Cardiovascular risk and the use of oral contraceptives

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Abstract

The use of combined oral contraceptives (COCs) is associated with approximately 2-fold and over 4-fold increased relative risks of arterial and venous thromboembolic events, respectively. The highest risk of venous thromboembolism occurs in the first year of use (OR: 4.17) and is reduced to 2.76 over baseline risk after 4 years of therapy. The risk of myocardial infarction does not correlate to the length of therapy and disappears after treatment termination. Most of women, using COCs, have low absolute cardiovascular risks and benefits outweigh the risk associated with this method of birth control. However, in some cases, COCs may be contraindicated due to excessively increased cardiovascular risks. Current users of COCs, older than 35 years, appear to show an estimated 2.5-fold and 10-fold increased risk of venous thromboembolism in comparison to younger than 35 years COCs non-users and users, respectively. COCs users, who are current smokers, have 10-fold increased risk of myocardial infarction, whereas the risk of stroke increases nearly 3-fold. The presence of poorly controlled hypertension is associated with approximately 3-fold increased risks of myocardial infarction and ischemic stroke, while the risk of haemorrhagic stroke rises 15-fold. In women suffering from hypertension, discontinuation of COCs may improve blood pressure control. Women, who had their blood pressure measured before COCs use, have 2–2.5-fold decreased risk of myocardial infarction and ischaemic stroke. In women with multiple cardiovascular risk factors the use of progestogen-only contraceptives (POCs) should be considered. POC therapy is associated with substantially less risk of cardiovascular events than COCs.

Abbreviations:

COCs	- combined oral contraceptives
VTE	- venous thromboembolism
EE	- ethinyl estradiol
WHO	- World Health Organization
BMI	- body mass index
POCs	- progestogen-only contraceptives
ACOG	- American Congress of Obstetricians and Gynaecologists

REVIEW ARTICLE

INTRODUCTION

Over 50 years of common use of hormonal oral contraceptives provided further information on their safety and adverse effects. Combined oral contraceptives (COCs) constitute the basic birth control method in 58% women in their 20s or 30s. COCs are preferred by 15% of women between 35 and 39 years of age and 5% of women over 45 years of age. Introduction of hormonal contraceptives requires adequate qualification with possible risk factors being considered. Since the first COC was introduced, the problem of cardiovascular adverse effects has been widely discussed.

Venous thromboembolism (VTE) includes deep vein thrombosis (DVT), pulmonary embolism and cerebral venous sinus thrombosis. The risk of VTE increases in women using COCs compared to the overall population. The highest risk is observed within the first year of COC use (OR: 4.17) and decreases as the therapy advances down to 2.98 in years 1–4 and to 2.76 after 4 years of COC use, maintaining the higher level compared to the overall population (Lidegaard *et al.* 2009). At present COCs containing ≤35 μg are believed to pose a lower risk of cardiovascular complications. Nevertheless, there are no definitive data that would enable evaluation of the influence of therapy with ≤20 μg ethinyl estradiol (EE). Lidegaard *et al.* noted 18% reduction of incidence of thrombotic complications in females receiving COCs containing 20 μg EE combined with desogestrel or gestoden compared to 30–40 μg EE (Lidegaard *et al.* 2009). Results of the EURAS trial demonstrated only statistically insignificant reduction of thromboembolic complications in females receiving 20 μg EE compared to 30 μg EE (Dinger *et al.* 2007). Studies carried out in Danish population did not reveal such correlation (Severinsen *et al.* 2010). The literature is also lacking long-term studies that would analyse COCs containing natural estrogen. It is believed that the overall risk of thromboembolic complications for this type of tablets should be considered comparable to other COC methods.

Introduction of new generation progestogens brought on a revolution in the use of COCs. Therefore, it was quite surprising to discover that the study results confirm 7.3- and 5.6-fold increase of thrombotic complication risk in females receiving COCs with desogestrel and gestoden, respectively (van Hylckama Vlieg *et al.* 2009). Whereas the risk related to norgestimate, which is metabolised to levonorgestrel is comparable to second generation progestogens (Jick *et al.* 2006). In case of levonorgestrel the risk is 3.6-fold higher than in the overall population. Other progestogens, such as drospirenone (fourth generation) are associated with 6.3-fold higher risk, whereas cyproterone is associated with 6.8-fold higher risk of VTE (van Hylckama Vlieg *et al.* 2009). In the meta-analysis of 13 trials third generation progestogens were found to involve 1.7-fold higher risk of thromboembolic incidents compared to the second generation (Kemmeren *et al.* 2001). Moreover, the risk increases in females who introduce hormonal contraceptives for the first time and decide to use advanced generation formulations.

The risk of VTE related to using COCs in females <30 years of age is estimated to 3.7/10,000 cases annually compared to 1.2/10,000 in subjects, who do not use this therapy. The risk increases considerably with age. In COCs users aged 30–40 the risk amounts to 10/10,000 and in the group of 40–50 years of age it is 13.3/10,000. In females aged 40–50, who do not use hormonal therapy, the values increase up to 2.3/10,000 (Heinemann L *et al.* 2007, RCOG 2010).

The trials also indicate that obese women with body mass index (BMI) ≥30 kg/m^2 who receive COCs may be exposed to increased risk of VTE. The risk of deep vein thrombosis is also 5 to 8-fold higher than in obese females, who do not use contraceptive pills and 10-fold higher than in women, who are not obese and do not use COCs. The World Health Organization (WHO) recommends prescribing COCs for obese women only, when the benefits outweigh the risk related to this method (WHO 2009). It is recommended that COCs may be used in women with BMI within the range of 30–34.9 kg/m^2, if the benefits outweigh the risk related to this method. In case of BMI ≥35 kg/m^2, the risk of COCs use may outweigh the benefits resulting from the therapy. In unclear clinical cases the progestogen-only contraceptives (POCs) may be used, regardless of females' weight (RCOG 2010).

According to WHO recommendations COCs should not be prescribed for women with active or resolved VTE as well as in stable clinical conditions regardless of anticoagulant therapy (WHO 2009). The American Congress of Obstetricians and Gynaecologists (ACOG) also do not recommend COCs in females with evidence of thromboembolism in history, whereas they allow COC treatment when combined with anticoagulant therapy (Kemmeren *et al.* 2001). The oral contraceptive pill should not be taken during major surgical procedures with expected long-term immobilisation and in women with diagnosed thrombogenic mutation (van Hylckama Vlieg *et al.* 2009). However, it is worth mentioning that the trait of thrombogenic mutation in young, heterozygous females with no thromboembolism in history is a relative contraindication for hormonal contraceptives. The combined contraceptive pill may be offered in case of short-lasting immobilisation during a major surgical procedure, superficial phlebitis as well as family history of VTE in first degree relatives, if the benefits outweigh the risks related to the therapy (WHO 2009). In some of the clinical cases mentioned above, POC may be a good alternative in females showing deep vein thrombosis risk factors in particular. The oral progestogen therapy was demonstrated to be associated with no thromboembolism risk or to pose a minor thromboembolism risk (Lidegaard *et al.* 2009; WHO 1998). The risk of deep vein thrombosis in women using POCs with the content of 30 μg

levonorgestrel or 350 μg norethisterone, is estimated to be slightly lower (OR: 0.59), and for 75 μg desogestrel slightly higher (OR: 1.10) than in the overall population (Lidegaard *et al.* 2009). The randomised trial to compare the effect of 75 μg desogestrel and 30 μg levonorgestrel did not indicate deviations of parameters in the coagulation system in either of the study arms (Winkler *et al.* 1998).

Low-dose hormonal contraceptives cause a 1.84 and 2.12-fold increase of the risk of myocardial infarction and ischemic stroke, respectively (Baillargeon *et al.* 2005). The risk of stroke increases with age (Straka & Trapezanlidis 2013). Approximately 13% of all the strokes in European females aged 20–44 are estimated to be related to COCs (WHO 1998). Contraceptives containing <50 μg EE increase the stroke risk in European females to a lesser extent (OR: 1.41) compared to high-dose formulations (OR: 2.71). The risk of cardiovascular incidents also depends on the type of progestogen. The incidence of ischemic strokes is the highest with the first generation progestogens (Heinemann *et al.* 1998). Second generation progestogens increase the risk of myocardial infarction (OR: 1.85) and ischemic stroke (OR: 2.54), and in case of the third generation only the incidence of ischemic stroke increases considerably (OR: 2.03) (Baillargeon *et al.* 2005). The risk of cardiovascular events does not correlate to the duration of the therapy and disappears, when the therapy is terminated (Baillargeon *et al.* 2005; Heinemann *et al.* 1998). Positive history of low-dose COCs decreases the risk of myocardial infarction as well as ischemic stroke; however, it does not influence the incidence of haemorrhagic stroke (Baillargeon *et al.* 2005; Schwartz *et al.* 1998; Sidney *et al.* 1998). In the group of COCs users aged ≤35 no increase in the risk of haemorrhagic stroke was demonstrated and in the group >35 years of age the risk rose 2-fold (WHO 1996). According to WHO recommendations lack of additional risk factors allows the use of COCs until the menopause. Moreover, the age >35 does not constitute a risk factor for progestogen therapy (WHO 2009).

In women reporting migraines the use of COCs causes a 2.08 and 2.15-fold increase in the incidence of ischemic and haemorrhagic stroke, respectively (Schwartz *et al.* 1998). Migraines with aura are associated with a higher stroke risk compared to migraines without aura. WHO does not recommend COCs in women suffering from migraines without aura, if they are ≥35 years old and women suffering from migraines with aura regardless of their age (WHO 2009). ACOG developed a similar recommendation, although they allow consideration of COCs, if the migraines are not accompanied by neurological focal symptoms and the patient does not smoke cigarettes, reports good general condition, and is <35 years old. In spite of the above, other birth control methods are recommended such as POCs, intrauterine device or mechanical contraceptives (ACOG 2006).

The use of COCs in cigarette smokers provokes a 10-fold increase of myocardial infarction incidence and 2–3-fold increase of stroke incidence (Webberley & Mann 2006). The results of the RATIO study indicate that the incidence of ischemic stroke in patients who are smokers and COCs users with additional risk factors is raised 4.4-fold (Kemmeren *et al.* 2002). In a Danish clinical-follow up trial a significant increase in the myocardial infarction incidence was observed in women using oral contraceptives and smoking cigarettes or having family history of myocardial infarction (Lidegaard *et al.* 2009). Mortality due to cardiovascular incidents in smokers of ≤15 cigarettes a day using COCs amounts to 1/16,000, whereas in non-smokers it is 4 times lower. On the other hand, the risk of death in females ≥30 and ≥45 smoking >25 cigarettes a day is 6-fold and 8-fold, respectively, higher than in non-smokers (Oliveira *et al.* 2007). Moreover, smokers with low, as well as, high risk of cardiovascular disorders have an identical, poor chance of smoking cessation (Zvolska *et al.* 2012). Among hormonal contraceptives for smokers over 40 years of age the POCs may be considered an alternative as there are no contraindications to use it in those cases (WHO 2009). The data indicate low risk of cardiovascular incidents (OR: 0.9) associated with this method of contraception.

COC-related cardiovascular risk in females with arterial hypertension is well established. COC use in this group of patients increases the incidence of myocardial infarction 2–3-fold, the incidence of ischemic stroke 3-fold, and the incidence of haemorrhagic stroke even 10–15-fold (Baillargeon *et al.* 2005; Heinemann *et al.* 1998; Webberley & Mann 2006). A blood pressure measurement before combined contraceptives are introduced causes a 2.5-fold decrease in the risk of ischemic stroke and 2-fold decrease in the risk of acute coronary syndrome but does not influence the incidence of haemorrhagic stroke (Heinemann *et al.* 1998; Lubianca *et al.* 2005). Before contraceptives are introduced in women with currently normal blood pressure values it is worth ruling out hypertension during past pregnancies. The studies indicate increased risk of myocardial infarction as well as VTE in women who had history of abnormal blood pressure values during past pregnancies and used COCs later on compared to COC users with a negative history of pregnancy-induced hypertension (WHO 2009). According to ACOG recommendations, combined contraceptives may be used in females with well-controlled hypertension, aged ≤35, non-smokers with no additional conditions or symptoms of vascular diseases (ACOG 2006). WHO recommendations treat COCs use in women with hypertension as a situation, where the risk outweighs the benefits resulting from this method. Although the amount of data is still insufficient, POCs may become an alternative for COCs (WHO 2009). The therapy in women suffering from arterial hypertension is associated with a low risk of cardiovascular events compared to a group of women

with hypertension, who did not use hormonal contraceptives (WHO 1998). Discontinuation of combined contraceptives in hypertension patients may improve the control of blood pressure (Lubianca *et al.* 2005).

Introduction of hormonal contraceptives in clinical practice does not require routine screening for lipid disorders. However, if the patient reports dyslipidaemia, the type and severity of it should be diagnosed as well as the occurrence of other risk factors should be assessed (WHO 2009). According to ACOG women with well-controlled lipid disorders may use COCS with estrogen component ≤35 μg. In case of poorly-controlled dyslipidaemias such as hyperlipidaemia, hypertriglyceridemia or concurrent several risk factors of ischemic heart disease, other birth control methods should be considered (ACOG 2006). In the cases mentioned above POC may be used, if the benefits outweigh the risks related to the treatment (WHO 2009).

Low-dose hormonal contraceptives influence the metabolism of carbohydrates to a minimum extent. Long-term surveillance studies did not demonstrate increased incidence of glucose intolerance and diabetes mellitus, regardless of the COC content (Rimm *et al.* 1992; Chasan-Taber *et al.* 1997). Among females with type 1 or type 2 diabetes it does not affect long-term glycaemic control, progression of diabetic retinopathy or daily insulin requirement (WHO 2009, Diab & Zaki 2000; Garg *et al.* 1994). COC use does not provoke changes either in the lipidogram or coagulogram (ACOG 2006; Diab, Zaki 2000; Petersen *et al.* 1995). Combined contraceptives do not increase the risk of retinopathy and neuropathy in young women with type 1 diabetes (Garg *et al.* 1994). No increase of mortality due to cardiovascular reasons was found. According to ACOG recommendations in diabetic patients COC should be limited to women <35, non-smokers with no vascular diseases (ACOG 2006).

History of pregnancy-induced diabetes increases the risk of glucose intolerance as well as diabetes mellitus in more advanced age. In women with history of pregnancy-induced diabetes no effect of low-dose COCs was found on changes in the carbohydrates metabolism and development of type 2 diabetes mellitus (WHO 2009; Kjos *et al.* 1998). Neither combined, nor single-compound contraceptives influence lipidogram in women with a history of pregnancy-induced diabetes (WHO 2009). COC is hence believed to be an adequate birth control method in this group of women. However, the results of studies investigating the influence of POC on the development of type 2 diabetes mellitus in women with a history of pregnancy-induced diabetes are inconsistent (WHO 2009).

The risk of cardiovascular events in women with numerous cardiovascular risk factors is well established. In a Dutch clinical follow-up trial the highest myocardial infarction risk was found in oral contraceptives users with a history of smoking, diabetes mellitus, and hypercholesterolemia. However, the MI risk was not affected by factor V Leiden mutation or prothrombin gene mutation (Dunn *et al.* 1999). Then, presence of antiphospholipid antibodies increases the risk of venous and arterial thromboembolic complications hence constitutes a contraindication for hormonal contraceptives. In women presenting numerous cardiovascular risk factors, aged >35 in particular, COCs are contraindicated (WHO 2009). In case of women with ischemic heart disease, congestive heart failure or other cerebrovascular conditions as well as with numerous cardiovascular risk factors ACOG and WHO recommend progestogen-only contraceptive, if hormonal contraceptives are required (WHO 2009; ACOG 2006). In clinical practice particular attention should be paid to the numerous group of patients with metabolic syndrome or polycystic ovary syndrome, who, apart from the increased cardiovascular risk, may require long-term use of contraceptives.

REFERENCES

1 ACOG (2006). Committee on Practice Bulletins-Gynecology. ACOG practice bulletin. No. 73: Use of hormonal contraception in women with coexisting medical conditions. Obstet Gynecol. **107**(6): 1453–1472.

2 Baillargeon JP, McClish DK, Essah PA, Nestler JE (2005). Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis. J Clin Endocrinol Metab. **90**(7): 3863–3870.

3 Chasan-Taber L, Colditz GA, Willett WC, Hunter DJ, Colditz GA, Spiegelman D et al (1997). A prospective study of oral contraceptives and NIDDM among U.S. women. Diabetes Care. **20**: 330–335.

4 Diab KM, Zaki MM (2000). Contraception in diabetic women: comparative metabolic study of norplant, depot medroxyprogesterone acetate, low dose oral contraceptive pill and CuT380A. J Obstet Gynaecol R. **26**: 17–26.

5 Dinger JC, Heinemann LA, Kühl-Habich D (2007). The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance study on Oral Contraceptives based on 142,475 women-years of observation. Contraception. **75**: 344–354.

6 Dunn N, Thorogood M, Faragher B, de Caestecker L, MacDonald TM, McCollum C, et al (1999). Oral contraceptives and myocardial infarction: results of the MICA case control study. BMJ. **318**: 1579–1583.

7 Garg SK, Chase HP, Marshall G, Hoops SL, Holmes DL, Jackson WE (1994). Oral contraceptives and renal and retinal complications in young women with insulin-dependent diabetes mellitus. JAMA. **271**: 1099–1102.

8 Heinemann LA, Dinger JC (2007). Range of published estimates of venous thromboembolism incidence in young women. Contraception. **75**: 328–336.

9 Heinemann LA, Lewis MA, Spitzer WO, Thorogood M, Guggenmoos-Holzmann I, Bruppacher R (1998). Thromboembolic stroke in young women. A European case-control study on oral contraceptives. Transnational research group on oral contraceptives and the health of young women. Contraception. **57**: 29–37.

10 Jick SS, Kaye JA, Russmann S, Jick H (2006). Risk of nonfatal venous thromboembolism in women using a contraceptive transdermal patch and oral contraceptives containing norgestimate and 35 mcg of ethinyl estradiol. Contraception. **73**: 223–228.

11 Kemmeren J, Algra A, Grobbee D (2001). Third generation oral contraceptives and risk of venous thrombosis: metaanalysis. BMJ. **323**: 131–134.

12 Kemmeren JM, Tanis BC, van den Bosch MA, Bollen EL, Helmerhorst FM, van der Graaf Y et al (2002). Risk of arterial thrombosis in relation to oral contraceptives (RATIO) study; oral contraceptives and the risk of ischemic stroke. Stroke. **33**: 1202–1208.
13 Kjos SL, Peters RK, Xiang A, Thomas D, Schaefer U, Buchanan TA (1998). Contraception and the risk of type 2 diabetes mellitus in Latina women with prior gestational diabetes mellitus. JAMA. **280**: 533–538.
14 Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C (2009). Hormonal contraception and risk of venous thromboembolism: national follow-up study. BMJ. 13;339:b2890. Available at: http://www.bmj.com/content/339/bmj.b2890.pdf%2Bhtml
15 Lubianca JN, Moreira LB, Gus M, Fuchs FD (2005). Stopping oral contraceptives: an effective blood pressure-lowering intervention in women with hypertension. Journal of Human Hypertension. **19**: 451–455.
16 Oliveira A, Barros H, Maciel M, Lopes C (2007). Tobacco smoking and acute myocardial infarction in young adults: a population-based case-control study. Prev Med. **44**: 311–316.
17 Petersen KR, Skouby SO, Jespersen J (1995). Balance of coagulation activity with fibrinolysis during use of oral contraceptives in women with insulin-dependent diabetes mellitus. Int J Fertil. **40**: 105–111.
18 RCOG (2010). Venous Thromboembolism and Hormonal Contraception. Green-top Guideline No. 40. July 2010. Available at: http://www.rcog.org.uk/files/rcog-corp/GTG40VenousThromboEmbolism0910.pdf
19 Rimm EB, Manson JE, Stampfer MJ, Colditz GA, Willett WC, Rosner B et al (1992). Oral contraceptive use and the risk of type 2 (non-insuline-dependent) diabetes mellitus in a large prospective study of women. Diabetologia. **35**: 967–972.
20 Schwartz SM, Petitti DB, Siscovick DS, Longstreth WT Jr, Sidney S, Raghunathan TE et al (1998). Stroke and use of low-dose oral contraceptives in young women: a pooled analysis of two US studies. Stroke. **29**(11): 2277–2284.
21 Severinsen MT, Kristensen SR, Overvad K, en C, Tjønneland A, Johnsen SP (2010). Venous thromboembolism discharge diagnoses in the Danish National Patient Registry should be used with caution. J Clin Epidemiol. **63**: 223–228.
22 Sidney S, Siscovick DS, Petitti DB, Schwartz SM, Quesenberry CP, Psaty BM et al (1998). Myocardial infarction and use of low-dose oral contraceptives: a pooled analysis of 2 US studies. Circulation. **98**(11): 1058–1063.
23 Straka M, Trapezanlidis M (2013). Periodontitis and stroke. Neuro Endocrinol Lett. **34**(3): 200–206.
24 van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJ, Rosendaal FR (2009). The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study. BMJ. **339**: b2921. Available at: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2726929/pdf/bmj.b2921.pdf
25 Webberley H, Mann M (2006). Oral contraception – updated. Curr Obstet Gynecol. **16**: 21–29.
26 Winkler UH, Howie H, Bühler K, Korver T, Geurts TB, Coelingh Bennink HJ (1998). Randomized controlled double-blind study of the effects on haemostasis of two progestogen only pills containing 75 microgram desogestrel or 30 microgrammes levonorgestrel. Contraception. **57**: 385–392.
27 WHO (2009). Medical eligibility criteria for contraceptive use. 4th ed. A WHO family planning cornerstone. Geneva: WHO; 2009. Available at http://www.who.int/reproductivehealth/publications/family_planning/9789241563888/en/index.html
28 WHO Collaborative Study of Cardiovascular Disease and Steroid hormone Contraception (1996). Haemorrhagic stroke, overall stroke risk, and combined oral contraceptives: results of an international, multicentre, case-control study. Lancet. **348**: 505–510.
29 WHO Collaborative Study of Cardiovascular Disease and Steroid Hormonal Contraception (1998). Cardiovascular disease and use of oral and injectable progestogen-only contraceptives and combined injectable contraception. Contraception. **57**: 315–324.
30 Zvolska K, Kralikova E, Kmetova A, Stepankova L, Blaha M, Sticha M, et al (2012). The role of a center for tobacco-dependent in cardiovascular prevention. A retrospective study. Neuro Endocrinol Lett. **33**(Suppl 2): 102–107.