk of VTE associated with the use of hormonal contraception was overall low, therefore providing reassurance about its use in this particular group of patients [42].

### *6.3. Treatment of abnormal menstrual bleeding after start of oral anticoagulants*

Anticoagulant therapy increases the risk of developing abnormal menstrual bleeding in women with VTE, although solid estimates from well-designed studies are lacking, especially regarding the quantification of the prevalence of abnormal menstrual bleeding off and on treatment [7, 43]. One study assessed the effect of initiation of VKA on menstrual bleeding in 90 women and found an increase of self-reported menorrhagia from 44% to 71% ($p < 0.001$) [44]. In a second study, 70% of women reported a change in the bleeding pattern of their menstrual cycle after initiation of VKA therapy with a mean increase in duration from 5.4 to 6.6 days ($p < 0.0008$) [45]. Among these women, 66% met the predefined criteria of menorrhagia. Consistently, the mean hemoglobin concentration of the participants dropped (minimally) from 13.0 g/dL before treatment to 12.6 g/dL after treatment [45]. It must be noted that abnormal menstrual bleeding generates negative perceptions and limits the social and professional activities: in addition, women with exaggerated bleeding are characterized by a poorer quality of life compared with patients with normal menstrual bleeding [46–48]. As such, it could be one of the explanations of the reported decreased quality of life in female PE survivors [49–52], and this complication of anticoagulant therapy should be taken very seriously and prompt counselling by an expert gynaecologist.

A number of post-hoc analyses of the phase III trials that led to the approval of DOACs demonstrated, overall, that the class of Factor Xa inhibitors are associated with a higher risk of abnormal uterine bleeding than VKA [19,53,54]. This risk seems lower for patients treated with the direct thrombin inhibitor dabigatran [22], although differences between studies in the definition of abnormal uterine bleeding and prevalence of hormonal contraception use exist (Table 1). Moreover, differences in study design (e.g., selection criteria, duration of follow-up) prevent strong conclusions with regard to the comparison of the risk of abnormal uterine bleeding associated with the commercially available DOACs. Even so, with DOACs being the treatment of choice for VTE, it may be anticipated that the prevalence of abnormal menstrual bleeding may further increase over the years.

The use of hormonal contraceptives significantly decreases menstrual blood loss and increases haemoglobin levels in women with abnormal menstrual bleeding [47]. This beneficial effect is generally extrapolated to anticoagulated patients with abnormal menstrual bleeding, although firm evidence is still missing [48]. Some data became available for levonorgestrel releasing intrauterine systems in this setting. In a small observational study, 82% of anticoagulated women reported either amenorrhea or reduction of bleeding, 70% used fewer sanitary pads and 53% reported shorter duration of the bleeding [55]. In a second study, 9 of 10 women (90%) were effectively treated with a levonorgestrel releasing intrauterine system, with the system expelled in the remaining patient [56]. A third study found a good effect of a levonorgestrel releasing intrauterine systems for anticoagulation-associated abnormal menstrual bleeding in 17 women, as well as a significant absolute increase in mean hemoglobin concentration of 0.6 g/dL [57]. In a final study, insertion of a levonorgestrel releasing intrauterine system caused a significant decrease in menstrual bleeding in 20 anticoagulated women compared to 20 anticoagulated women treated with placebo [58]. Finally, a post-hoc analysis of the EINSTEIN DVT/PE studies, which assigned patients with acute VTE to either oral anti-Xa inhibitor rivaroxaban or to warfarin, showed that the rates of abnormal uterine bleeding were similar in users and non-users of hormonal contraceptives. Although this result was consistent across anticoagulant treatment arms, the likely presence of confounding by indication (women with most severe bleeding prior to enrolment

been continued on hormonal contraception) prevented the authors to provide firm conclusions [19].

In summary, studies focusing on treatment of abnormal menstrual bleeding in anticoagulated patients are scarce, often retrospective, and characterized by a high risk of bias. Available data confirms the aggravating effect of anticoagulant treatment on the menstrual bleeding pattern and the potential protective effect of hormonal contraceptives. Of note, while risk factors for menstrual bleeding are not part of current available bleeding prediction scores for patients with VTE and published studies on optimal duration of anticoagulant therapy hardly consider menstrual bleeding per se [59–61], uncontrollable abnormal menstrual bleeding is a strong argument to discontinue anticoagulant therapy after an initial 3-month period in women with unprovoked VTE [37,62]. As such, evaluation of menstrual bleeding patterns should be part of routine counselling after an episode of VTE.

## 7. Conclusion and recommendations for daily practice

Optimal management of hormonal contraception requires an individualized approach considering its potential benefits and complications during and after anticoagulant treatment. Current evidence suggests that patients may opt for a continuation of hormonal contraception during anticoagulant treatment, provided that they are adequately informed by the treating physicians. Combined oral contraceptives should be stopped before anticoagulant therapy may be discontinued, preferably after the second last menstrual cycle of the intended anticoagulant treatment period. If hormonal contraceptive treatment needs to be initiated in patients with a history of VTE, oral prostagen-only therapy or intra-uterine devices are to be preferred: this may be independent of the anticoagulation status and in light of a negligible risk of (recurrent) VTE associated with their use. These recommendations are summarized in the UK Medical Eligibility Criteria for Contraceptive Use (UKMEC) [63].

## 8. Resolution of the case

Returning to our patient, the PE was considered to be secondary to the recent start of combined oral contraceptives. She had a strict indication for anticoagulant treatment that may aggravate the menorrhagia, and she wished to continue some kind of effective contraceptive measure. It was decided to initiate treatment with dabigatran preceded by seven days of low molecular weight heparin, and to continue the combined oral contraceptive. Shortly after the second menstrual period (on day 63 of treatment), she stopped the oral contraceptives and a norgestrel releasing intrauterine device was inserted. She completed a 3-month treatment with dabigatran. During the treatment period, the menstrual blood loss remained roughly stable and comparable to what she was used to before the oral contraceptives were started.

## Conflict of interest statement

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