

## EDITORIAL

## Third generation oral contraceptives and vascular risks

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Third generation oral contraceptives (OC), containing the progestins desogestrel and gestodene, were introduced in the 1980s in an attempt to lower the risk of cardiovascular side effects. However, the observation that desogestrel and gestodene in combined OC were related to a 50 to 100% greater risk of venous thromboembolism (VTE) suggested that the issue is more complex than originally thought.<sup>1–3</sup>

At the end of 2001, the Committee for Proprietary Medicinal Products (CPMP) of the European Agency for the Evaluation of Medicinal Products (EMA)<sup>4</sup> released a Public Assessment Report providing comparative evaluation of relative and absolute risk of VTE for third generation OC. Changes were also proposed for the Summaries of Product Characteristics (SPC), in particular for OC containing 20 µg or more of ethinylestradiol and desogestrel or gestodene, and a 'Dear Doctor' letter was sent by several National Regulatory Agencies. The summary message was that there was no urgency to modify the pattern of OC prescription for current OC users, but OC containing levonorgestrel (i.e. second generation OC) should be preferred to third generation ones when an OC is used by a woman for the first time. This procedure allowed the avoidance of a further 'pill scare' throughout Europe.

In terms of risk/benefit assessment, an open issue was however related to other vascular effects, and mainly to the risk of myocardial infarction or stroke. There are now five published studies considering the risk of acute myocardial infarction (AMI) in users of second and third generation OC. One of these<sup>5</sup> compared the AMI risk of current users of third versus second generation OC: the relative risk (RR) was about 0.7, but was based on only five cases reporting current use of second generation and two cases reporting current use of third generation OC, and the results were far from significant.

The main results of four other studies giving the RRs of users of second and third generation OC versus non-users

are given in *table 1*, together with the number of exposed cases. The first report<sup>6,7</sup> was of an international (Transnational) case-control study from 16 centers in Austria, France, Germany and the United Kingdom, including 182 cases and 635 controls. Of these, 28 were current users of second generation OC (RRs 3.0) and seven of third generation (RR=0.9). The second report was from the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception,<sup>8</sup> and included 368 cases and 941 controls recruited in 21 centers from Africa, Asia, Europe and Latin America. Of these, 13 were current users of second generation OC (RR 1.6) and 3 of third generation ones (RR=1.0). The third report was from the MICA study, including 448 incident cases of myocardial infarction and 1,728 controls from interviews and general practice records in England, Scotland and Wales.<sup>9</sup> Of these, 20 cases were current users of second generation OC (RR=1.1), and 20 of third generation OC (RR=2.0). The fourth study<sup>10</sup> was a national, population-based case-control study from the Netherlands, including 248 AMI cases and 925 controls. Fifty-nine of the cases were current users of second generation OC (RR=2.5), and 20 of third generation OC (RR=1.3).

Overall, in the four studies considered there were 120 cases of current users of second generation OC, and 50 of third generation OC. The pooled RR of AMI was 2.3 (95% confidence interval, CI, 1.8 to 2.8) for current users of second generation OC, and 1.5 (95% CI: 1.1–2.3) for current users of third generation OC. These pooled estimates, however, should be considered only indicative,<sup>11</sup> since the results of the four studies were significantly heterogeneous. This is not surprising, since the populations studied were different, as were the methods used and the allowances for possible confounding factors.

There are, in conclusion, limited data to compare the risk of AMI in current users of third versus second generation OC, but these suggest that the RR may be lower for third generation ones. This observation could be compatible with a more favourable lipid profile of third generation OC, which are associated with a slight increase in high density lipoprotein cholesterol.<sup>1,12,13</sup>

Given the small number of cases, and the heterogeneity of the results across studies and populations, any comparative assessment of absolute risk with reference to the excess risk of VTE and the potentially reduced risk of

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AMI in users of third generation OC remains open to further evaluation.

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**Table 1** Risk of acute myocardial infarction in studies considering second and third generation oral contraceptives

Study	Second generation		Third generation	
	RR	N	RR	N
Lewis et al., 1997 (Transnational) <sup>6,7</sup>	3.0	28	0.8	7
WHO, 1996 <sup>8</sup>	1.6	13	1.0	3
Dunn et al., 1999 (MICA) <sup>9</sup>	1.1	20	2.0	20
Tanis et al., 2001 <sup>10</sup>	2.5	59	1.3	20
Total (95% CI)	2.3 (1.8-2.8)	120	1.5 (1.1-2.3)	50

RR: Relative risk; N: Number of cases