Myocardial infarction and third generation oral contraceptives: aggregation of recent studies

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BACKGROUND: Arterial cardiovascular and cerebrovascular adverse events associated with oral contraceptives (OC) are a major concern to the clinician. This paper aggregates the findings of seven recent oral contraceptive studies on the risk of acute myocardial infarction (MI) among users of second (2gen) and third (3gen) generation OC. METHODS: Odds ratios (OR) from seven original studies published between 1996 and 2001 underwent meta-analysis. They had accrued 6464 subjects since 1996. In addition, estimates of 22 studies published from 1965 to 1966 were synthesized using medians and ranges as an historical point of reference. RESULTS: Four meta-analyses were performed for each of the relevant comparisons. The point estimates for 3gen versus 2gen OC ranged from 0.44 (0.24–0.80) to 0.62 (0.38–0.99). Compared with non-users, the aggregated OR for 3gen OC was 1.13 (0.66–1.92); for 2gen OC it was 2.18 (1.62–2.94). CONCLUSIONS: This overview of seven controlled observational studies confirms that 3gen OC do not convey harm in regard to MI compared with non-users of OC. The aggregate data and the continuing replication of findings allow interpretation of benefit compared with older combined OC.

Key words: case–control study/epidemiology/myocardial infarction/oral contraceptives

Introduction

The introduction of oral contraceptives (OC) in the 1960s was the beginning of a revolution in family planning (Pincus, 1965; Fuertes de la Haba et al., 1973). Almost 40 years later, >100 million women of childbearing age control fertility or family size with huge benefits to health and quality of life for the women themselves and their immediate families (Edwards and Cohen, 1999). As early as the 1960s, concerns about adverse effects were heard from the professions using the products (Jordan, 1961; Pincus, 1965), and ever since, reports about research on cardiovascular and cerebrovascular events have been published (Guillebaud, 1997). The cardiovascular and cerebrovascular outcomes are still the chief worries, especially for the women and the counselling clinicians. The hierarchy of concern is usually stroke, myocardial infarction (MI) and deep vein clots in the legs. Stroke is probably at the top because the survivors are visible long-term reminders of the few negative experiences with OC in any community. Case reports and observational studies have kept alive an index of suspicion about the relationship between OC and MI for many years (Boyce et al., 1963; Inman and Vessey, 1968; Mant et al., 1987; Stampfer et al., 1988; Sidney et al., 1996).

Initial research findings about associations of cardiovascular and cerebrovascular adverse events with the use of OC dealt with a generation of the earliest marketed products. The included doses of ethinyl estradiol (EE) >50 µm, often 75 or 100 µg, frequently designated today as the first generation (1gen) OC. The subsequent generations are defined by type of progestogen and not by dose of estrogen, i.e. both second (2gen) and third (3gen) have <50 µg. The generations according to progestins are defined as follows. 1gen OC: norethisterone, norethisteroneacetate, ethynodiolacetate, lynesterol; 2gen OC: norgestrel, levonorgestrel (LNG); 3gen OC: desogestrel, gestodene (norgestimate under debate because of the close relation with levonorgestrel).

The generations are also discernible by their progestogenic and androgenic activity: 2gen increases progestogen binding and 3gen reduces androgenic receptor binding compared with their predecessors. Third generation products all appeared on the market most recently; chronology has been important in taxonomy.

Recent controversies about the safety of oral contraceptives have dwelt upon venous cardiovascular side-effects (venous thromboembolism, VTE), which has the lowest morbidity and mortality (World Health Organization, 1995a,b; Edwards and Cohen, 1999). The initial interpretations were that the newest (3gen) OC on the market had higher risk of VTE than for users of the older (2gen), more established, OC. Later studies and analyses requested by the Committee on Proprietary Medicines and Products (CPMP) of the European Medicines’
Evaluation Agency (EMEA) in March of 1996, conducted or reported between 1996 and 1999 (Farmer et al., 1997, 1998, 1999; Suiissa et al., 1997; Lewis et al., 1999; Lidegaard et al., 1998; Todd et al., 1999; Suiissa et al., 2000), have offered objective opinions about the controversial data (Farmer et al., 1997; Benagiano and Primiero, 1999; Cohen and Edwards, 1999; International Federation of Fertility Societies, 1999).

Less attention has been paid to the safety record of newer OC products in respect to arterial events. The low incidence of stroke among users and the undetectable differences between users of 2gen and 3gen OC are important (Petitti et al., 1996; World Health Organization, 1996a,b; Schwartz et al., 1997; Heinemann et al., 1998; Lidegaard and Kreiner, 1998).

The aim of this paper is to aggregate and present the findings of recent research on the risk of 2gen and 3gen OC for acute MI. Because the absolute risk of this disorder among young women aged <45 years, and especially <25 years, is very low, the category of event appears much less frequently in the literature. Comparative recent studies, except the Transnational Case Control Study of Oral Contraceptives and Health (Lewis et al., 1996b, 1997a) all lack statistical power if analysed as stand-alone projects. Initially, we considered all investigations reported from 1996 to 1999 and meta-analysed the findings.

As an historical reference and baseline we derived medians of pertinent studies from 1965 to 1966. With delays in usual rigorous peer review, we have now been able to extend the coverage of the aggregating process to two major papers published during 2001. The main findings of this data aggregation are the pooled odds ratios (OR, relative risks) of the newer 3gen OC as determinants of MI. The referents are older 2gen OC or ‘no use’ of OC.

Materials and methods

To avoid missing any older or obscure published studies, computer-assisted Medline, Dervent, Embase, Biosis and DDBF searches were done. We reviewed original peer-reviewed papers from 1965 to December 2002. We required the reported research to be experimental trials or controlled epidemiological research that were discrete databases or investigators from one project to another. Conventional definitions, methods and analyses were criteria. Review articles were studied but not aggregated; their references assisted us to find suitable papers. Only articles in English or French were assessed. Twenty-two pre-1996 articles and seven published after January 1996 having methods with comparison of exposed subjects and unexposed controls provided the original data and were synthesized in this article.

Before 1996, we found one single randomized controlled trial (Fuertes de la Haba et al., 1973). All other studies included were observational and controlled. Given the appreciable differences in the methods, definitions and approach to analysis of pre-1996 reports over three decades, we have only derived medians within category, when feasible, as well as the range of the values estimated. Aggregation prior to 1996 was not a meta-analysis in this paper. Formal comparisons of findings before and after 1996 were not part of the objective. For the case–control studies between January 1996 and December 2001, we used the meta-analytic method that Petitti has adapted from others (Greenland, 1987; Greenland and Longnecker, 1992; Petitti, 2000). Her quantitative methods, now in a second edition, have become mainstream when synthesising observational studies (Petitti, 2000). The aggregation of the data as a meta-analysis is justified because we only include case–control studies. The main pooled OR is presented four times, including and excluding one study (MIC, myocardial infarction and oral contraceptives) and then including and excluding Dunn 2001 and finally including and excluding the Danish study (Lidegaard and Kreiner, 1998). We reiterate that the reader can choose the combination of studies he/she deems most appropriate.

Results

Early studies (1965–1995)

Randomized controlled trial

Fuertes de la Haba gave the initial evidence of the efficacy of OC in the landmark controlled experimental trial among Puerto Rican women in the 1960s (Fuertes de la Haba et al., 1970). He was also among the first to consider the safety of OC. He found two users and one non-user who had experienced an MI (Fuertes de la Haba et al., 1970). The risk ratio derived was 2.9 [not significant (NS)] based on very few women-years (WY) of observation (29,508 WY).

Cohort studies, relative risks

The cohort project of The Royal College of General Practitioners (UK) published several relative risks (current users versus non-users) for MI and for non-rheumatic diseases of the heart (Beral, 1977; Royal College of General Practitioners, 1977, 1981, 1983; Kay, 1982). They represent a useful benchmark. We cite four statistically significant risk ratios: 5.2 (in 1974) (Royal College of General Practitioners, 1974); 3.2 (in 1977) (Royal College of General Practitioners, 1977); 6.4 (1982) (Kay, 1982); and 2.0 (1983) (Royal College of General Practitioners, 1983). Vessey, comparing ever users to non-users in the Oxford Family Planning Study (1968–1980), reported 4.7 (NS) for fatal MI (Vessey et al., 1977). In the USA, Ramcharan’s reported risk ratio for non-fatal MI was 1.1 (NS) from the Walnut Creek Study (1968–1977) (Ramcharan et al., 1981). The median point estimate for relative risks derived from early cohort projects was 3.2 (Figure 1).

Case–control studies, OR

The studies compare current users or ever users of OC with non-users or never users between 1968 and 1991 (Inman and Vessey, 1968; Mann and Inman, 1975; Mann et al., 1976; Krueger et al., 1980; Adam et al., 1981; Thorogood et al., 1991). For fatal MI the range of six OR (risk ratios) was from 0.96 to 4.2 and the median was 2.1. The risk ratio of OC for non-fatal MI was summarized in nine studies with 13 sets of findings (Vessey and Doll, 1968, 1969; Mann et al., 1975a,b; Stolley et al., 1975; Arthes and Masi, 1976; Rosenberg et al., 1976, 1980; Jick et al., 1978a,b; Maguire et al., 1979; Shapiro et al., 1979; Slone et al., 1981). The median was 1.8 and the range was 0.0 to 15.0 (Figure 1).

Cohort studies, absolute risks

Absolute risks reported in the cohort studies were as follows for the Oxford, RCGP and Walnut Creek cohort studies: among never users, considering both fatal and non-fatal events, the range was 1.4 to 23 MI per 100,000 women years (WY) (Beral, 1977; Vessey et al., 1977, 1981; Ramcharan et al.,
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Summary estimates of relative risks & odds ratios 1966 - 2001

<table>
<thead>
<tr>
<th>Relative risks or odds ratios</th>
<th>Pre (1966 - 1995)</th>
<th>7 case control studies</th>
<th>Pooled ORs of 7 studies</th>
<th>Odds ratios Post (1996 - 2001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All MI cases</td>
<td>2.3 (1.1, 4.4)</td>
<td></td>
<td></td>
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<tr>
<td>Fatal MI cases</td>
<td>3.2 (1.4, 7.1)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Non-Fatal MI cases</td>
<td>1.8 (0.8, 3.9)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3rd Gen versus no-use</td>
<td>1.11</td>
<td>1.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Gen versus no-use</td>
<td>1.29</td>
<td>2.18</td>
<td></td>
<td></td>
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<tr>
<td>3rd Gen versus 2nd Gen</td>
<td></td>
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Figure 1. Summary estimates of relative risks and odds ratios (OR), 1966–2001. RR = relative risk; MI = myocardial infarction.

The median was 1.5 MI per 100,000 WY. In users, the values ranged from 7.5 to 30 per 100,000 WY and the median was 13.0 per 100,000 WY. The range for absolute attributable risks can also be derived from Realini and Goldzieher’s large review. It was from 4.0 to 15 per 100,000 WY; the median was 5.7 (Realini and Goldzieher, 1985).

Summarizing cohort and case–control studies, for any OC on the market, when the early studies were combined, the overall relative risk hovered around 2.0. It was 3.0 when comparing current users or ever users against non-users or never users. There appears to be no material difference in rates between fatal and non-fatal MI. None of the early studies compared categories of combined OC or individual drugs classified by progestin content head-to-head against one another. There was an appreciable difference in the absolute rates of MI comparing users of any OC and non-users (Figure 2).

Recent studies (1996–2001)

There were seven original case–control studies on this topic published from January 1, 1996 and December 31, 2001 which contribute data suitable for aggregation (Table I).

The Boston Collaborative Drug Safety Programme study

Jick et al. analysed data from 303,470 women exposed to selected OC between January 1991 and October 1994 with data recorded in the General Practice Research Database (GPRD) (Jick et al., 1995, 1996). Eleven women were identified with a diagnosis of MI (n = 10) or sudden death (n = 1). The absolute incidence of MI among women using OC was 1.8 per 100,000 WY. The brand-specific analyses demonstrate lower but non-significant OR for MI when comparing 3gen with 2gen OC: desogestrel versus LNG, 0.7 (NS); gestodene versus LNG, 0.6 (NS), combined by us from data published [mean: 0.65; 95% confidence interval (CI): 0.05–4.97].

The Danish case–control study

In an ongoing Danish case–control study (Lidegaard and Kreiner, 1998) with three cardiovascular outcomes, an analysis with data useable in a meta-analysis was published as an abstract in 1996 (Lidegaard and Edstrom, 1996). For 88 cases
of MI (1994–1995) and 1045 controls compared with non-use, the adjusted OR were 4.1 (1.55–10.9) for first generation OC and 1.9 (0.7–4.9) for 2gen OC, and for 3gen OC users the OR was 1.9 (0.4–9.2) in the first year, 0.5 (0.1–3.9) in years 1–5 and 0.8 (0.2–2.7) for use >5 years. Based on these point estimates and CI we calculated an overall OR of 0.51 (0.15–1.72) for 3gen OC users compared with 2gen OC use (Table I). There was another follow-on abstract published after March 2001 and we found no subsequent full paper. Thus we also show aggregate estimates of the recent studies excluding the Danish work for that reason (Table I, Figure 1).

The World Health Organization study

Overall, 21 centres in this study recruited 368 cases of MI and 941 controls matched by age within 5 year bands (World Health Organization, 1997). We refer only to the European findings here. There had been 198 cases accrued in Europe and 480 controls. In a scientific meeting at Geneva, three cases and five controls exposed to 3gen OC and 24 cases and 22 controls to levonorgestrel (LNG) were reported. The resulting unpublished crude OR for MI in users of 3gen OC versus 2gen OC is 0.55 (NS). Eventually, having eliminated the Hungarian centre, the data for the UK and Germany (World Health Organization, 1997) reduced the cases on LNG to 13 cases and 17 controls with an OR of 0.59 (0.09–3.75) for 3gen combined OC versus 2gen LNG.

The Transnational study on oral contraceptives and the health of young women

The Transnational study had 182 cases of MI and 635 matched controls within 5 year age bands (Spitzer et al., 1993; Lewis et al., 1996a,b, 1997a). The OR for MI in 1gen, 2gen and 3gen OC compared with non-use were 4.7 (1.52–14.3), 2.99 (1.51–5.91), and 0.85 (0.30–2.39). The OR (3gen versus 2gen) was <1.0 and statistically significant: 0.24 (0.07–0.78).

The MICA study

The MICA study (myocardial infarction and oral contraceptives, a retrospective case–control study in England and Scotland) (Dunn et al., 1997, 1999) was conducted mostly after October 1995 and was vulnerable to the publicity bias generated by the British pill scare. The eligible MI events had occurred mostly before October 1995; the interviews on cases and controls were all done after that date. It is noteworthy that the study showed large differences between the findings of interview data and those based on the data of general practitioners who had written records on the study subjects. The difference almost certainly reflects the publicity bias. Another indication of systematic error is the considerable excess of healthy controls that were observed to be users of levonorgestrel-containing OC when compared with readily available data from UK prescription databases. It is a concern that four separate sequential analyses with pronounced fluctuations of OR had been performed prior to submission of the research report for publication, raising doubts about the validity and appropriateness of the final findings based on acceptable criteria for a suitable analysis plan. The MICA findings proved to be the outliers.

The Dunn mortality study in Great Britain

The study (Dunn et al., 2001) evaluated issues similar to those of MICA and followed it on with a second case–control study.

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### Table I. Meta-analysed odds ratios (OR) of the seven most recent case control studies of oral contraceptives (OC) and myocardial infarction (1996–2001)

<table>
<thead>
<tr>
<th>Study and year</th>
<th>Subjects in study</th>
<th>Adjusted odds ratio (95% confidence interval)</th>
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<tr>
<td></td>
<td></td>
<td>3gen versus non-use OC</td>
</tr>
<tr>
<td>GPRD, 1996</td>
<td>55</td>
<td>NR</td>
</tr>
<tr>
<td>(Jick et al., 1996)</td>
<td></td>
<td>(estimated(^c))</td>
</tr>
<tr>
<td>Danish, 1996</td>
<td>1133</td>
<td>0.96 (0.4–2.29)</td>
</tr>
<tr>
<td>(Lidegaard et al., 1998)</td>
<td></td>
<td>(estimated(^e))</td>
</tr>
<tr>
<td>WHO, 1997 (World Health Organization, 1997)</td>
<td>678</td>
<td>0.97 (0.14–6.96)</td>
</tr>
<tr>
<td>Transnational, 1997</td>
<td>817</td>
<td>0.85 (0.30–2.39)</td>
</tr>
<tr>
<td>(Lewis et al., 1997b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MICA, 1999</td>
<td>2176</td>
<td>1.96 (0.87–4.39)</td>
</tr>
<tr>
<td>(Dunn et al., 1999)</td>
<td></td>
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<tr>
<td>Dunn, 2000(^d)</td>
<td>432</td>
<td>0.83 (0.25–2.81)</td>
</tr>
<tr>
<td>(Dunn et al., 2001)</td>
<td></td>
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<tr>
<td>Leiden, 2001</td>
<td>1173</td>
<td>1.3 (0.7–2.5)</td>
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<td>(Tanis et al., 2001)</td>
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Factors for which adjustments were made all similar. Refer to original publications.

Total subjects in studies = 6464. The number of subjects in the four studies most suitable for meta-analysis [General Practice Research Database (GPRD), WHO, Transnational study and Tanis] was 2753.

\(^a\)Limited to levonorgestrel (LNG).

\(^b\)A summary OR and confidence interval calculated for separate OR desogestrel versus LNG (0.7) and gestodene versus LNG (0.6).

\(^c\)Calculation of estimates from data in published paper.

\(^d\)Deceased cases only.

\(^e\)Subset of 2176 in previous row: not duplicated with MICA, 1999.

3gen = third generation; 2gen = second generation; NR = not reported.
However, cases were limited to fatalities and the controls were survivors. An important bias seen in the earlier morbidity study was corrected in that clinical notes from the doctors’ surgeries were used to determine exposure to the risk factor. There was incompatibility of definitions in the choice of cases and controls when comparing with the other six studies. Despite its improved design, its care in minimizing bias and its adequate size (432 subjects), the study was both included and excluded in the aggregated analyses we did (Figure 1). Exclusion was primarily justified by the unconventional choice of controls (‘survivors’ as distinct from ‘unaffected’). The reader can judge which of the pooled values is best.

The Tanis oral contraceptive and risk of MI study
A large case–control study was conducted in The Netherlands coordinated from Leiden (Tanis et al., 2001). There were 248 cases with a first MI and 925 controls in an unmatched design. The adjusted OR for 2gen OC versus no use was 2.5 (1.5–4.1); for 3gen OC versus no use it was 1.3 (0.7–2.5). From data in the paper we estimated an OR of 0.52 (0.23–1.2) for 3gen OC versus 2gen OC. We did not find any important biases of methods or field work in the published paper. The OR for ‘any OC’ versus no use was 2.0 (1.5–2.8). Despite the large size of the study with 1173 subjects the authors report it as inconclusive.

Aggregating the seven recent studies
We conducted a meta-analysis of seven case–control studies published since January 1, 1996 (Jick et al., 1996; Lewis et al., 1997b; World Health Organization, 1997; Lidegaard et al., 1998; Dunn et al., 1999; Tanis et al., 2001). A summary of pertinent findings from those seven case–control– matched studies is in Table I. The outcome is MI. The key finding is the OR (relative risk) contrasting 3gen and 2gen OC with levonorgestrel only (LNG) as well as 3gen OC versus no use. We included MICA in two meta-analyses of the data and excluded it from two others. We included and excluded the Dunn 2001 study. The Danish study was also excluded from two aggregations. The reader can choose which resulting estimate he/she deems best (Figure 1). The seven studies published from 1996 to 2001 included 6464 subjects (Table I). The four studies we aggregated that seem to us to be least affected by bias, design or field problems are WHO, GPRD, Transanalostudy and Leiden (Tanis et al., 2001). They accrued 2723 patients. We propose that the best estimates of an OR of 3gen versus 2gen OC are 0.44 (0.24–0.89) with four studies and 0.62 (0.38–0.99) with all seven studies (Figure 1).

Absolute rates of MI in recent publications were only reported in the WHO study (World Health Organization, 1997), the GPRD study (Jick et al., 1996), and the Danish study (Lidegaard and Edstrom, 1996). Both the WHO and the Jick studies report 1.8 events of MI per 100 000 WY. The Danish study reports 4.8 MI per 100 000 WY among users of 2gen OC products and 0.6 per 100 000 WY among users of 3gen OC products. A formal aggregation is not appropriate but a cautious and conservative estimate is 1.3 events per 100 000 WY (Figure 2) combining users and non-users.

Discussion
The data in this paper corroborate that all oral contraceptives currently on the market, formally studied in the 1990s as risk factors for MI, are safe when used according to the regulatory label. The rates of occurrence of MI among users of OC in reports since 1995 are low, unequivocally lower than those reported earlier between 1966 and 1995 (Figure 2). In the early studies published before 1996, a median risk ratio just above 2.0 for any OC then on the market for MI was observed compared with no use. In the more recent studies, we observed pooled risks of 1.13 for all seven studies and 1.11 for the four that excluded the Danish, MICA and Dunn 2001 studies comparing 3gen OC with no use. For 2gen OC we determined pooled OR of 2.18 (seven studies) and 2.54 (four studies) versus no use since 1996. The range of four aggregated pools of 3gen versus 2gen OR, when the reference is 2gen OR, is narrow: 0.43 < 0.44 < 0.45 < 0.62 (all P < 0.05). The profile is robust. The choice of any single summary is reasonable. Both 0.44 and 0.62 are consistent with ‘no harm’ and/or ‘benefit’.

The aetiology of OC-associated MI has been the subject of lengthy debate. Endothelial damage does not seem to be a prerequisite for formation of a venous thrombus (Thomas et al., 1985). In contrast, haemodynamic considerations alone make it unlikely that an arterial thrombus will accumulate on an entirely intact endothelium. An imbalance in the normal cycle of arterial endothelial damage and repair, or the endothelial and intimal lesions seen in OC users, could result in platelet adhesion and activation and thrombus accumulation in an apparently normal artery. Either way this process will be opposed by circulating factors which promote endothelial integrity and will be furthered by those factors which disrupt endothelial function. There are three major candidates for involvement in these processes: serum triglycerides, insulin and high density lipoprotein (HDL) (Godsland et al., 1995).

Publications from 1982 onwards show consistently that OC containing 3gen progestogens improve the HDL-cholesterol to total cholesterol ratio (Bergink et al., 1982, 1983, 1984; Pentilla et al., 1983). The progestogen component of OC had been identified as an important risk factor for arterial disease. Bergink wrote, ‘in view of the available epidemiological evidence a low ratio of HDL-cholesterol to total cholesterol should be avoided and an important consideration in the choice of an oral contraceptive is the anticipated directional change in serum lipoprotein composition’ (Bergink et al., 1982). Bergink’s concern that low HDL-cholesterol ratios be avoided has been corroborated in a recent report (Brown et al., 2001). They linked regression of coronary artery disease to selected drugs and exercise. The empirical data from Brown’s major paper justify theoretical postulates about a favourable effect of OC on HDL to a considerable extent. It had already been noted (Solyom, 1972) that androgens are known to lower HDL-cholesterol. Following the discovery of the difference of intrinsic androgenticity between desogestrel and levonorgestrel as typical representatives of 3gen and 2gen progestagens (Bergink et al., 1981) it was the intention to develop OC with a favourable lipid profile which would be positive risk factors for arterial disease. What has been achieved for arterial disease,
as demonstrated by recent epidemiological research, is not only true with respect to MI but also stroke, as indicated in the introduction of this paper (World Health Organization, 1996a). Attainment of equivalence between the risks of exposure to 3gen OC and non-use of any OC product in respect to MI allowed goals of laboratory investigators involved in the development of newer and safer preparations for many years to be realized (Petitti et al., 1996; Schwartz et al., 1997).

The later MICA Study (Dunn et al., 1997, 1999), which followed our Transnational protocol closely and which accrued 2176 subjects, failed to attain statistical significance. It is encouraging that other investigative groups have tested the same question. None of six studies (Jick et al., 1996; Lidgaard and Edstrom, 1996; Lewis et al., 1997b; World Health Organization, 1997; Lidgaard et al., 1998; Dunn et al., 1999, 2001; Tanis et al., 2001) attained significant estimates of risks for MI in comparisons of risks other than the Transnational study (Table 1).

We do not conduct meta-analyses or syntheses to test hypotheses. We only do such overviews to corroborate findings or to generate hypotheses, especially when aggregating observational epidemiological studies. Petitti’s adaptation of Greenland and Longnecker’s method was found to be particularly appropriate for this analytic synthesis (Petitti, 2000). The pooled OR from all studies since 1995 is 0.62 (0.38–0.99). For the four most rigorous studies it is 0.44 (0.24–0.80). The MICA study alone corroborates the Transnational Study. MICA was conducted exclusively in the UK and the Transnational findings for the UK were very similar. Clearly, at worst, the findings show no difference between 3gen and 2gen OC and the absolute risks are all very low. It has now been repeatedly demonstrated that 3gen OC do not add risk for MI compared with non-use. Moreover, interpreting moderate benefit is consistent with the findings of six of the seven studies. This was a goal of the basic scientists who developed the product.

The findings with respect to checking blood levels when counselling about OC and the impact on MI are also clinically important to the doctor and the woman counselled.

The greater danger of smoking as a risk factor for arterial diseases becomes clear in the studies where the lifestyle was assessed. As Tanis has emphasized, it cannot be ignored (Tanis et al., 2001).

What are the implications for clinicians? (i) Since OC have become the mainstay of prevention of pregnancy the secular trends of the pill as a risk factor for MI, beginning in the 1960s, have demonstrated increasing safety. This applies to all OC on the market (except 1gen OC) and applies to 3gen OC preparations in particular. Nevertheless, none of the data presented here, nor our conclusions in this discussion, should be interpreted as recommendations against 2gen OC or as strong recommendations favouring 3gen OC in any clinical context as policy. The choice of an approved OC should always be that of the counselling physician, based primarily on clinical judgement of one patient at a time. The 3gen OC preparations are clearly safe in respect to MI compared with non-use. The Transnational results and the corroborating meta-analyses of epidemiological studies now demonstrate benefit in comparison with 2gen OC. Only the British MICA study shows no difference. The subset(s) of older women, of women with a family history of MI or of an unfavourable profile of cardiovascular risk factors should be candidates for 3gen OC as first line reversible prevention of pregnancy. (ii) Smoking, adjusted or not for OC use, is a very strong risk factor for MI. If a woman cannot or will not cease smoking and insists on oral contraception, the data favour 3gen OC (Lewis et al., 1996b). (iii) Women with elevated blood pressure should be prescribed OC only with great caution and after it has been brought down. That is true for both 2gen and 3gen OC products. The evidence shows that measuring the blood pressure when administering OC favours the woman counselled (Lewis et al., 1996b).

With respect to arterial adverse events in relation to 3gen OC, the recent literature offers grounds for reassurance, especially in regard to acute MI. That is true whether the interpretation is either benefit or no difference. The aggregated findings presented here suggest that it would be imprudent to curtail the armamentarium of OC for first-line use.

References


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