Contraception and venous thromboembolism

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Keywords

Venous thromboembolism (VTE), thrombosis, combined contraception, gestagen, gestagen-only contraception, emergency contraception, pregnancy

Summary

In Germany approximately 20 million women are in their reproductive age. One third of them are taking combined oral contraceptives (COC), which consists mostly of Ethinylestradiol (EE) and a synthetic gestagen. Basic risk for venous thromboembolism (VTE) in women of this age is low, but rises during pregnancy or when combined hormonal contraceptives (CHC) are used. Therefore, women have a higher risk than men for VTE until the age of 35, after that time point the risk remains equal. Elevation of the thrombotic risk depends on the selected contraceptive. Older COC with norgestimat or levonorgestrel have a lower risk than newer COC. This is also true for nonoral KHK. Consequently, these older COC are the first choice in many international guidelines. Newer generations of contraceptives should only be prescribed, if a secondary reason other than contraception exists. The risk of newer COC containing Estradiol and not Ethinylestradiol instead of EE is not clear due to missing data. The use of gestagen only hormonal contraception with does not contain any significant increase of the risk for VTE with the exception of depot depot medroxyprogesterone acetate (DMPA). Emergency contraception, which do not contain ee, but only contains Levonorgestrel or Ulipristalacetat does not result in a higher risk for VTE. Oral desogestrel or levonorgestrel only contraceptives, intrauterine device (IUD) and Etonogestrel implants are the contraception of choice in women with a history of VTE or suffering from thrombophilia. These safe contraceptives should be offered to women with high risk of VTE due to the much higher VTE risk in pregnancy. The screening for thrombophilia is not indicated in every woman with the wish for contraception. This should be restricted to certain cases, e. g. to women with a positive history for VTE or with close relatives suffering from VTE in young age under 50 years.

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Schlüsselwörter

Venöse Thromboembolie (VTE), Thrombose, kombinierte Kontrazeptiva, Gestagene, reine Gestagen-Kontrazeptiva, Notfall-Kontrazeption, Schwangerschaft

Zusammenfassung

Etwa 20 Millionen Frauen befinden sich aktuell im reproduktiven Alter. Ein Drittel von ihnen wendet kombinierte hormonelle Kontrazeptiva an (KHK), welche meist aus Ethinylestradiol und einem synthetischen Gestagen bestehen. Das Grundrisiko für venöse Thromboembolien (VTE) für Frauen im reproduktiven Alter ist gering, steigt aber deutlich an durch Anwendung von KHK oder auch in der Schwangerschaft/Wochenbett. Dies gilt auch für nichtorale KHK. Hierdurch haben junge Frauen ein merklich höheres VTE Risiko als Männer bis zum Alter von 35 Jahren, danach gleicht sich das VTE-Risiko zwischen den Geschlechtern an. Die Erhöhung des VTE Risikos hängt vom verwendeten KHK ab. Ältere KHK mit Norgestimat oder Levonorgestrel als Gestagen haben ein niedrigeres VTE-Risiko als neuere KHK. In vielen internationalen Leitlinien gelten daher mittlerweile die älteren KHK als erste Wahl. Neuere KHK sollten daher nur noch verordnet werden, wenn besondere Gründe hierfür vorliegen. Das VTE-Risiko von KHK mit Estradiol bzw. Estradiolvalerat statt EE ist noch unklar durch fehlende Datenlage. Die Anwendung von rein gestagenhaltiger Kontrazeption erhöht das VTE-Risiko nicht signifikant mit Ausnahme von Depot-Medroxyprogesteronacetat (DMPA). Die Notfallkontrazeption („Pille danach"), welche keine Östrogene enthalten, sondern nur Levonorgestrel bzw. Ulipristalacetat erhöhen das VTE-Risiko nicht. Orale reine Gestagenkontrazeptiva (mit Desogestrel oder Levonorgestrel), Intrauterine Kontrazeption und Etonogestrel Implantate sind die Verhütungsmittel der Wahl bei Frauen mit erhöhtem VTE-Risiko. Ein Thrombophilie-Screening ist nicht bei jeder Frau indiziert mit Kontrazeptionswunsch. Diese Testung sollte limitiert werden z.B. auf Frauen mit positiver VTE Eigenanamnese oder auf Frauen mit VTE-Fällen in jungen Jahren unter 50 in der nächsten Verwandtschaft.

Classification of contraceptives

Combined hormonal contraceptives (CHC)

Combined oral contraceptives (COC) are the most commonly prescribed contraceptives and therefore represent the far largest proportion of the classic contraceptive pills. COC consist of an estrogen component and a synthetic progestogen. The estrogen used is overwhelmingly ethinylestradiol (EE), a synthetic oestradiol with a prolonged half-life. Only 2 newer COC use the natural estradiol (Zoely®) or estradiol valerate (Qlaira®).

Combined contraceptives can also be used transdermally as a patch (Evra®) or vaginally as a ring (Nuvaring®).

A distinction is drawn within COC between the group of older COC with the progestogens levonorgestrel, norgestimate or norethisterone and the newer COC with the progestogens desogestrel, gestodene, drosperinone and also dienogest, chormadinone and nomegestrol. Products with 35 µg EE and cyproterone acetate occupy a special position. These are not approved as contraceptives (although they have a contraceptive effect), but only for the treatment of acne and hirsutism.

The term CHC = combined hormonal contraceptives also includes the non-oral combined contraceptives.

Progestogen-only preparations (POP)

POP are far less commonly prescribed and contain no estrogen component. POP can be used in a great variety of ways. Besides the oral preparations (e.g. Cerazette®, Microlut®), there are also preparations for intrauterine use (e.g. Mirena®, Jaydass®, Kyleena®), for intramuscular use as 3-month injections (e.g. Depot-Clinovir®, Sayana®), contraceptive sticks for implantation into the upper arm (e.g. Implanon®) or preparations for oral emergency contraception (e.g. EllaOne®, PiDaNa®).

Statistical data

There are approximately 20 million women of reproductive age in Germany and about one-third of them use COC. Other hormonal contraceptives are far more rarely used (1). Depending on their age, up to 74% of those under 20 years of age use hormonal contraceptives (▶ Fig. 1). The considerably less frequent prescription of POP might be related to the better control of menstruation with COC and the desired side effects of COC such as the improvement in acne and hirsutism.

It is therefore a mass market. Especially in young women, the newer COC with an increased risk of venous thromboembolism (VTE) are still predominantly prescribed (▶ Fig. 2).

General risk of VTE in young women

The risk of VTE in women of child-bearing age is low at about 2 – 5/10,000 per year (2). Pregnancy is associated with a considerable, roughly 6-fold higher risk of VTE and this increases by as much as 22 times during the post-partum period (3, 4).

Due to the prescribing of COC, young women experience pulmonary embolisms far more often than young men. This sex-specific difference disappears approximately above the age of 32–33 years, i.e. at the age when many women usually stop using contraceptives in order to have a child (5) (▶ Fig. 3).

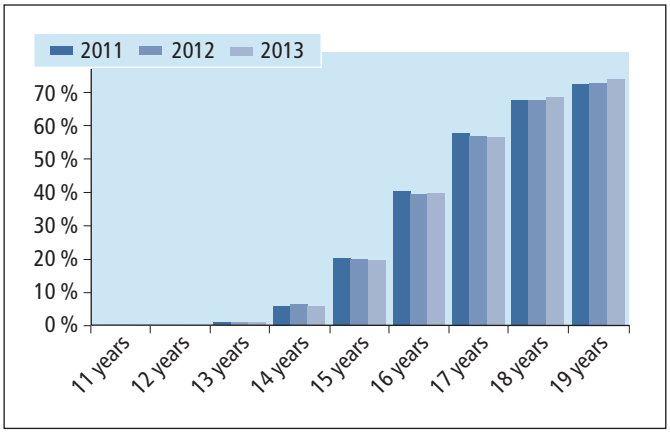

Fig. 1 Percentage frequency of ingestion of hormonal contraceptives in young women (Pill Report of the Techniker Krankenkasse – a German health insurance scheme – 2015)

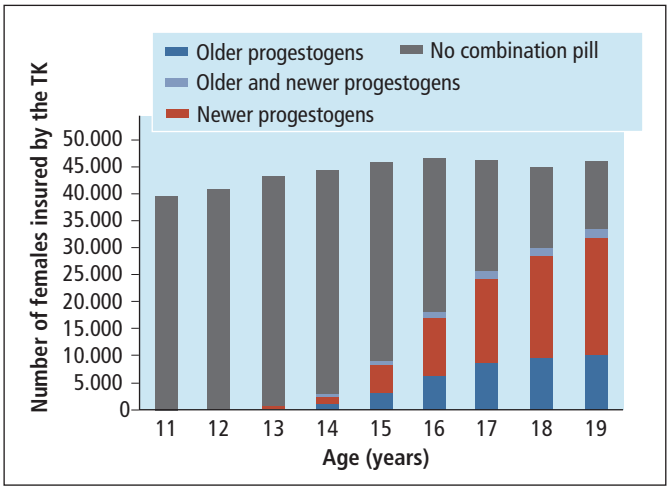

Fig. 2 Distribution of the prescription of COC to young women in the year 2013, Pill Report of the Techniker Krankenkasse 2015

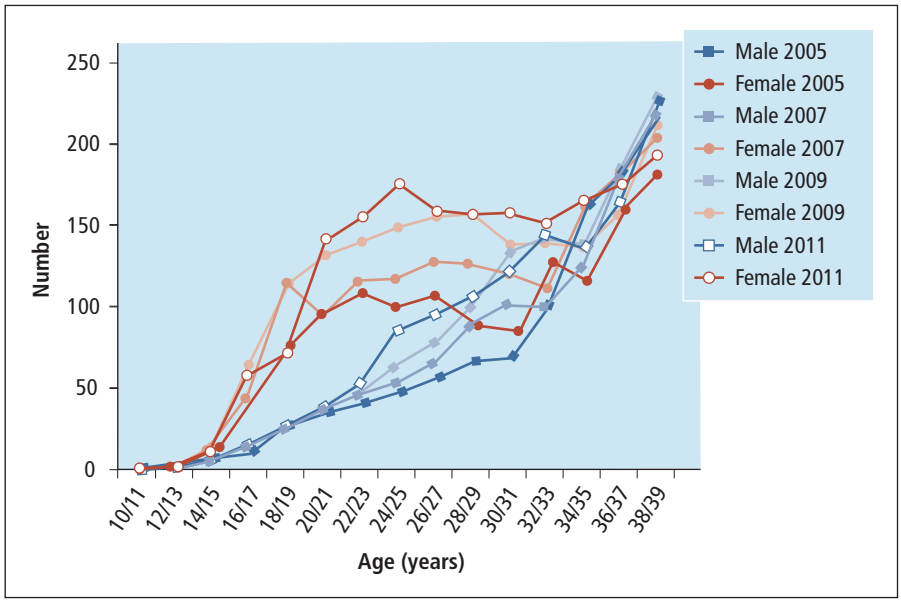

Fig. 3 Absolute numbers of hospitalised pulmonary embolisms in young patients in 2005 – 2011 according to sex (5)

VTE risk under combined hormonal contraceptives (CHC)

The risk of VTE for CHC is highest in the first year of use (OR 4.1 in the first 3 months and OR 2.1 in the first 12 months), but remains at an elevated level even after 12 months (OR 1.9 in the first 4 years) (6). This also applies to a restart after a pause in taking the pill. The elevated VTE risk is due to the increase in procoagulators such as factor VIII and fibrinogen and a decrease in anticoagulators, such as protein S (7, 8). This procoagulatory effect is once again more marked in overweight women with a BMI above 25 (9). Pill pauses are therefore – in terms of VTE risk – counterproductive.

The hypercoagulatory effect of COC lasts for up to roughly 6 – 8 weeks after discontinuation (e.g. the decrease in protein S). A brief pause in taking the pill before a surgical procedure is therefore of no purpose whatsoever and also, due to the increased VTE risk on resumption, more harmful than beneficial (10).

The markedly reduced risk of recurrent VTE in women who suffered their first event under CHC and immediately stopped taking CHC demonstrates the importance of CHC as a trigger for VTE (11).

If women are re-exposed to CHC after deep vein thrombosis (DVT), then they have a high risk of recurrence (12).

Depending on the dose of estrogen and the nature of the progestogen used, COC cause a marked increase in the risk of VTE. Most of the COC used today have an estrogen dose of 20 – 35 mg. The higher the estrogen dose, the higher the VTE risk. The type of progestogen used also considerably affects the risk of VTE. Thus, newer COC have at least double the risk of VTE than the older COC with levonorgestrel (6, 13). A "Red Hand Letter" (German warning letter to physicians) of 30.04.2014 already drew attention to this (https://www.akdae.de/ Arzneimittelsicherheit/RHB/Archiv/2014/20140130.pdf) (▶ Table 1)

A doubling in the risk of VTE has also been demonstrated for COC in studies with drospirenone and cyproterone acetate (14).

As possible reason is discussed here the different inhibitory action of various progestogens on ethinylestradiol, which once again leads to differing effects on pro-and anticoagulators (e.g. desgestrel COC cause a marked increase in some clotting factors and a greater decrease in protein S) (13) (15).

COC with estradiol/nomegestrol acetate (Zoely®) and estradiol valerate/dienogest (Qlaira®) are in a unique position. The avoidance of ethinylestradiol leads to a reduced recirculation of the estrogen in the liver and hence to lower activation of clotting, comparable to that with the older COC (16, 17). However clinical data are still awaited on this point.

The transdermal (ethinylestradiol + norelgestromin = Evra®) or transvaginal COC (ethinylestradiol + etonogestrel = Nuvaring® or Circlet®) also lead to a doubling of the VTE risk compared to older COC with levonorgestrel or to COC with norgestimate (18, 19).

In France, COC containing desogestrel and drospirenone were removed from reimbursement by the health insurance schemes in 2013 . This led to a 45% decline in the number of these COC prescribed, whereas COC of the 1st and 2nd generation were prescribed approx. 30% more

Tab. 1 VTE risk with COC depending on the progestogen used. [1]Further studies are being undertaken or planned to obtain meaningful data about the risk with these products. E2=estradiol

Progestogens that are contained in CHC (combined with ethinylestradiol, unless otherwise stated)	Relative risk compared with levonorgestrel	Estimated incidence (per 10000 women and years of use)
Non-pregnant non-users	-	2
Levonorgestrel	Reference	5–7
Norgestimate/norethisterone	1.0	5–7
Gestoden/desogestrel/drospirenone	1.5–2.0	9–12
Etonogestrel/norelgestromin	1.0–2.0	6–12
Chlormadinone acetate /dienogest/ nomegestrol acetate (E2)	Still to be confirmed[1]	Still to be confirmed[1]

often. At the same time, the number of hospitalisations for pulmonary embolism among the 15 – 49-year-olds dropped by 11.2% and among the 15 – 19–year-olds by even 27.9%. In contrast, the referral rates of men in the same age groups and of older women did not change. The French drug regulatory authorities took this as confirmation that VTE morbidity can be reduced by the choice of less risk-bearing COC (20).

VTE risk under progestogen-only preparations

The majority of POP do not increase the risk of VTE. One exception is the 3-month injection (DMPA [subcutaneous depot medroxyprogesterone acetate], e.g. Depo-Clinover®), for which one study found a 3.6-fold increase in VTE risk (21). However, the WHO concluded that the benefits of use of this product in VTE patients outweigh the risks (22). Nevertheless, caution when prescribing it in women with increased risk of VTE is justified.

However, all other POP can be used without problems in women with a history of VTE, because they do not increase the risk of VTE (22, 23). There is therefore no fundamental reason to withhold hormonal contraception from women with VTE or increased risk of it. This is all the more important to avoid unwanted pregnancies, since pregnancy itself is also associated with a markedly increased risk of VTE – as discussed above.

Regrettably this is in strong contrast to the package leaflets and information for healthcare professionals of POP, which in Germany unfortunately continue to list VTE as a contraindication, although it was clinically proved several years ago that there is no increased risk of VTE with almost all POP clinically, apart from the 3-month injection (▶ Table 2).

Tab. 2 Overview of hormonal contraceptives and VTE risk

Contraceptive	Oestrogen	Progestogen	Tradename example	DVT risk
Combined hormonal preparations (oestrogen and progestogen)				
Older COC	EE	Levonorgestrel Norgestimate Norethisterone	Leios® Cilest® Conceplan M®	↑
Newer COC	EE	Desogestrel Gestoden Drosperinone Dienogest Chlormadinone	Marvelon® Femovan® Yasmin® Maxim® Enriqa®	↑↑
Newer COC	Estradiol or estradiol valerate	Nomegestrol	Zoely® Qlaira®	↑-/↑ ↑?
Drugs against acne/hirsutism	EE	Cyproterone acetate	Diane 35®	↑↑
Vaginal ring	EE		Nuvaring®	↑↑
Contraceptive patch	EE		Evra®	↑↑
Progestogen-only preparations				
Estrogen-free ovulation inhibitors	-	Desogestrel	Cerazette®	-
Minipill	-	Levonorgestrel	Microlut®	-
Intrauterine system		Levonorgestrel	Mirena® Jaydess® Kyleena®	-
Stick – upper arm	-	Etonogestrel	Implanon®	-
3-month injection	-	Medroxyprogesterone acetate	Depo-Clinovir® Sayana®	↑?
Emergency contraception	-	Ulipristal acetate Levonorgestrel	EllaOne® PiDaNa®	-

VTE risk under CHC in women with thrombophilia

The VTE risk under CHC in women with thrombophilia (24) is markedly increased by a factor of around 7 compared with women without thrombophilia and taking COC.

Thus, an OR of 20.6 for VTE was demonstrated for women with factor V Leiden mutation under CHC (25). Another study found the following VTE associations for women with COC and thrombophilia: factor V Leiden mutation OR 15.62, antithrombin deficiency OR 12.60, protein C deficiency OR 6.33, protein S deficiency OR 4.88 and for the combination of factor V Leiden mutation and prothrombin mutation G20210A, an OR of 7.5 (26).

Apparently it is not only hereditary thrombophilia that plays a role. Women, who for various reasons (including smoking, overweight) show elevated levels of various clotting factors (factors II, V, VIII, XI) even before CHC is prescribed, have an elevated risk of VTE under CHC (27) (28).

The increased risk of VTE in women with factor V Leiden mutation taking COC containing drospirenone or cyproterone acetate compared to COC containing levonorgestrel or norgestimate could also be confirmed (29).

Estimation of the risk of VTE before prescribing CHC

It is essential to undertake an individual VTE risk assessment before prescribing any CHC. In every case, a careful recording of the patient's own history and the family history in relation to VTE and risk factors must be carried out. The question of co-

morbidities, smoking, BMI, age and any forthcoming operations or periods of immobilisation is also important.

A full diagnostic thrombophilia workup is not recommended. If necessary, a specialist in coagulation disorders can be brought in to help decide whether such a workup should be considered. However, a thrombophilia workup is recommended in young patients with a positive history of VTE and also in women whose direct blood relatives suffered a VTE below the age of 50 or under the influence of estrogens/pregnancy.

In addition, before prescribing CHC, every patient is to be informed of the typical symptoms of VTE and that in cases of an operation or immobility, she must inform clinicians that she is taking CHC (30).

Current official recommendations on contraception and risk of VTE, guidelines

In the Pharmacovigilance Bulletin (Issue 4/2011) of the Paul Ehrlich Institute and the BfArM (German Federal Institute for Drugs and Medical Devices), it was pointed out that more attention should be paid when prescribing COC to the different VTE risk of the various progestogens. It was also mentioned that some European countries (The Netherlands, Belgium, Denmark, England, Norway) had already published national recommendations on the basic prescribing of COC, with levonorgestrel and norethisterone as agents of first choice.

In the meantime, a special warning has been added to the information for healthcare professionals for COC about the increased risk of VTE of other COC compared with COC containing norethisterone, norgestimate and levonorgestrel.

A Red Hand Letter of 30.01.2014 (30) again referred to the lower risk of VTE of COC containing levonorgestrel, norethisterone and norgestimate compared with the more modern COC. It recommended that these differences should be taken into account on an individual basis.

The new S3 Guideline "Contraception", publication of which is planned for 2018, basically advises that the individual risk of VTE should be carefully recorded before prescribing hormonal contraception, especially in first-ever users. The guideline advises against the prescribing of CHC if the VTE risk is elevated, and if hormonal contraception is desired in these cases, then POP should be prescribed.

Contraception in women with fresh VTE under anticoagulation

Hormonal contraception is still often automatically stopped on occurrence of a fresh VTE, frequently because of lack of data or outdated recommendations. However, a prothrombotic activation of coagulation by COC is generally absent if anticoagulation is adequate. In one study from 2016 with 475 women under anticoagulation and hormonal contraception, it was shown that neither the use of CHC nor of POP increased the risk of VTE recurrence (27).

Other important aspects here are the avoidance of hypermenorrhoea under anticoagulation, which in extreme cases can assume life-threatening proportions (31). The continuation of a CHC markedly reduces the risk of hypermenorrhoea under anticoagulation. But it must be borne in mind that approx. 6–8 weeks before ending anticoagulation, the CHC is also to be stopped, because of the prolonged hypercoagulatory effect of these preparations.

The second important aspect is naturally the prevention of a pregnancy under ongoing anticoagulation, because not only vitamin K antagonists, but also the new direct oral anticoagulants are contraindicated in pregnancy. According to the S3 Guideline "Contraception", soon to be published, the patient is also to be explicitly informed about this and if necessary, should be referred to a gynaecologist.

Conflict of interests

The authors state that there is no conflict of interests.

Ethical guidelines

Preparation of the manuscript did not involve any studies on humans or animals.

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