**ARTICLE**

# Potential impact of oral contraceptive choice on myocardial infarction mortality and deep vein thrombosis

Karin Martin, Yola Moride, Colleen Metge, Nicholas Moore, Bernard Bégaud

## Abstract

**Objectives** To summarise the epidemiological evidence on the relationship between second- (OC2) and third-generation (OC3) oral contraceptives (OC) and the mortality associated with deep vein thrombosis (DVT) and myocardial infarction (MI), and to extrapolate and balance the evidence for these risks to the population of French OC users.

**Methods** All studies published on the risk of MI during OC2 and OC3 use were analysed. For DVT the Committee for Proprietary Medicinal Products public assessment report published in 2001 and more recent studies published on this topic were used. The estimates of odds ratios (OR) for risk of death from DVT or MI were extracted from the published manuscripts. ORs were used to calculate the aetiological fraction of risk for death from DVT and MI in the population; the relative impact of OC3 compared to OC2 use was expressed as an excess risk of death overall and by age group for French women.

**Results** Compared with OC2, the use of OC3 would prevent a maximum of 24 deaths from MI per year and induce a maximum of 16 deaths. Conversely, OC3 would induce 282–940 excess cases of DVT per year, resulting in 28–94 pulmonary embolisms and 3–19 deaths in the 4.7 million French OC users.

**Conclusion** Balancing the evidence, it is difficult to conclude that the overall cardiovascular risk is significantly lower for either of the two OC schemes.

---

**Key message point**

- **There does not appear to be any overall difference in cardiovascular risk between second- and third-generation oral contraceptives.**

---

**Department of Pharmacology, Victor Segalen University, Bordeaux, France**
Karin Martin, PharmD, MPH, *Senior Registrar*
Nicholas Moore, MD, PhD, *Professor*
Bernard Bégaud, MD, PhD, *Professor*

**Faculty of Pharmacy, Montreal University, Quebec, Canada**
Yola Moride, PhD, FISPE, *Professor*

**Faculty of Pharmacy, Manitoba University, Winnipeg, Canada**
Colleen Metge, PharmD, PhD, *Associate Professor*

**Correspondence to:** Karin Martin, EA 3676, MP2S, IFR 99, Département de Pharmacologie, Université Victor Segalen – CHU, 146 rue Léo Saignat, 33076 Bordeaux cedex, France. Tel: (+33) 557 571 561. Fax: (+33) 557 574 660. E-mail: karin.martin@pharmaco.u-bordeaux2.fr

## Introduction

Physicians want their decision to prescribe an oral contraceptive (OC) to result in an effective prevention of pregnancy; that is, for the OC to do what it is intended to do with a limited amount of harm. However, balancing benefit with risk can be a challenging endeavour in the face of conflicting or diffuse evidence of harm. This is particularly true for the choice of prescribing either a second- or third-generation OC (OC2 or OC3).

There is a dearth of comparative evidence to help physicians balance the risks of death from deep vein thrombosis (DVT) and myocardial infarction (MI) with the benefits of oral contraception, especially on a population basis. However, there is now some evidence that tries to quantify these two effects, albeit separately. For example, based on a review of the main studies published at this time[1–19] (and an unpublished Wyeth-Ayerst Research Report, 1997), the Committee for Proprietary Medicinal Products (CPMP) expert report stated that, compared to OC2, OC3 were associated with an increased risk of DVT, the OC3/OC2 relative risk being said to be in the range of 1.5 to 2.[20] This is in agreement with the meta-analysis published the same year by Hennessy *et al*.[21] that concluded in a relative risk of 1.7 [95% confidence interval (CI) 1.3–2.1]. Conversely, the case-control study published in 2002 by Lidegaard *et al*.[22] found an odds ratio (OR) of 1.3 (95% CI 1.0–1.8).

The relative impact of OC2 and OC3 on the mortality associated with MI is also not clear. For Dunn *et al*.,[23] OC3 users could have a higher risk of MI (OR$_{OC3/OC2}$ = 1.8, 95% CI 0.66–4.83) while no difference was shown by the World Health Organization study[24] (OR$_{OC3/nonOC}$ = 1.0, 95%CI 0.1–7.0 and OR$_{OC2/nonOC}$ = 1.6, 95% CI 0.5–5.5). In contrast, Lewis *et al*.[25] (OR$_{OC3/OC2}$ = 0.28, 95% CI 0.09–0.86), Tanis *et al*.[26] (OR$_{OC3/OC2}$ = 0.52, 95% CI 0.23–1.18) and Lidegaard and Estrom[27] (OR$_{OC3/OC2}$ = 0.51, 95% CI 0.15–1.72) found a reduction in risk in OC3 users.

In the present study, we used the epidemiological evidence to summarise the potential impact of OC choice on women's DVT and MI mortality in the actual population of OC users of a European country, namely France.

## Methods

*DVT computing*
The studied population were women aged between 20 and 44 years. For both the OC3/OC2 relative risk of DVT and the baseline incidence of DVT in these age groups we used two sources: (1) the CPMP public assessment report published by the European Medicines Evaluation Agency in 2001[20] which reviewed the studies published on the subject until 2001[1–19] (and an unpublished Wyeth-Ayerst Research Report, 1997) and (2) the results of two studies published later on the same topic, namely a meta-analysis[21] and a case-control study[22] retrieved after a MEDLINE literature search[28] using the MeSH terms 'oral contraceptive' and 'deep venous thrombosis'. In a sensitivity analysis we considered the two extreme estimates of the relative risk mentioned in these sources, i.e. 1.3 and 2.

The baseline incidence of DVT in women not using OCs and aged 15–44 years is 5–10 per 100 000 woman-

37

## ARTICLE

years.[20,29] The incidence of DVT in women using OC2 was estimated to be about 20 per 100 000 woman-years.[20] It is currently stated[20,29] that about 10% of DVT lead to pulmonary embolism and 1–2% to death.

The number of excess fatal DVT associated with OC3 use was obtained by multiplying the overall risk of DVT in OC2 by the relative risk, OC3/OC2 (i.e. 1.3 or 2, according to the sources previously mentioned). The two values of the absolute risk (OC2 and OC3) were applied to the actual population of French OC users. Data on the number of users in France and in each age group were obtained from the COCON study.[30]

### MI computing

First, we conducted a MEDLINE literature search[28] using the MeSH terms 'oral contraceptive' and 'myocardial infarction', or 'cardiovascular disease'. This search was restricted to studies classified as case-control or cohort studies. We identified five studies that attempted to assess the risk of MI associated with the use of OC2 and OC3.[23–27] We applied the values of the OR published in these studies to the actual population of French OC users (categorised into 5-year age groups). First, the numbers of MI deaths for this population were extracted from the gender- and age-specific mortality rates for the French general population published yearly by the Institut National de la Santé et de la Recherche Médicale.[31] As regards DVT, data on the number of OC users in France and in each age group were obtained from the COCON study.[30] The proportion of fatal MIs that would be avoided or induced by the systematic use of OC3 by all OC users in each age group was obtained through the classical formula for the aetiological fraction of the risk in a population ($EFR_{pop}$):

$$EFR_{pop} = \frac{E_{pop} \times (OR-1)}{1+[E_{pop} \times (OR-1)]} \ ,$$

where $E_{pop}$ is the proportion of OC users among women of a given age group and OR is the estimate of the odds ratio obtained in each study. These ratios, which vary from 0.28[27] to 1.8[25], estimate the relative risk in OC3 users vs OC2 users. As the studies did not give a specific OR value for fatal MIs, we assumed that the relative risks found in the studies apply both to non-fatal and fatal MIs. In other words, no study has to date shown a difference in mortality between MI cases induced by OCs and by other causes.

The number of fatal MIs associated with OC use was obtained simply by multiplying in each age group the total number of MI deaths by the corresponding $EFR_{pop}$.

### Results

As mentioned above, the OC3/OC2 relative risk of DVT was between 1.5 and 2 for the CPMP expert group,[20] 1.7 (95% CI 1.3–2.1) for Hennessy et al.[21] and 1.3 (95% CI 1.0–1.8) for Lidegaard et al.[22]. These values lead to an estimate of 0.6–4 DVT cases per million woman-years of use. For the 4.7 million OC users in the French population, this corresponds to 282–940 excess cases of DVT per year, resulting in 28–94 pulmonary embolisms and 3–19 excess deaths.

Table 1 shows for each study the expected number of deaths from MI that would be associated with systematic OC3 vs OC2 use. On account of the wide variability in the published OR values (i.e. ranging from 0.28 to 1.80), the systematic use of OC3 would prevent a maximum of 24 deaths or induce a maximum of 16 deaths per year among the 4.7 million women aged 20–44 years currently using OCs in France (i.e. –2.32 or +1.55 per million and per year). The $EFR_{pop}$ varies from 0.24 to 0.43 according to age group.

Balancing the figures for DVT and MI deaths, the systematic use of OC3 would prevent 21 deaths per year or induce 35 cardiovascular excess deaths in this population (i.e. –2.03 or +3.39 per million and per year).

### Discussion

The comparative cardiovascular risks of OC2 and OC3 have been debated for a number of years; the publication of the first studies having resulted in the infamous 'pill scare' in Europe, mainly in the UK.[32] From public health and clinical practice points of view, the key issue is to assess the impact in real-life conditions of differences between OC2 and OC3 suggested by published studies.

The main contribution of the present study to this debate is the quantification, through deaths, of these differences by applying estimates of relative risks found in the above five studies to an actual population of OC users in a developed country.

The results were derived from observed clinical practice in one of these countries, namely France, and took into account the number of users and the data on mortality from MI, both adjusted for age groups. The presented model allows one to produce an estimate of the relative impact of a given strategy, even if an *ad hoc* study is not available for the considered country.

On account of the wide variability in the OR estimates found in the various studies published to date, and the differences in the study designs that were used, we ruled out the possibility of conducting a meta-analysis. We preferred to enter each study result separately in the modelling process. On account of the very low incidence of cardiovascular mortality in the age groups for which the prevalence of OC use is the highest, the population impact of the choice between OC2 and OC3 appears to be relatively small.

**Table 1** *Impact of the use of second- and third-generation oral contraceptives on myocardial infarction mortality in France*

| Parameter | OR$_{OC3/OC2}$ | Age group (years) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 20–24 | 25–29 | 30–34 | 35–39 | 40–44 | All ages |
| Women (general population) *(n)* | | 1 831 363 | 2 088 946 | 2 132 023 | 2 189 656 | 2 146 892 | 10 338 880 |
| MI in 1999 *(n)* | | 1 | 3 | 13 | 14 | 47 | 78 |
| OC use (%) | | 68.3 | 56.7 | 43.8 | 33.2 | 28 | – |
| Excess death difference | | | | | | | |
| Lidegaard and Eström (1996)[27] | 0.51 (0.15–1.72) | –0.5 | –1.17 | –3.55 | –2.72 | –7.47 | –15.16 |
| Lewis *et al*. (1997)[25] | 0.28 (0.09–0.86) | –0.97 | –2.07 | –5.99 | –4.4 | –11.87 | –23.92 |
| WHO (1997)[24] | 0.59 (0.09–3.75) | –0.39 | –0.9 | –2.85 | –2.2 | –6.09 | –11.83 |
| Dunn *et al*. (1999)[23] | 1.80 (0.66–4.83) | +0.35 | +0.93 | +3.37 | +2.9 | +8.6 | +15.53 |
| Tanis *et al*. (2001)[26] | 0.52 (0.23–1.18) | –0.49 | –1.11 | –3.46 | –2.65 | –7.3 | –14.27 |

The figures in parentheses given for OR$_{OC3/OC2}$ represent the 95% confidence interval.

MI, myocardial infarction; OC, oral contraceptive; OC2, second-generation OC; OC3, third-generation OC; OR, odds ratio; WHO, World Health Organization.

It could be argued that one of the parameters used for the computation of the number of MI deaths was the OC3/OC2 relative risks found in the five studies conducted in other European countries. The main and obvious reason was that no such study was available for France. Furthermore, even if one could argue that these risks could be in part country dependent, such an extrapolation of evidence is currently accepted for those regulatory decisions concerning both approval and drug safety. Moreover, our conclusions would not be altered dramatically even when considering a higher baseline risk of MI in some European countries because of its low incidence in these age groups of women.

When considering the size and the type of population concerned, i.e. healthy women, the question of the relative benefit/risk ratio between OC2 and OC3 is crucial both for prescription and regulatory decisions. The concerns about the impact of OC2 and OC3 on DVT and MI risks have induced intense controversies and marketing pressures.[32] The relevant answer should be expressed in terms of actual impacts and not of relative risks of statistical significance.

The low magnitude of the differences found in the present study are in agreement with figures derived from the meta-analysis by Spitzer *et al*.[33] in which it was found that the risk of MI was about two times lower (OR = 0.44) for OC3 compared to OC2. Applying this estimate to the population considered in the present study generates a figure of 18 prevented deaths, i.e. 1.74 per million inhabitants and per year.

Even if the present analysis did not consider other types of adverse reactions and risks possibly associated with OC use (e.g. breast cancer and liver tumours), it is difficult to conclude that the global cardiovascular risk is significantly lower for either of the two OC strategies.

*References*
1  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**: 1582–1588.
2  Jick H, Jick SS, Gurewich V, Myers MW, Vasilakis C. Risk of idiopathic cardiovascular death and nonfatal venous thromboembolism in women using oral contraceptives with differing progestagen components. *Lancet* 1995; **346**: 1589–1593.
3  Bloemenkamp KWM, Rosendaal FR, Helmerhorst FM, Buller 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**: 1593–1596.
4  Spitzer WO, Lewis MA, Heinemann LA, Thorogood M, MacRae KD. Third generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study. Transnational Research Group on Oral Contraceptives and the Health of Young Women. *BMJ* 1996; **312**: 83–88.
5  Lewis MA, Spitzer WO, Heinemann LA, MacRae KD, Bruppacher R, Thorogood M. Third generation oral contraceptives and risk of myocardial infarction: an international case-control study. Transnational Research Group on Oral Contraceptives and the Health of Young Women. *BMJ* 1996; **312**: 88–90.
6  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**: 83–88.
7  Farmer RD, Todd JC, Lewis MA, MacRae KD, Williams TJ. The risks of venous thromboembolic disease among German women using oral contraceptives: a database study. *Contraception* 1998; **57**: 67–70.
8  Lidegaard O, Edstrom B, Kreiner S. Oral contraceptives and venous thromboembolism. A case-control study. *Contraception* 1998; **57**: 291–301.
9  Bloemenkamp KW, Rosendaal FR, Buller HR, Helmerhorst FM, Colly LP, Vandenbroucke JP. Risk of venous thrombosis with use of current low-dose oral contraceptives is not explained by diagnostic suspicion and referral bias. *Arch Intern Med* 1999; **159**: 65–70.
10  Herings RM, Urquhart J, Leufkens HG. Venous thromboembolism among new users of different oral contraceptives. *Lancet* 1999; **354**: 127–128.
11  Parkin L, Skegg DC, Wilson M, Herbison GP, Paul C. Oral contraceptives and fatal pulmonary embolism. *Lancet* 2000; **355**: 2133–2134.
12  Jick H, Kaye JA, Vasilakis-Scaramozza C, Jick SS. Risk of venous thromboembolism among users of third generation oral contraceptives compared with users of oral contraceptives with levonorgestrel before and after 1995: cohort and case-control analysis. *BMJ* 2000; **321**: 1190–1195.
13  Suissa S, Blais L, Spitzer WO, Cusson J, Lewis M, Heinemann L. First-time use of newer oral contraceptives and the risk of venous thromboembolism. *Contraception* 1997; **56**: 141–146.
14  Suissa S, Spitzer WO, Rainville B, Cusson J, Lewis M, Heinemann L. Recurrent use of newer oral contraceptives and the risk of venous thromboembolism. *Hum Reprod* 2000; **15**: 817–821.
15  Farley TM, Meirik O, Marmot MG, Chang CL, Poulter NR. Oral contraceptives and risk of venous thromboembolism: impact of duration of use. *Contraception* 1998; **57**: 61–65.
16  Lewis MA, MacRae KD, Kuhl-Habichl D, Bruppacher R, Heinemann LA, Spitzer WO. The differential risk of oral contraceptives: the impact of full exposure history. *Hum Reprod* 1999; **14**: 1493–1499.
17  Todd J, Lawrenson R, Farmer RD, Williams TJ, Leydon GM. Venous thromboembolic disease and combined oral contraceptives: a re-analysis of the MediPlus database. *Hum Reprod* 1999; **14**: 1500–1505.
18  Farmer RD, Lawrenson RA, Todd JC, Williams TJ, MacRae KD, Tyrer F, *et al*. A comparison of the risks of venous thromboembolic disease in association with different combined oral contraceptives. *Br J Clin Pharmacol* 2000; **49**: 580–590.
19  Kemmeren JM, Algra A, Grobbee DE. Third generation oral contraceptives and risk of venous thrombosis: meta-analysis. *BMJ* 2001; **323**: 131–134.
20  European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, Public Assessment Report (EMEA/CPMP/2201/01/en/Final). Combined oral contraceptives and venous thromboembolism. 2001. http://www.emea.eu.int/pdfs/human/regaffairs/0220101en.pdf) [Accessed 3 February 2004].
21  Hennessy S, Berlin JA, Kinman JL, Margolis DJ, Marcus SM, Strom BL. Risk of venous thromboembolism from oral contraceptives containing gestodene and desogestrel versus levonorgestrel: a meta-analysis and formal sensitivity analysis. *Contraception* 2001; **64**: 125–133.
22  Lidegaard O, Edstöm B, Kreiner S. Oral contraceptives and venous thromboembolism: a five-year national case-control study. *Contraception* 2002; **65**: 187–196.
23  Dunn N, Thorogood M, Faragher B, de Caestecker L, MacDonald TM, McCollum C, *et al*. Oral contraceptives and myocardial infarction: results of the MICA case-control study. *BMJ* 1999; **318**: 1579–1583.
24  World Health Organization. Acute myocardial infarction combined oral contraceptives: results of an international multicentre case-control study. *Lancet* 1997; **349**: 1202–1209.
25  Lewis MA, Heinemann LA, Spitzer WO, MacRae KD, Bruppacher R. The use of oral contraceptives and occurrence of acute myocardial infarction in young women: results from the Transnational Study on Oral Contraceptives and the Health of Young Women. *Contraception* 1997; **56**: 129–140.
26  Tanis BC, van den Bosch MA, Kemmeren JM, Cats VM, Helmerhorst FM, Algra A, *et al*. Oral contraceptives and the risk of myocardial infarction. *N Engl J Med* 2001; **345**: 1787–1793.
27  Lidegaard O, Eström B. Oral contraceptives and acute myocardial infarction: a case-control study (Abstract). *Eur J Contracep Reprod Health Care* 1996; **1**: 74.
28  PubMed. National Library of Medicine. NCBI Databases. http://www.ncbi.nlm.nih.gov/pubmed [Accessed 23 August 2004].
29  Rosendaal FR. Venous thrombosis: a multicausal disease. *Lancet* 1999; **353**: 1167–1173.
30  Bajos N, Leridon H, Goulard H, Oustry P, Job-Spira N and the COCON Group. Contraception: from accessibility to efficiency. *Hum Reprod* 2003; **18**: 994–999.
31  Gender- and age-specific mortality rates for the French general population published yearly by the Institut National de la Santé et de la Recherche Médicale (INSERM). http://sc8.vesinet.inserm.fr:1080 [Accessed 23 August 2004].
32  Szarewski A, Mansour D. The 'pill scare': the responses of authorities, doctors and patients using oral contraceptives. *Hum Reprod Update* 1999; **5**: 627–632.
33  Spitzer WO, Faith JM, MacRae KD. Myocardial infarction and third generation oral contraceptives: aggregation of recent studies. *Hum Reprod* 2002; **17**: 2307–2314.x