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Hormonal contraceptives and arterial disease: An epidemiological update

Geneviève Plu-Bureau, MD, PhD, Professor of Gynecology [a,b,*], Justine Hugon-Rodin, MD, Clinical Gynecologist [a,b], Lorraine Maitrot-Mantelet, MD, Clinical Gynecologist [a,b], Marianne Canonico, PhD, Research Fellow [b,c]

[a] *Department of Gynecology and Endocrinology, Hôpital Universitaire Paris Centre, Paris-Descartes University, Paris, France*
[b] *Hormones and Cardiovascular Disease, CESP U1018, Inserm, Villejuif, France*
[c] *Paris Sud 11 University, UMRS 1018, Villejuif, France*

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The cardiovascular safety of widely used combined hormonal contraceptives is still debated. Newer generations of oral formulations as well as non-oral contraceptives (transdermal and vaginal) have been recently evaluated in the context of cardiovascular disease. This review provides a summary of the association between combined oral contraceptives (COCs) and arterial diseases, with an emphasis on new formulations of hormonal contraceptives, as well as routes of administration. A systematic search of the Medline database was performed to find all relevant articles which included women who had widely use third generation pills, and the development of new progestins. Eligible articles published in English and reporting risk of arterial events (myocardial infarction [MI] and stroke) among users of hormonal contraceptives were reviewed. A quantitative assessment was made from included studies. Overall, current use of oral combined contraceptives increased the risk of MI and ischemic stroke (pooled OR: 1.7; 95% confidence interval [95% CI]: 1.2–2.3 and OR: 1.8; 95% CI: 1.2–2.8, respectively), but this was not associated with the risk of hemorrhagic stroke (OR: 1.1; 95% CI: 0.7–1.9). The increase in ischemic arterial disease was higher among first generation pill users compared with second or third generation pill users. In contrast, risk of ischemic arterial disease among current users of second or

* Corresponding author. Department of Gynecology and Endocrinology, Port-Royal Hospital, 53 avenue de l'Observatoire, 75014 Paris, France.
E-mail address: genevieve.plu-bureau@cch.aphp.fr (G. Plu-Bureau).

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third generation pill was similar ($p = 0.23$ for MI risk and 0.99 for ischemic stroke). In conclusion, newer generation formulations of COCs, as well as the non-oral hormonal contraceptive, do not seem to be safer than second generation hormonal contraceptives.

Introduction

Arterial disease is an uncommon disease among women of childbearing age. The annual incidence of myocardial infarction (MI) is two per million among healthy women aged 30–34 year old, rising to 20 per million from the age of 40–44 years.[1] With respect to stroke, the annual incidence also increases with age (6 per million from age 20–24 years, 10 per million from age 30–34 years, and 16 per million from age 40–44 years).[1] Hormonal contraceptive use explains a substantial part of the arterial events among young women. Therefore, arterial disease is an important determinant of the benefit/risk profile of hormonal contraception.

Hormonal contraceptives delivered as either oral, transdermal or vaginal contraceptives are one of the most commonly prescribed birth control methods, used by several million women worldwide. In several countries, hormonal contraceptives have been used by approximately more than 80% of women at some point in their reproductive life.

Initially, COCs delivered a daily dose of at least 50 μg of ethinylestradiol or mestranol, and a progestin such as norethisterone acetate or norethindrone. Due to early reports showing that these drugs increase the risk of cardiovascular disease, formulations of COC have dramatically changed over the past 50 years. Modern COCs contain 35 to 15 μg of ethinylestradiol or estradiol combined with new progestins.[2] Subsequently developed newer generation progestins now have a stronger progestogenic activity and reduced androgenic effects, such as acne, hirsutism and deleterious lipid changes. Non-oral delivery methods represent a recent advancement in COC, including the contraceptive vaginal ring and the transdermal contraceptive patch.

Early epidemiological studies investigating high dose combined oral contraceptives showed a significantly increased risk of cardiovascular disease.[3–6] In recent years, new formulations of oral contraceptives and non-oral delivery methods have been evaluated in the context of cardiovascular risk. This article aims to review and to quantitatively assess the association between these new formulations and the risk of arterial thrombosis including myocardial infarction and stroke. We distinguish between COC and progestin only contraception (POC).

Combined hormonal contraceptives

Usually, COC classification includes estrogen dose or molecule, type of progestin and route of administration. While the first pills contained high doses of synthetic estrogen (150 μg of ethinylestradiol or mestranol), current COCs now deliver 50 to 15 μg per day of ethinylestradiol.[2] New formulations delivering natural estradiol (E2) have recently been marketed. A quadriphasic COC combining E2 valerate and dienogest has recently been approved in Europe and the USA, and a second monophasic COC that combines E2 with nomegestrol acetate, a progesterone-derived progestin, is now available in several European countries.[7–10] Nevertheless, there are no epidemiological data on the association of cardiovascular disease with these new pills.

COCs can also be classified into generations (first, second, third and other) depending upon the type of progestin and their introduction into market. The so-called first generation pills that contained either norethisterone acetate, lynestrenol, ethnodiol acetate or norethynodrel are currently no longer used. The presently available oral contraceptives are both second and third generation pills; second generation pills containing norgestrel or levonorgestrel, and third generation containing desogestrel, norgestimate or gestodene. Pills with other type of progestins are classified as other generation pills and contain either progesterone or testosterone-derived progestins including cyproterone acetate, drospirenone, dienogest, chlormadinone acetate or nomegestrol acetate. Drospirenone, an aldosterone antagonist, and cyproterone acetate are molecules presenting high anti-androgenic effects.