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Understanding and Management of Venous Thromboembolism (VTE) – Section 17

Update On Oral Contraception And Venous Thromboembolism

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Take-home messages:

- Combined oral contraceptive (COC) is one of the causes of about 50% of VTE among women of reproductive age.
- The risk of COC-related VTE is determined by characteristics of the pill (dose of estrogen, type of progestin) and of the user (both acquired and genetic risk factors).
- COC-related VTE prediction models would be clinically useful, with ongoing research.
- Women should be advised not to stop the COC right at the time of VTE, but seek prompt contraceptive advice during the period of anticoagulant treatment.

Introduction

Deep vein thrombosis and pulmonary embolism, together known as venous thromboembolism (VTE), occur at an annual incidence of 5/10,000 women of reproductive age,[1] corresponding to ~67,000 VTE annual cases at the scale of the European Union (134 million women between 15 and 54 years). Hormonal contraceptives, and in particular combined oral contraceptives (COC), found in 30% to 70% of such VTE,[*2] represent a major cause of such VTE. This short update will review the determinants of COC-associated VTE risk and the management of contraception in case of VTE.

COC determinants of VTE risk

The type of progestin and the dose of estrogen influence the risk of VTE.

Multiple systematic reviews and meta-analyses have demonstrated that, compared with a 2nd generation progestin (levonorgestrel), more modern progestin is associated with greater risks of VTE. In the most recent review,[3] compared with levonorgestrel, the relative risk (RR) of incident VTE for a 3rd generation progestin (desogestrel, gestoden) was ~1.5 to 1.8 and that of cyproterone and drospirenone was 1.6 to 2.0. This incremental risk of drospirenone has been challenged by the EURAS and LASS pharmaceutical-funded prospective studies, showing similar risks as levonorgestrel.[4] Such discrepant findings have been debated in the literature, with a highlighted lack of detailed methodology and a potential for non-differential measurement error. Biologically, switchers of COC from a 2nd generation to drospirenone increase their resistance to activated protein C, a recognized biomarker of COC-related VTE.[5] Therefore, given the current epidemiological and biological evidence, levonorgestrel should be viewed as the safest choice of COC for VTE risk and drospirenone as a more prothrombotic COC.

The first contraceptive pills in the 1960s had high-dose potent synthetic estrogens. Ethinylestradiol (EE) now represents the most common estrogen of COC, impacts the hepatic synthesis of hemostatic proteins in both oral and non-oral forms, and should be prescribed at the lowest dose tolerated by the user. Indeed, in a recent large French retrospective cohort, the risk of pulmonary embolism was lower in users of EE 20 mcg than EE 30 to 40 mcg, independently of the progestin type (HR 0.75, 95%CI 0.67–0.85).[*6] Whether the type of estrogen influences cardiovascular events is unknown, but some COC now integrate a natural estrogen (estradiol) instead of EE. The limited biological and epidemiological comparative evidence suggests that estradiol/dienogest (a new progestin) carries a similar VTE risk as EE/LNG.[7,8]

User determinants of VTE risk

Older women, obese women (RR = 3),[9] and active smokers (RR = 2)[10] are at greater risks of COC-related VTE (Table 1). Recently, an association between polycystic ovary syndrome (PCOS, RR = 1.7) and VTE was found in a meta-analysis, which appeared independent of hormonal treatment and obesity,[11] and this adds complexity to the management of PCOS. Surgeries, hospitalizations, and limb immobilizations are transient high-risk periods.

Genetics are responsible for 35% to 60% of VTE,[12] of which little is characterized. There are >20 single nucleotide polymorphisms (SNP) known to cause VTE, but these explain only 10% of the genetic variance. The most potent are Factor V Leiden (*FVL*, rs4025), the G20210A prothrombin mutation (*PTG20210A*,

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Table 1

Non-transient VTE risk factors of COC users.

Acquired risk factor	Genetic risk factor
Advanced age	Factor V Leiden (rs4025)
Obesity	G20210A prothrombin mutation (rs1799963)
Active smoking	Non-O blood group
Polycystic ovary syndrome	First-degree family history of VTE
Personal history of VTE	

rs1799963) and a non-O blood group, and the other SNP have weak associations with VTE.

In COC users, some of these factors are specifically important. Not only does *FVL* or *PTG20210A* increase the risk of VTE 6-times among COC users (OR 5.9, 95%CI 4.2–8.2),[*13] but a synergism between these SNP and COC was suggested already 25 years ago, meaning that the relative risk associated with *FVL* and with COC do not simply add but at least multiply. For example, in a recent Swedish case-control study, the use of COC was associated with a 3.4-fold increased risk, that of *FVL* with a 2.6-fold increased risk and the combination with a 20.6-fold increased risk of VTE.[14]

A first-degree family history is readily-obtained and doubles the risk of VTE, even among carriers of *FVL*.[15] It triples and even quadruples in case of a VTE event in a first-degree relative <50 years and of multiple relatives with VTE. Whether the relative with VTE is male or female appears unimportant, unless the relative was a woman who had suffered a hormone-related VTE, which further potentiates the risk associated with the family history.[16] Importantly, a positive family history is poorly correlated with thrombophilia testing. In the MEGA study, at least 1 genetic risk factor (*FVL*, *PTG20210A*, low AT/PC/PS levels) was found in 29.7% of VTE cases with a positive 1st-degree family history and 22.1% of VTE cases without a family history.[15]

Blood group is easily measured, often known by patients, and a clear genetic predisposition to VTE: a non-O blood group doubles the risk of incident VTE in the general population and among COC users.[17]

Predicting the risk of COC-related VTE

High-risk women should not be prescribed a COC, especially given the available alternative effective contraceptives without thrombotic risk. Avoiding COC in women with a combination of risk factors (described above) or with known thrombophilia factors, as guided by the WHO,[18] is a rough approach, and developing a genetic and acquired risk score for COC-related VTE would be an invaluable effort of personalized medicine. At this time, recommendations advise not to undergo broad thrombophilia testing prior to the prescription of COC, because of a negative cost-effectiveness balance.

Beyond *FVL*, *PTG20210A* and blood group, among women, individual SNP (*F11* rs2289252, *PROC* rs1799810, *KNG1* rs710446, and *FGG* rs2066865) may be independently associated with risk of VTE, albeit with weak relative risks.[19] Yet, we lack data specific for COC-related VTE with good generalizability. The French *PILLGRIM* study suffers from selection bias in controls,[17] which impacts its genetic associations. However, Its data have been used to develop a clinical and genetic prediction model (Pill Protect®),[20] which is available in Switzerland. At this time, the high potential for bias and the lack of external validation of this tool indicate that it is not ready to be used in clinical practice,[21] and more research is needed in this field.

Management of COC in case of VTE

At the time of COC-related VTE, the goals are to prescribe an effective treatment against VTE while minimizing the risk of bleeding and protecting women from unwanted pregnancies. Guidelines advise against the use of COC after the diagnosis of VTE, including during the period of therapeutic anticoagulation.[18]

According to an international web-based survey of the management of COC with VTE, about 50% of physicians advise to stop it at the time of VTE diagnosis, and 50% either during or at the end of anticoagulation.[*22] In routine practice, we also observe that women and a proportion of physicians tend to stop the COC at the time of diagnosis, in fear of a higher recurrent VTE risk. This may increase the likelihood of abnormal uterine bleeding, especially during the first 1 to 3 weeks of more intense anticoagulation with direct oral anticoagulants,[*23] and of unwanted pregnancies that cause problems after VTE, with potentially teratogenic anticoagulants.

In the rivaroxaban in VTE phase III EINSTEIN trials, the continuous use of hormonal treatments during therapeutic anticoagulation was not associated with a greater risk of VTE (HR 0.56, 95%CI 0.23–1.39),[*23] suggesting that the very potent protection of high-quality therapeutic anticoagulation against recurrent VTE (90%–95% relative risk reduction) outweighs the hypercoagulability induced by estrogens. In contrast to the guidelines, but in accordance with the majority of thrombosis experts,[*22] it appears therefore safe to continue with estrogenic contraceptives during the period of anticoagulation, unless a low compliance with anticoagulants is anticipated. Women should be advised to seek their gynecologist promptly to discuss non-prothrombotic contraceptive alternatives, such as intra-uterine devices (hormonal or not), progestin-only pills or implants. Although the duration of persistant prothrombotic influence of COC after their withdrawal is largely unknown, we suggest stopping COC at least 4 to 6 weeks prior to the cessation of anticoagulation. Clearly, once the anticoagulant treatment is stopped, it is contra-indicated to restart any contraceptives containing estrogens.

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