

Hormonal contraception in thrombophilic adolescents

Risk of thrombosis and recommendations

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Keywords

Thrombophilia, contraception, adolescents, COC, progestagen only pills

Summary

About 3.2 million women in Germany are between 14 and 19 years old representing about 19% of women. 55% of them use combined oral contraception (COC). The risk of venous thromboembolism (VTE) during the use of COC is increased 2–6 times. For thrombophilic patients depending on the kind of thrombophilic defect it is much higher. Pregnancy and postpartum period lead to a much higher increase of VTE than any COC use at all, both in women with and without thrombophilic defect. VTE risk in COC is highly dependent on the content of ethinylestradiol (EE) and the kind of progestagen used in COC. Progestagen-only contraceptives (POC) do not increase the VTE risk, since they do not activate the coagulation system. **Conclusion:** It is not justified to withhold any hormonal contraception to thrombophilic women, especially considering the much higher VTE risk in (maybe unintended) pregnancy. Adolescents thrombophilic women should rather be informed about the opportunity to use POC.

Schlüsselwörter

Thrombophilie, Kontrazeption, Jugendliche, KOK, Gestagenpillen

Zusammenfassung

Ungefähr 3,2 Millionen Frauen in Deutschland sind zwischen 14 und 19 Jahre alt, dies entspricht ca. 19% der Frauen. 55% von ihnen verwenden kombinierte orale Kontrazeptiva (KOK). Das Risiko für venöse thromboembolische Erkrankungen (VTE) während der Einnahme von KOK ist ca. 2- bis 6-fach erhöht. Für thrombophile Patientinnen ist das Risiko je nach Schweregrad der Thrombophilie deutlich höher. Schwangerschaft und Wochenbett sind allerdings mit einem deutlich höheren Risiko für VTE verbunden im Vergleich zur KOK-Einnahme, sowohl bei Frauen mit wie auch ohne thrombophilen Defekt. KOK unterscheiden sich im VTE-Risiko je nach der Art des enthaltenen Gestagen-Anteils und der Östrogendosis. Reine gestagenhaltige Verhütungsmittel, z. B. rein gestagenhaltige Pillen, erhöhen dagegen das Thrombosrisiko nicht, da Gestagene nicht zur Gerinnungsaktivierung führen. **Schlussfolgerung:** Es ist also nicht gerechtfertigt, thrombophilen Patientinnen generell eine hormonelle Kontrazeption zu verweigern, insbesondere im Hinblick auf das deutlich höhere VTE-Risiko im Rahmen einer evtl., ggf. auch ungewollten, Schwangerschaft. Vielmehr sollte auf die Möglichkeit der rein gestagenhaltigen Kontrazeption aufmerksam gemacht werden v. a. bei adolescenten Frauen.

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Contraception and pregnancy terminations in adolescents

In Germany actually about 17.2 millions of women are in reproductive age, that means about 41% of women. Of these 17.2 million women, 3.2 millions (19% of women in reproductive age) are aged between 14 and 19 years. Condoms are the preferred method for contraception in young couples.

However, 16% of boys and 11% of the girls use no contraception at their first sexual intercourse.

About one third of women younger than 20 years have problems with acne vulgaris.

60% of women aged between 16 and 30 years use hormonal contraceptives, mostly combined oral contraceptives (COC), i. e., a contraceptive pill with estrogen and progestagen. Concerning the use of other contraceptive methods: ► Table 1.

About 38% of girls in the age between 14 and 16 years have sexual coitus experience.

In Germany in 2008, we had 114 500 terminations of pregnancy; 5% (or 5700) of them were conducted in women younger than 18 years. The number is decreasing, in the year 2007 there were 800 cases more (1).

Risk for venous thromboembolism in young women

Real data for the overall risk for deep vein thrombosis (DVT) in Germany only exist for inpatients. In 2005 we had about 50 000 thromboembolisms in inpatients (ICD-code I80, I82, I87), i. e. about 44 to 70/100 000 cases depending on German federal state (2). Due to the fact, that more and more cases of venous thrombo-

contraception		millions	%	relation
hormonal methods containing estrogen	women in reproductive age (14–44 years)	17.2	41	of women
	users of COC total	6.6	38.5	of all women in reprod. age
	women < 20 years with COC use	1.5	55	of women between 14 and 19 years
	vaginal ring (Nuvaring®)	0.13	0.8	of women in reprod. age
	combined estrogen-progestagen patch (Evra®)	no data available		
hormonal methods progestagen only	estrogen-free ovulation inhibitor (Cerazette®)	0.19	1.1	of women in reprod. age
	other progestagen-only pills (28 mini®, microlut®)	0.01	0.06	
	intrauterine system (Mirena®)	1	6	
	injectable medroxyprogesteronacetat (Depo-Clinovir®, Sanaya®)	0.2	1	
	etonogestrel implant (Implanon®)	0.15	0.9	
	postcoital pill	0.2	1	
without hormones	copper intrauterine device	1	6	
	condom	4.8	28	
	natural family planning (e. g. temperature methods, Knaus-Ogino)	1.4	8	
	sterilisation	women	1.4	
		men	0.45	2

Tab. 1

Frequency of contraceptive methods in actual use in Germany

embolism (VTE) in Germany are treated in outpatients, the real incidence for thromboembolism is much higher. Furthermore, relevant epidemiological data about VTE derive from large treatment studies, so they reflect symptomatic rather than asymptomatic disease.

Asymptomatic disease is not infrequent especially in young women, because of a tendency of underdiagnosis of thromboembolism.

Therefore, the estimated risk in the literature for the 3.2 million young women between 14 and 19 years of about 1/20 000 to 1/100 000 women-years (that would mean only 32 – 160 cases of VTE in Germany in this age-group per year!) seems to be much to low from the view of a practicing haemostaseologist. For adolescents, unfortunately, no real data exist at all. A national registry is therefore urgently needed.

COC and other estrogen-containing contraceptives

New data show that the overall hazard ratio for thromboembolism and COC use in women is 2–6 (3). It is much higher in thrombophilic women depending on the kind of thrombophilia and depending on whether the patient has a single oder combined thrombophilic defect (3, 4) (► Tab.2). In addition, the risk of VTE is highest

- in the first year of use of COC (5) and
- in first-time users of COC (6).

Both conditions apply to young women. The risk of VTE turns to be lower after one year of use, but remains significantly higher than in non-users. Moreover, the rates of two major risk factors for VTE are rising according to data from the Federal Statistical Office in Germany (1) in girls between 15 and 20 years

- obesity (body mass index > 25 kg/m²) in 18% and
- cigarette smoking in 15%.

Only after 8 to 12 weeks after cessation of COC the VTE-risk turns to normal. Therefore, it is not recommended to stop COC before planned surgery. Instead of that COC users should better receive a pharmacological thromboprophylaxis post surgery according to the German thromboprophylaxis guidelines (7).

The hormonal contraception method of first choice in adolescents is COC: 55% of adolescents use this method (► Tab. 1). Its advantages are

- the contraceptive safety,
- easy use and
- a beneficial effect on acne and hyper- or dysmenorrhagia.

The VTE-risk of COC is highly dependent on the

- content of estrogen: < 50 µg vs. > 50 µg ethinyl-estradiol (EE),
- type of progestagen used in COC and differs significantly between COCs.

EE and progestagens have totally different effects on haemostasis. EE acts as a haemo-

static activator. Procoagulants increase and anticoagulants (especially protein S) decrease shortly after intake of EE. In contrast, intake of progestagens alone leads to an increase in protein S and fibrinolytic potency (8–12) (► Tab. 3). No coagulation activation can be measured in progestagen only contraceptives.

The VTE risk furthermore clearly differs by type of progestogen used in COC (► Tab. 4). COC containing EE +

- levonorgestrel or norethisterone are called COC of 2nd generation,
- gestoden or desogestrel COC of 3rd generation,
- drospirenone COC 4th generation,
- cyproteronacetate, chlormadinoacetate or dienogest are so-called antiandrogenic COC.

The use of COC containing EE + levonorgestrel is associated with an almost fourfold increased VTE risk (OR 3.6) relative to non-users, whereas the risk of VTE compared with non-use (13) was increased

- 5.6-fold for gestodene,
- 7.3-fold for desogestrel,
- 6.8-fold for cyproterone acetate and
- 6.3-fold for drospirenone.

Antiandrogenic COC have a fourfold higher risk for VTE compared with levonorgestrel-containing COC. They seem to have the highest VTE risk of all COC (14); for the hierarchy of VTE risk in different COCs ► Table 5.

A crossover study showed, that the fibrinolytic potential is decreased in users of COC, but more pronounced in users of desogestrel-containing COCs compared with levonorgestrel-containing COCs (15). Furthermore, the increase in activity of some coagulation factors is higher in desogestrel-containing COCs compared with levonorgestrel-containing COCs (16).

Recently, a new COC has been developed, containing estradiolvalerat instead of EE + dienogest (Qlaira®). Nothing is known, whether this change of estrogen type leads to a change in thrombotic risk. As long as we have no data about this, at least the same thrombotic risk as in COCs of 3rd and 4th generation should be estimated.

Tab. 2 Risk of venous thrombosis in different thrombophilias with and without hormonal contraception

thrombophilia		DVT risk, OR	
		without COC	with OC
factor V Leiden mutation	heterozygous	5	16
	homozygous	10	*
prothrombin G20210A mutation	heterozygous	3	6
	homozygous	no data due to rarity	*
factor V Leiden mutation + prothrombin G20210A mutation	heterozygous heterozygous	4–15	8–17
congenital deficiency	protein S	5–11	5
	protein C	3–15	6–24
	antithrombin type I/II	4–50 depending on type	13 28% of OC users suffer thrombosis
factor VIII elevation		5–8	9–13
antiphospholipid antibodies (lupus anticoagulants, anti-cardiolipin antibodies, anti-β2-glycoprotein I antibodies)		2–16 depending on antibody or combination	insufficient study results
hyperhomocysteinaemia		risk rises by 1.3 for each 5 μmol	insufficient study results
lipoprotein (a) > 300 mg/l		1.8	no data
MTHFR C677T polymorphism		not elevated	not elevated
* Data form a metaanalysis of heterozygous and a few homozygous cases. The VTE risk for homozygote carriers with OC use has thus far not been sufficiently studied and could lie considerably higher.			

COC are contraindicated in patients with a history of VTE (17) and should also be restricted in patient with known thrombophilia, especially in patients with a hereditary deficiency of anticoagulants (protein C, protein S, antithrombin) (3).

WHO recommendations for contraceptive use: ► Table 6.

The transdermal contraceptive patch Evra® and the vaginal contraceptive ring Nuvaring® both contain EE + a progestagen. There is some evidence, that the thrombotic risk while using EE is not dependent on the route of administration. Even transvaginal and transdermal use of EE leads to an activation of haemostatic system and to a thrombotic risk similar to COCs (18,19). Both transdermal contraceptive methods therefore are contraindi-

cated in patients with a history of VTE and with thrombophilia, too.

Progestogen-only contraceptive methods

There is no evidence for an activation of the haemostatic system by progestagen-only contraceptive methods (POC) (► Tab. 3).

Few studies have been large enough to quantify the risk of VTE associated with the use of progestogen-only contraception. A hospital-based, case-control study by WHO in Africa, Asia, Europe, and Latin America evaluated the risks of cardiovascular disease with the use of oral and injectable POC. A total of 1137 women with VTE and 9997 control subjects were recruited. Cases and controls were matched for age,

Tab. 3 Effects on haemostatic balance for COC and progestagen-only methods

haemostatic parameter	COC	progesta- gen-only
protein S	↓	↑
prothrombinfragment 1.2	↑	↓
factor VIII	↑	↓
t-PA	↓	↑
APC-ratio	↓	-
HDL-cholesterin	↓	-
LDL-cholesterin	↑	-
blood pressure	↑	-

COC: combined oral contraceptives (estrogen + progestogen)

body mass index and live births. Cases were more likely to have other cardiovascular risk factors (hypertension, diabetes mellitus, or rheumatic heart disease) or to be smokers. No significant increase in odds ratio for VTE was identified with the use of

any progestogen-only method. The odds ratio for progestogen-only pill-users was 1.74 (95% CI 0.76–3.99) and for women using progestogen-only injectables (OR 2.19, 95% CI 0.66–7.26). Although limited by small numbers, these data suggest that there is little or no increase in risk of VTE associated with use of oral or injectable progestogen-only methods (10, 20).

In another study, injectable depot–medroxyprogesterone acetate contraceptives were associated with a 3.6-fold (95% CI, 1.8- to 7.1-fold) increased risk of venous thrombosis compared with non-users of hormonal contraceptives (21). If injectable depot–medroxyprogesterone acetate (MPA) contraceptives might be associated with a small increase of thrombotic risk is still a matter of debate. In Germany, Sayana® is approved, a new subcutaneous injectable depot–medroxyprogesterone acetate contraceptive with only two thirds of the dose of MPA compared with Depot-Clinovir®. It is still not clear, if this lower dose of MPA decreases the risk of VTE, till now no post-marketing data exist. Also no

data regarding VTE risk exist for Norethisteronenantat (Noristerat®), another injectable progestogen-only contraceptive.

A post-marketing study evaluated the safety of levonorgestrel-only implants in developing countries (22). It included 7977 women with over 95% completing five years of follow-up. Only one levonorgestrel-only implant-user developed a DVT and no increase in mortality was identified. No data were identified regarding the etonorgestrel-only implant (Implanon®).

Further evidence supporting no increased risk of VTE with POC is provided by a 1999 case-control study (adjusted RR 1.3, 95% CI 0.3–6.8) (23). There seems to be no increased risk of VTE for the levonorgestrel-releasing intrauterine system (Mirena®) (21).

Although COCs containing desogestrel have been described to have an increased risk of VTE compared with those containing levonorgestrel or norethisterone, the desogestrel-only pill, Cerazette® has not been associated with an increased risk. However, data are limited. A randomised, controlled, double-blind trial of desogestrel-only and levonorgestrel-only pills did not identify any clinically significant alterations in haemostatic parameters (10, 24).

In Germany, only two preparations are approved for emergency contraception, so called postcoital pills:

- 750 µg levonorgestrel (Levogynon®) or
- 30 mg Ulipristalacetat (ellaone®).

Both preparations are not associated with an increase in VTE according to the summary of product characteristics (in Germany called „Fachinfo“) and therefore can be used safely in thrombophilic patients.

High dose progestogens for therapeutic reasons

High-dose progestogens for therapeutic indications like menorrhagia appear to be associated with an increased risk of VTE (adjusted RR 5.3, 95% CI 1.5–18.7). Reanalysis of data from the WHO Collaborative Study (25) also showed an increase in VTE risk with therapeutic progestogens (OR 5.92, 95% CI 1.16–30.1), but small numbers have resulted in wide confidence intervals (26). Therefore, these agents should be avoided in thrombophilic patients.

Tab. 4 Approved hormonal contraceptives in Germany

contraceptive	estrogen	progestagen	examples	
COC	2 nd generation	ethinylestradiol 20–35 µg	levonorgestrel or norethisterone	Leios®, Miranova®, Microgynon®
			desogestrel or gestoden	Lovelle®, Marvelon®, Desmin®, Lamuna®
			drospirenone	Petibelle®, Yasmin®, Aida®
	antiandrogenic	ethinylestradiol 30–50 µg	cyproteroneacetate, chlormadinonacetate, dienogest	Diane 35®, Neo-Eunormin®, Valette®, Maxim®
	new	estradiolvalerat 1–3 mg	dienogest	Qlaira®
vaginal ring	EE 15 µg/day	etonogestrel	Nuvaring®	
transdermal patch	EE 20 µg/day	norelgestromin	Evra®	
„minipill“	none	levonorgestrel	28 mini®, Microlut®	
estrogen-free ovulation inhibitor		desogestrel	Cerazette®	
intrauterine system		levonorgestrel	Mirena®	
postcoital contraception		levonorgestrel	Unofem®, Levogynon®	
etonogestrel implant		etonogestrel	Implanon®	
injectable medroxyprogesterone acetate		medroprogesterone-acetate	Sayana®, Depo-Clinovir®	
EE: ethinylestradiol				

Pregnancy and postpartum period

The VTE risk in pregnancy and postpartum period is much higher than during use of any COC. The overall VTE risk in women with no thrombophilic defect, a single or combined defect is 0.73 (0.30–1.51), 1.97 (0.94–3.63) and 7.65 (3.08–15.76) per 100 person-years.

The risk is highest in postpartum period with hazard ratio of 16.0 (8.0–32.2) per 100 person-years.

Even the a priori absolute risk of VTE during pregnancy-postpartum in women without any thrombophilic defect is higher than noted in COC users (3).

For the odds-ratios for VTE of the different hereditary thrombophilic defects in pregnancy (27, 28): ► Table 7.

Recommendations

Contraception in thrombophilic adolescents

In women with a history of VTE and/or a known thrombophilic defects the use of COC and other contraceptive methods with EE are contraindicated (► Tab. 6) (WHO-recommendations for contrac-

Tab. 5

Thrombotic risk of different COCs

thrombotic risk	COC
high	antiandrogenic COC with cyproteroneacetat or chlormadinonacetat or dienogest
intermediate	COC with desogestrel, gestoden (3 rd generation), drospirenone (4 th generation)
low	COC with levonorgestrel or norethisterone (2 nd generation)
unknown	new COC with estradiolvalerat (instead of ethinyl-estradiol) + dienogest

tion). On the other hand, the even much higher risk for VTE in pregnancy and postpartum period has to be put into account. For this reason an adequate alternative contraception has to be offered to thrombophilic patients, especially adolescents!

But as shown, there is no reason to withhold hormonal contraception generally in adolescents with thrombophilia.

Estrogen-free, progestagen-only contraception methods are safe regarding VTE risk, as shown.

The following contraceptives therefore can be used in thrombophilic adolescents:

- progestagen-only pills, like Cerazette[®], 28 mini[®] or microlut[®],
- intrauterine copper-device or intrauterine system with desogestrel (Mirena[®]),

- etonorgestrel implant (Implanon[®]),
- postcoital pills (ellaone[®], Levogynon[®]),
- MPA-injectables: low dose should be preferred (Sayana[®]) because of a questionable small increase in VTE risk.

Typical side effects of progestagen-only contraceptives are

- a tendency to irregular menstrual bleeding and spotting, especially in women with relatively low von Willebrand-factor (e. g. patients with bloodgroup 0),
- worsening of acne vulgaris,
- weight gain.

If acne is worsening after cessation of COC, other therapeutic options should be discussed with a dermatologist.

Tab. 6 WHO medical eligibility criteria for contraceptive use 2008

condition		COC, CIC, vaginal ring, patch	progesteron only pills, DMPA, NET-EM, LNG/ETG implants	intrauterine device	
				copper	levonorgestrel
deep venous thrombosis (DVT) / pulmonary embolism (PE)	history of DVT/PE	4	2	1	2
	acute DVT/PE	4	3	1	3
	DVT/PE and established anticoagulant therapy	4	2	1	2
	family history (first degree)	2	1	1	1
major surgery	with prolonged immobilization	4	2	1	2
	without prolonged immobilization	2	1	1	1
minor surgery without immobilization		1	1	1	1

1: no restriction for the contraceptive method; 2: the advantages of using the method generally outweigh the theoretical or proven risks;

3: theoretical or proven risks usually outweigh the advantages of the method; 4: unacceptable health risk of the contraceptive method

COC: combined oral contraceptive; CIC combined injectable contraceptives; DMPA: depot medroxyprogesterone acetate;

NET-EN: norethisterone enantate injectables; LNG: levonorgestrel; ETG: etonogestrel

thrombophilic defect		odds ratio
factor V Leiden	heterozygous	9
	homozygous	34
prothrombin G20210A mutation	heterozygous	7
	homozygous	26
deficiency in	protein C	5
	protein S	3
	antithrombin	31–49% of women develop VTE without thromboprophylaxis
MTHFR polymorphisms		1

VTE: venous thromboembolism

Tab. 7

VTE risk during pregnancy and postpartum period in thrombophilic defects

Testing for heritable thrombophilia in adolescents

Nowadays general testing for thrombophilia is not recommended in all women, who wish contraception. Some gynecologists offer thrombophilia testing as a self-paid option to women who wish testing before the prescription of COC.

Testing should be performed in adolescents with personal history of VTE and/or a positive family history, i. e. relatives of first degree younger than 45 years with a history of VTE. However, testing should also be discussed in adolescents with several external risk factors for VTE like cigarette smoking, obesity, diabetes mellitus and other.

Forensic aspects

In Germany, in adolescents < 14 years before prescribing contraceptives a consent from one of the parents is recommended. However, this is not essential in individual cases, but the prescribing physician should document that he or she is convinced that the girl is capable to oversee her acts, decisions including their consequences. In girls aged from 14 to 18 years it is not necessary to have a consent from the parents before

prescribing contraceptives, unless doubts arise about the capability to act.

According to a court decision in 2005 in Germany physicians have to explain to all patients every possible thromboembolic complication before prescribing COC or other contraceptives containing EE. It is recommended to let the patient sign an information handout concerning the side-effects of contraceptive use, an example is seen in ►Figure 1 (29).

Conflict of interest

The author declares, that she has no conflict of interest regarding the subject of research reported in the manuscript.

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MIKROKONTAKTGEBRAUCH, RAUCHEN UND RISIKEN

Ich wurde ausführlich über die mir verordneten Medikamente, ihre Wirkungsweise, Nebenwirkungen und evtl. auftretende Wechselwirkungen mit anderen Arzneien beraten.

Ich wurde von meinem behandelnden Frauenarzt ausdrücklich darauf aufmerksam gemacht, dass **bestimmte Verhaltensweisen, z.B. Rauchen, z.B. Alkoholgenuß, ein erhöhtes Risiko für meine Gesundheit darstellen. Diese Gesundheitsgefahr ist in Verbindung mit einigen Medikamenten, u.a. bei der Anwendung hormoneller Kontrazeptiva (sog. Anti-Baby-Pille und anderer hormonhaltiger Verhütungsmittel), erhöht.**

Speziell für die Anwendung der hormonellen Verhütungsmittel gilt: Mir ist bekannt, dass die Anwendung dieser Medikamente mit einem erhöhten Risiko für einen Blutdruckanstieg, für Lebererkrankungen, für Venenentzündungen und für die Bildung von Blutgerinnseln (Thrombosen) und für Verschleppung dieser Gerinnsel (Embolien) verbunden ist. In der Folge kann es zu Schädigungen (z.B. Lungenembolie, Schlaganfall mit Lähmungen oder Sehverlust, Herzinfarkt) kommen: Die Schäden können vorübergehend oder bleibend, im schlimmsten Fall tödlich sein. Einzelheiten finden sich auch in den Fachinformationen (Beipackzettel) der entsprechenden Präparate.

Ich wurde darüber informiert, dass ich bei allen Erkrankungen andere Ärzte auf die Anwendung dieser Verhütungsmittel hinweisen, dass ich Veränderungen meines Gesundheitszustandes (z.B. Herzinfarkt, Hörsturz, Zuckerkrankheit, Blutdruckanstieg) bzw. die Einnahme anderer Medikamente meinem Frauenarzt mitteilen sollte.

Unterschrift Patientin/Patient

Fig. 1 Example for a handout for patients to inform them before prescribing contraceptives

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