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Abstract

The risk of venous thrombosis (VT) varies according to the type of progestogen that is found in combined oral contraceptives (COCs). When combined with the estrogen component ethinylestradiol (EE), the androgenic progestogens are better able to counteract the EE-induced stimulation of liver proteins and hence are associated with a twofold decreased risk of VT compared with non- or antiandrogenic progestogens, which exert limited counteraction of EE. Because EE is responsible for the increased risk, novel estrogens such as estradiol were developed and seem to have a lower risk of VT than EE. Besides COCs, there are other methods of hormonal contraceptives, such as progestogen-only contraceptives, which do not increase VT risk, except for injectables. Other nonoral contraceptives are combined vaginal rings and patches. There is insufficient evidence regarding the risk of VT associated with these two methods compared with COCs. The increased risk associated with COCs is more pronounced in women with inherited thrombophilia. In these women, the progestogen levonorgestrel seems to be associated with the lowest risk of VT. Currently, there are no studies that have investigated the risk of VT in women who switch COCs. We hypothesize that switching COCs, even when switching from a high- to a low-risk COC, increases the risk of VT. Finally, risk prediction models in women who use COCs are lacking. Since there is a large number of VT cases associated with COC use, it is important to identify women at risk of VT and advise them on alternative contraception methods.

Keywords
- contraceptives
- oral
- combined oral contraceptives
- thrombosis
- risk

Combined oral contraceptives (COCs), which contain both an estrogen and a progestogen component, are associated with a two- to fourfold increased risk of venous thrombosis (VT) compared with nonuse, depending on the type of COC.[1] Despite the low incidence of VT among women of reproductive age (~3 per 10,000 women per year),[2] the impact on the burden of VT is large since worldwide over 100 million women are using COCs,[3] and hence COC use is responsible for a large number of VT cases. Moreover, VT is associated with both increased morbidity and mortality.[4]

In this review, we will summarize the literature regarding the risk of VT associated with COC use and also focus on novel topics which are not investigated and/or understood thoroughly.

These topics include the risk of VT associated with the newer types of COCs containing the estrogen component estradiol, the risk of VT in women using COCs and who also have inherited thrombophilia, and the risk of VT in women switching COCs. Lastly, available literature on risk prediction modelling for VT in women using COCs is summarized and further recommendations for future studies are given.

The Risk of Venous Thrombosis Associated with Combined Oral Contraceptives

Shortly after the introduction of the first COC in the 1960s, the first case of VT associated with its use was reported.[5] Because

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the estrogen component ethinylestradiol (EE) in COCs was thought to increase the risk of VT, the dose of estrogen was lowered in the 1970s. The lowering of the dose of estrogen in COCs was indeed associated with a reduced risk of VT.[6–8] In an effort to further reduce the risk, the progestogen component was also changed over time. After the introduction of the first COC (which contained among others the progestogens lynestrenol and ethynodiol diacetate), new progestogens were developed in the 1970s (main agent: levonorgestrel) and 1980s (e.g., gestodene and desogestrel). Four studies in the years 1995 to 1996 reported a twofold increased risk of VT in women using a COC containing the progestogens gestodene and desogestrel compared with women using COCs containing levonorgestrel (►**Table 1**).[9–12] The four publications were followed by a large correspondence and a series of other publications pointing at confounding and biases, such as healthy user bias, recency of introduction bias, and prescribing bias. These issues were addressed in a clinical opinion article and a meta-analysis in which it was shown that confounding or bias could not explain the differences between the different progestogens in COCs on the risk of VT.[13,14]

Other progestogens have been developed since the introduction of the previously mentioned progestogens, that is, cyproterone acetate (1988) and drospirenone (2001). Several large studies, including a review by the European Medicines Agency as well as a Cochrane network meta-analysis, have shown that the risk of VT in women using a COC containing cyproterone acetate or drospirenone is approximately twofold higher than with COCs containing levonorgestrel (►**Table 1**).[15,16] These studies also reconfirmed the previous findings regarding the increased risk among users of gestodene and desogestrel compared with levonorgestrel.

Historically, the majority of available COCs contained EE, and it is this estrogen component in COCs that seems to be responsible for the occurrence of VT in women using them. Progestogens when given alone do not increase the risk of VT (as discussed in more detail in the next section). When combined with EE, the more androgenic progestogens, for example, levonorgestrel, counteract the potent EE-induced stimulation of liver proteins and change the procoagulant, anticoagulant, and fibrinolytic factors, but in contrast, non- or antiandrogenic progestogens (such as gestodene, desogestrel, cyproterone acetate, and drospirenone) exert a limited counteraction on the EE action, thereby increasing the risk of VT.[17]

EE use leads to hypercoagulability, due to changes in both procoagulant and anticoagulant proteins.[17] EE increases the levels of fibrinogen, prothrombin, and coagulation factors VII, VIII, and X, and slightly decreases the level of factor V. The increase of prothrombin and factor VII levels and the decrease of factor V levels are more obvious during the use of COCs containing the progestogen desogestrel than during the use of COCs containing the progestogen levonorgestrel. There are also changes in the protein C pathway, that is, there is a slight increase in the concentration and activity of protein C. This is counterbalanced by higher levels of the protein C inhibitors, that is, protein C inhibitor, α1-antitrypsin (α1-antiprotease), and α2-macroglobulin. The total and free protein S levels as well as the activated protein C (APC) independent anticoagulant activity of protein S declines. This reduction is more pronounced in women using the more non- or antiandrogenic progestogens than the androgenic progestogens. Lastly, EE enhances the fibrinolytic activity in plasma. There is a decrease in the concentration and activity of plasminogen activator inhibitor (PAI) 1 and an increase in levels of tissue plasminogen activator and plasminogen. This is, however, counteracted by increased levels of thrombin-activatable fibrinolysis inhibitor.[18]

From these findings, it has become clear that the EE component in combined contraceptives is responsible for the increased risk of VT. This finding has led to the search for novel estrogens, with less procoagulant effects on the coagulation system. After many trial and errors, contraceptives containing the estrogen estradiol valerate (E2V) and 17β-estradiol (17β-E2) were marketed in the year 2009 and 2011, respectively.[19,20]

E2V was combined with the progestogen dienogest, as it has particularly potent effects on the endometrium, that is, it inhibits ovulation and minimizes breakthrough bleeding.[19] There are several studies that have compared coagulation and hemostatic markers between the lowest risk COCs containing EE/levonorgestrel and COCs containing E2V/dienogest. In a crossover study performed in 29 women and in a randomized trial performed in 58 women, changes in hemostatic parameters were more pronounced in COCs containing EE/levonorgestrel versus E2V/dienogest, but the changes

Table 1 Risk of venous thrombosis associated with hormonal contraceptives

	Exposure	Reference	Relative risk
COCs containing EE	EE/gestodene, EE/desogestrel, EE/drospirenone, EE/cyproterone acetate	EE/levonorgestrel	~2[9–12,15,16]
COCs containing E2	E2V/dienogest 17β-E2/nomegestrol	EE/levonorgestrel	0.5 (95% CI: 0.2–1.5)[26,27] Unknown
POCs	Subcutaneous implant, IUDs, and progestogen-only pills Injectables (DMPA)	Nonuse of hormonal contraceptives	1[30,31] 2–3[30,31]
Combined vaginal ring and patch	EE/etonogestrel and EE/norelgestromin	COCs containing EE	Unknown

Abbreviations: 17β-E2, 17β-estradiol; CI, confidence interval; COC, combined oral contraceptives; DMPA, depot medroxyprogesterone acetate; E2, estradiol; E2V, estradiol valerate; EE, ethinylestradiol; IUD, intrauterine devices; POC, progestogen-only contraceptives.

remained within the normal range. The changes were seen in the concentrations of factors VII and VIII, antithrombin, proteins C and S, or in APC resistance, PAI-1 activity, D-dimer, and fibrinogen levels.[21,22]

Previous studies have shown that differences in the risk of VT between various COCs, that is, those containing the higher versus the lower risk progestogens, could at least partially be explained by the differential effects of these COCs on APC resistance and levels of sex hormone binding globulin (SHBG).[23,24] In a randomized trial with 74 women, comparing APC resistance and SHBG levels between E2V/dienogest and COCs containing EE/levonorgestrel, no differences were found in APC resistance and SHBG levels between users of these two COCs, suggesting a similar thrombotic risk.[25]

To date, there are only two reports that have investigated the risk of VT among E2V/dienogest and other COCs containing EE using VT as an end point. One study reported that in a total of 50,203 new COC users, who were followed for up to 5.5 years, COCs containing E2V/dienogest were associated with lower VT risk than COCs containing EE, with an adjusted hazard ratio (HR) of 0.4 (confidence interval [CI]: 0.2–1.0).[26] The COCs containing EE also contained the progestogen levonorgestrel, but there is no mention in the publication about which other types of progestogens were included. A comparison of the E2V/dienogest with the EE/levonorgestrel-only groups showed similar point estimates (i.e., similar to the comparison of E2V/dienogest vs. COCs containing EE) with wide CIs: an adjusted HR of 0.5 (95% CI: 0.2–1.5; ►**Table 1**). Similar results were obtained when the study was extended up to 2017, as reported by Fruzzetti and Cagnacci.[27]

17β-E2 has been combined with the progestogen nomegestrol acetate (NOMAC).[20] Two double-blind randomized studies using French and Finnish data have shown that 17β-E2/NOMAC has fewer adverse effects on blood biological coagulation, fibrinolysis, and hemostatic markers than EE/levonorgestrel.[28,29] Therefore, 17β-E2/NOMAC could have a more favorable VT risk profile than EE/levonorgestrel. However, studies with VT as an end point are needed to confirm this.

Other Forms of (Nonoral) Hormonal Contraceptives

Though the most common method of contraceptives among young women is COCs, other forms of (nonoral) contraceptives are increasing worldwide. These include progestogen-only contraceptives (POCs), that is, injectables, subcutaneous implant, intrauterine devices and progestogen-only pills, the combined hormonal patch, and the combined vaginal ring. Below, we provide a brief summary of evidence regarding the risk of VT in women using these other forms of contraceptives.

The Risk of VT Associated with Progestogen-Only Contraceptives

A systematic review from 2016[30] and a systematic review and meta-analysis from 2018[31] have suggested that the use of POCs are not associated with an increased risk of VT compared with nonuse of hormonal contraceptives, except for injectables containing depot medroxyprogesterone acetate (DMPA), which is associated with a two- to threefold higher risk than for nonuse (►**Table 1**).

Since the prothrombotic effect of COCs is due to the estrogen component found in COCs, POCs may be a good alternative in women who have a contraindication for estrogen use, such as those at high risk of VT. Progestogens, in general, do not have detrimental effects on hemostatic factors, with either oral or parenteral application, in cyclic or continuous regimens.[32] It is, however, still unclear why the risk of VT is increased in women using DMPA.

The Risk of VT Associated with Combined Hormonal Patch or Combined Vaginal Ring

The combined hormonal patch contains EE and the progestogen norelgestromin, whereas the combined vaginal ring contains EE and the progestogen etonogestrel. While some have argued that the risk of VT is increased for these two nonoral combined hormonal contraceptives, others have hypothesized that the risk might be lower or equal to the risk associated with COCs.[32]

Similar to COCs, the type of progestogen found in nonoral combined hormonal contraceptives may also be involved in modulating the risk of VT associated with the estrogen component.

The combined hormonal patch contains the progestogen norelgestromin, which is a metabolite of the progestogen norgestimate. COCs containing norgestimate have not been associated with higher risk of VT than COCs containing levonorgestrel. However, the concentration of norelgestromin (6 mg) in combined hormonal patch is much higher than the concentration of norgestimate (250 micrograms) in COCs. The progestogen found in combined vaginal ring, that is, etonogestrel, is a metabolite of a high-risk progestogen desogestrel. Therefore, this suggests that combined hormonal patch and combined vaginal ring may increase the risk of VT.

It has been argued that because EE is metabolized in the liver, nonoral administration of EE will avoid the first-pass effect on liver metabolism and therefore will have a low effect on coagulation proteins in the liver. However, it has been shown that changes in liver metabolism and hemostatic factors due to EE are not affected by the route of administration. A crossover study from 2007 compared the effects of oral and vaginal administration of the same dose of EE and found the same effects on hemostatic factors and estrogen-sensitive liver proteins.[32] Results from one study have suggested that regardless of the route of delivery, EE does not undergo an extensive hepatic metabolism and remains in the liver for a period of time. EE has a strong impact on the liver due to its 17a-ethinyl group. Due to this group, EE remains active in the liver, and this results in a slow metabolism of EE.[33] This probably explains why there is no difference in the coagulation proteins in the liver between oral and nonoral EE administration. This may suggest that combined hormonal patch and combined vaginal ring, which both contain EE, are associated with a similar risk of VT as COCs.

A systematic review from 2017 found conflicting results in women using the patch or the vaginal ring compared with

women using COCs (either containing EE/levonorgestrel or EE/norgestimate). Reasons for discordant results between studies were differences in the study population, study design, funding source, and ascertainment and confirmation of contraceptive use and outcomes. The authors concluded that further studies with standard methodology were needed to clarify any associations and better understand the mechanisms by which these two forms of nonoral combined hormonal contraceptives might influence the VT risk.[34] Along these lines, the American Society for Reproductive Medicine published a guideline in 2017 providing a summary statement saying that there is insufficient evidence regarding the risk of VT associated with combined hormonal patch and combined vaginal ring compared with COCs.[35]

The Risk of VT Associated with COCs and Inherited Thrombophilia

The increased risk associated with COCs is pronounced in women who already have an increased risk of VT, such as those with inherited thrombophilia (i.e., antithrombin, protein C and protein S deficiencies, and factor V Leiden [FVL] and prothrombin [F2] mutation).

Most studies have focused on FVL and F2 mutation since these are more prevalent in the general population (5 and 2%, respectively) than the deficiencies, which have a prevalence of $< 1\%$ in the general population. Results of these studies were combined in a recent systematic review and meta-analysis,[36] which showed that the presence of mild (FVL or F2 mutation) and severe thrombophilia (antithrombin, protein C or protein S deficiency, and double heterozygosity and homozygosity of FVL or F2 mutation) increases the risk of VT in COC users six- and sevenfold, respectively. The absolute risks were 0.49 to 2.0 per 100 pill-years for mild thrombophilia and 4.3 to 4.6 per 100 pill-years for severe thrombophilia. The incidence of VT in COC users with double heterozygosity or homozygosity of FVL or F2 mutation was 0.86 per 100 pill-years, suggesting that the absolute risk of this double defect is less serious than that of antithrombin, protein C, or protein S deficiency. In most case–control studies included in the meta-analysis, the number of thrombophilic controls who used COCs was small, yielding imprecise odds ratios of VT. Results from one of these small case–control studies suggested that the risk of VT associated with the joint effect of FVL and COC use is increased 10- to 15-fold compared with wildtype carriers without COC use rather than the previously reported 30-fold increased risk.[37] Currently, the World Health Organization states that COC use in women with inherited thrombophilia is associated with an unacceptably high risk of VT.[38] The authors of the meta-analysis suggested that COCs could be prescribed in women with mild thrombophilia (without a family history of VT), when alternative forms of contraception are not well tolerated.

A study published in 2018 investigated the interaction between the different types of generations of COCs and FVL mutation on the risk of VT.[39] They performed a case-only analysis, using 2,613 women with VT, to calculate the synergy index (SI) between the different generations of COCs and FVL. Their results showed that the interaction was higher in COCs containing third-generation progestogens (containing gestodene and desogestrel), drospirenone, or cyproterone acetate, compared with first-/second-generation progestogens (containing norethisterone, lynestrenol, and levonorgestrel). Although an attractive approach to calculate the combined effect of genes and environmental factors without the need to use control subjects, the SI from a case-only study represents interaction on the multiplicative scale. Several authors have pointed out the potential danger of using statistical interaction to draw conclusions about biological interaction.[40,41] Furthermore, the study grouped the different progestogens into generations. Several studies have shown that the risk of VT varies for the individual progestogens in COCs, for example, the progestogens desogestrel and gestodene are grouped as third-generation COCs, but desogestrel is associated with a higher risk of VT compared with gestodene.[42]

Most studies assessed the combined effect of COC use and the FVL or *F2* mutation. Thus, information regarding the combined effect of COCs and other genetic variants is scarce. Recently, we reported the joint effect of the different progestogens in COCs and genetic risk factors, that is, FVL, F2, and fibrinogen gamma.[43] The study had a case–control design. Although the number of control subjects with a genetic risk factor that also used a certain COC was small, we were able to estimate the joint effect (expressed as odds ratios with 95% CI) more precisely compared with a conventional logistic regression analysis by performing a constrained maximum likelihood estimation method. Our results showed that in women with inherited thrombophilia, COCs containing levonorgestrel were associated with the lowest risk of VT, albeit CIs were still wide and absolute risks were lacking. Therefore, interpretation of our results should be done with caution, and larger studies are needed to confirm these findings.

The combined effect of different types of COCs and genetic risk factors should be replicated in larger populations where absolute risks can be provided to confirm the previous findings regarding the lowest risk of VT in women who use COCs containing levonorgestrel and who have inherited thrombophilia.

The Risk of VT Associated with Switching COCs

To date, there are no studies that have investigated the risk of VT in women who switch COCs. We hypothesized that switching COCs, even when switching from a high- to a low-risk COCs, increases the risk of VT.[44]

The risk of VT associated with COC use is the highest in the first 3 to 12 months of starting, after which it remains stably elevated at a two- to fourfold increased risk compared with nonuse, depending on the type of COCs.[42] This "starters effect" occurs due to the redistribution of clotting factors after starting COCs and the so-called "attrition of susceptibles."[45] This is a phenomenon that applies to all drug-induced side effects, in which susceptible individuals are more likely to develop the side effect, in this case VT, shortly after the start of a prescription. In COC use, the magnitude of the risk increase in VT risk stabilizes after 12 months, when the peak in VT incidence

caused by the attrition of susceptibles has passed.[42] Some women tend to switch COC type, mainly due to side effects such as irregular periods, nausea, weight gain, and so on, or when their own (long used) COCs is no longer available, for example, during the pill shortage that occurred in The Netherlands during the period of September to December 2018.[46] One would expect a beneficial effect when women using a high-risk COC switch to a "safer" COC. However, the effect of switching COC type on VT risk has yet to be investigated. Apart from the potential risk reduction or increase depending on the type of switch made, the switching itself might exert an effect on the VT risk as clotting factors might again redistribute, possibly provoking an event among other susceptibles. Switching COC type may then temporarily induce an increased risk similar to the above-mentioned "starters effect." Additional studies are needed to test this hypothesis. Moreover, studies should be expanded to investigate the risk of VT in women switching from COCs to other forms of hormonal contraceptives.

Risk Prediction Model for VT in Women using COCs

The incidence of VT in premenopausal women is low at approximately 3 per 10,000 women per year.[2] However, since more than 100 million women worldwide use COCs, there is a large number of VT cases associated with COC use each year. Thus, one of the major challenges for medical doctors is to identify women at risk of developing VT related to COC use and advise them on alternative contraception methods.

Despite multiple studies that modeled VT risk using different combinations of predictors, none were specific to the use of COCs, except for one recent study performed by McDaid et al.[47] The aim was to identify women at risk of developing VT while using COCs and advise them on other forms of contraceptive methods. A case–control study was performed using 794 cases and 828 controls. The cases were part of the PIL1 Genetic Risk Monitoring (PILGRIM) study, and controls were recruited from different sources, with the majority ($N = 523$) being part of PILGRIM study. Four clinical and nine genetic variables were selected in the final model with significant p-values (< 0.05). The clinical variables were age, body mass index, smoking, and family history, and the genetic variables were *FVL* (rs6025), *F2* (rs1799963), *F11* (rs2289252), *KNG1* (rs710446), *PROCR* (rs9574), *2 ABO subtypes* (rs8176750 and rs8176719), *CYP2C9* (rs1799853), and *SUGCT* (rs4379368). The area under the curve (AUC) for the clinical model was 0.61, while the combined model, that is, clinical and genetic, had an AUC of 0.71. The authors mentioned that clinical information, which is often used during oral history taking of a woman during the doctor's visit for a COC prescription, is not sufficient to distinguish women at risk of VT while using COCs. This may indeed be the case for family history since several studies have shown that a positive family history does not correspond well with known genetic risk factors.[48] To assess a woman's risk of VT prior to prescribing COCs, a general practitioner often takes smoking habits into account. However, existing literature is controversial on whether smoking is a risk factor of VT, and at most it has a weak effect.[49,50] Therefore, genetic risk factors may improve the risk prediction, which, however, needs to be demonstrated in additional studies that also include medical and financial effects of widespread genetic testing.

Future studies should take the following into account when building a risk prediction model for VT in women using COCs. First, the risk assessment model should be developed in women who are starters (or who are about to start) COCs. This is important since women who already are using COCs for a long time have a low risk of VT due to attrition of susceptibles principle and the starters effect. Moreover, since the risk assessment in practice is done in women who are about to start COCs, it is crucial to develop the model in the same women. Second, information about risk factors that are not commonly included during the oral anamnesis should be included in the models, for example, transient provoking factors, such as surgery, immobilization, injury to the leg, cancer, and other comorbidities. While most of these risk factors are present only temporarily and are not highly prevalent in young women who want to start COCs, some of them may have a major effect. Studies should develop both internally and externally validated new prediction models since the performance of a predictive model is invariably overestimated in the discovery cohort. Furthermore, since the risk of VT varies for the different types of progestogens in COCs, risk assessment models that incorporate the progestogen type are needed since women with high risk would still be able to benefit from a lower risk COCs. Lastly, models that include other forms of contraceptives would also be beneficial to confirm the hypothesis that women with high risk could be prescribed alternative forms of contraception, such as POCs.

Conclusion

Some novel research questions in the field of COCs and the risk of VT have emerged recently. The newer types of COCs containing the estrogen component estradiol seem to have a lower risk of VT than COCs containing EE, but further studies that use VT as an end point are needed to confirm this. The combined effect of various types of COCs and genetic risk factors should be replicated where absolute risks can be provided to confirm the previous findings regarding the lowest risk of VT in women who use COCs containing levonorgestrel and who have inherited thrombophilia. The risk of VT in women switching COCs has not been investigated before and should therefore be examined in future studies. Finally, well-validated risk prediction models are urgently needed to identify women at high risk of VT while using COCs so that they can be advised about alternatives.

Conflict of Interest
None.

References

1 Vinogradova Y, Coupland C, Hippisley-Cox J. Use of combined oral contraceptives and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. BMJ 2015;350:h2135

2 Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. J Thromb Haemost 2007;5 (04):692–699

3 United Nations. Contraceptive use by method. 2019. Available at: https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/files/documents/2020/Jan/un_2019_-contraceptiveusebymethod_databooklet.pdf. Accessed July 28, 2020

4 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

5 Jordan WM. Pulmonary embolism. Lancet 1961;278 (7212):1146–1147

6 Vessey M, Mant D, Smith A, Yeates D. Oral contraceptives and venous thromboembolism: findings in a large prospective study. Br Med J (Clin Res Ed) 1986;292(6519):526

7 Bloemenkamp KW, Rosendaal FR, Helmerhorst FM, Büller HR, Vandenbroucke JP. Enhancement by factor V Leiden mutation of risk of deep-vein thrombosis associated with oral contraceptives containing a third-generation progestagen. Lancet 1995;346 (8990):1593–1596

8 Gerstman BB, Piper JM, Tomita DK, Ferguson WJ, Stadel BV, Lundin FE. Oral contraceptive estrogen dose and the risk of deep venous thromboembolic disease. Am J Epidemiol 1991;133(01):32–37

9 Thorogood M, Mann J, Murphy M, Vessey M. Risk factors for fatal venous thromboembolism in young women: a case-control study. Int J Epidemiol 1992;21(01):48–52

10 Vandenbroucke JP, Koster T, Briët E, Reitsma PH, Bertina RM, Rosendaal FR. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. Lancet 1994;344(8935):1453–1457

11 World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Effect of different progestagens in low oestrogen oral contraceptives on venous thromboembolic disease. Lancet 1995;346(8990):1582–1588

12 Farmer RD, Lawrenson RA, Thompson CR, Kennedy JG, Hambleton IR. Population-based study of risk of venous thromboembolism associated with various oral contraceptives. Lancet 1997;349 (9045):83–88

13 Vandenbroucke JP, Helmerhorst FM, Bloemenkamp KW, Rosendaal FR. Third-generation oral contraceptive and deep venous thrombosis: from epidemiologic controversy to new insight in coagulation. Am J Obstet Gynecol 1997;177(04):887–891

14 Kemmeren JM, Algra A, Grobbee DE. Third generation oral contraceptives and risk of venous thrombosis: meta-analysis. BMJ 2001; 323(7305):131–134

15 European Medicines Agency. Benefits of combined hormonal contraceptives (CHCs) continue to outweigh risks – CHMP endorses PRAC recommendation. EMA/709120/2013. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/11/news_detail_001969.jsp&mid=WC0b01ac058004d5c1. Accessed July 28, 2020

16 Stegeman BH, de Bastos M, Rosendaal FR, et al. Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis. BMJ 2013;347: f5298

17 Wiegratz I, Kuhl H. Metabolic and clinical effects of progestogens. Eur J Contracept Reprod Health Care 2006;11(03):153–161

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

19 Kiley JW, Shulman LP. Estradiol valerate and dienogest: a new approach to oral contraception. Int J Womens Health 2011; 3:281–286

20 Burke A. Nomegestrol acetate-17b-estradiol for oral contraception. Patient Prefer Adherence 2013;7:607–619

21 Parke S, Junge W, Mellinger U, et al. Comparative effects of a four-phasic regimen of estradiol valerate/dienogest versus ethinylestradiol/levonorgestrel on haemostatic parameters. Hum Reprod 2008;23(Suppl 1):i78–i79

22 Parks S, Nauhm G, Mellinger U, Junge W. Metabolic effects of a new four-phasic oral contraceptive containing estradiol valerate and dienogest. Obstet Gynecol 2008;111:3–12

23 Raps M, Helmerhorst F, Fleischer K, et al. Sex hormone-binding globulin as a marker for the thrombotic risk of hormonal contraceptives. J Thromb Haemost 2012;10(06):992–997

24 van Vliet HAAM, Frolich M, Christella M, et al. Association between sex hormone-binding globulin levels and activated protein C resistance in explaining the risk of thrombosis in users of oral contraceptives containing different progestogens. Hum Reprod 2005;20(02):563–568

25 Raps M, Rosendaal F, Ballieux B, et al. Resistance to APC and SHBG levels during use of a four-phasic oral contraceptive containing dienogest and estradiol valerate: a randomized controlled trial. J Thromb Haemost 2013;11(05):855–861

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

27 Fruzzetti F, Cagnacci A. Venous thrombosis and hormonal contraception: what's new with estradiol-based hormonal contraceptives? Open Access J Contracept 2018;9:75–79

28 Ågren UM, Anttila M, Mäenpää-Liukko K, et al. Effects of a monophasic combined oral contraceptive containing nomegestrol acetate and 17β-oestradiol compared with one containing levonorgestrel and ethinylestradiol on haemostasis, lipids and carbohydrate metabolism. Eur J Contracept Reprod Health Care 2011;16(06):444–457

29 Gaussem P, Alhenc-Gelas M, Thomas JL, et al. Haemostatic effects of a new combined oral contraceptive, nomegestrol acetate/17β-estradiol, compared with those of levonorgestrel/ethinyl estradiol. A double-blind, randomised study. Thromb Haemost 2011;105 (03):560–567

30 Tepper NK, Whiteman MK, Marchbanks PA, James AH, Curtis KM. Progestin-only contraception and thromboembolism: a systematic review. Contraception 2016;94(06):678–700

31 Glisic M, Shahzad S, Tsoli S, et al. Association between progestin-only contraceptive use and cardiometabolic outcomes: a systematic review and meta-analysis. Eur J Prev Cardiol 2018;25(10): 1042–1052

32 Schindler AE. Differential effects of progestins on hemostasis. Maturitas 2003;46(Suppl 1):S31–S37

33 Cedars MI, Judd HL. Nonoral routes of estrogen administration. Obstet Gynecol Clin North Am 1987;14(01):269–298

34 Tepper NK, Dragoman MV, Gaffield ME, Curtis KM. Nonoral combined hormonal contraceptives and thromboembolism: a systematic review. Contraception 2017;95(02):130–139

35 Practice Committee of the American Society for Reproductive Medicine. Electronic address: ASRM@asrm.org; Practice Committee of the American Society for Reproductive Medicine. Combined hormonal contraception and the risk of venous thromboembolism: a guideline. Fertil Steril 2017;107(01):43–51

36 van Vlijmen EF, Wiewel-Verschueren S, Monster TB, 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

37 Spannagl M, Heinemann LA, Schramm W. Are factor V Leiden carriers who use oral contraceptives at extreme risk for venous thromboembolism? Eur J Contracept Reprod Health Care 2000;5 (02):105–112

38 World Health Organization. Medical eligibility criteria for contraceptive use. 5th ed. GenevaWorld Health Organization2015

39 Hugon-Rodin J, Horellou MH, 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
40 Siemiatycki J, Thomas DC. Biological models and statistical interactions: an example from multistage carcinogenesis. Int J Epidemiol 1981;10(04):383–387
41 Wang X, Elston RC, Zhu X. Statistical interaction in human genetics: how should we model it if we are looking for biological interaction? Nat Rev Genet 2011;12(01):74
42 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
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(e-pub ahead of print). Doi:10.1111/bjh.16666
44 Khialani D, de Rooij E, le Cessie S, Rosendaal FR, van Hylckama Vlieg A. Thrombosis risk after switching oral contraceptive type. Available at: http://ecth2019.org/wp-content/uploads/2019/09/ECTH2019-ABSTRACT-BOOK.pdf. Accessed July 28, 2020
45 Tans G, Curvers J, Middeldorp S, et al. A randomized cross-over study on the effects of levonorgestrel- and desogestrel-containing oral contraceptives on the anticoagulant pathways. Thromb Haemost 2000;84(01):15–21
46 Dutch News. Shortage of contraceptive pills set to continue for 'weeks'. Available at: https://www.dutchnews.nl/news/2018/11/shortage-of-contraceptive-pills-set-to-continue-for-weeks/. Accessed July 28, 2020
47 McDaid A, Logette E, Buchillier V, et al. Risk prediction of developing venous thrombosis in combined oral contraceptive users. PLoS One 2017;12(07):e0182041
48 Bezemer ID, van der Meer FJ, Eikenboom JC, Rosendaal FR, Doggen CJ. The value of family history as a risk indicator for venous thrombosis. Arch Intern Med 2009;169(06):610–615
49 Cheng Y-J, Liu Z-H, Yao F-J, et al. Current and former smoking and risk for venous thromboembolism: a systematic review and meta-analysis. PLoS Med 2013;10(09):e1001515
50 Ageno W, Becattini C, Brighton T, Selby R, Kamphuisen PW. Cardiovascular risk factors and venous thromboembolism: a meta-analysis. Circulation 2008;117(01):93–102