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.
The incidence of DVT in women using OC2 was estimated to be about 20 per 100 000 woman-years. It is currently stated 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.

MI computing

First, we conducted a MEDLINE literature search 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. 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. As regards DVT, data on the number of OC users in France and in each age group were obtained from the COCON study. 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:

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

where $E_{\text{pop}}$ 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 0.227 to 1.825, 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 $E_{\text{pop}}$:

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>$\text{OR}_{\text{OC3/OC2}}$</th>
<th>Age group (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20–24</td>
<td>25–29</td>
</tr>
<tr>
<td>Women (general population) (n)</td>
<td>1 831 363</td>
<td>2 088 946</td>
</tr>
<tr>
<td>MI in 1999 (n)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>OC use (%)</td>
<td>68.3</td>
<td>56.7</td>
</tr>
<tr>
<td>Excess death difference</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

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

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. 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.
It could be argued that one of the parameters used for the computation of the number of MI deaths was the OC3/OC2 ratio. Therefore, the 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 the symmetry 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. 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. 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 1.74 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.

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References