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Progestogen-Only Contraceptives and the Risk of Acute Myocardial Infarction: A Meta-Analysis

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Context: The association between combined oral contraceptives (OC) and the risk of myocardial infarction (MI) has been intensively studied, and conclusions are controversial. While progestogen-only contraceptives (POC) are commonly used worldwide, their impact on cardiovascular diseases is poorly investigated and remains unclear.

Objective: We carried out a meta-analysis based on EMBASE- and MEDLINE-referenced literature corresponding to OC marketed since 1960.

Methods: Eligible articles published in English language describing OC or POC use and MI outcome were reviewed, and relevant ones were extracted. All types of POC and route of administration were considered.

Results: Six case-control studies were identified. The combined odds ratio showed no increase in the MI risk with POC use (odds ratio = 1.07; 95% confidence interval, 0.62–1.84). This result was similar according to the route of administration, including implant, injectable, and oral POC.

Conclusion: Data from observational studies suggest no increase in risk of MI with POC use. However, these results are based on limited data. Further investigations are needed, especially among women at high MI risk. **(*J Clin Endocrinol Metab* 96: 0000–0000, 2011)**

Myocardial infarction (MI) is an uncommon disease among childbearing-aged women. Its annual incidence is two per million among healthy women aged 30 to 34 yr old and rises to 20 per million between 40 to 44 yr (1). Over the past decades, many studies have debated the matter of combined oral contraceptives (OC) and the risk of cardiovascular disease. While some of them failed to show an association between OC use and MI risk (2–5), others found an increased incidence of coronary events among OC users (6–10). In addition, two meta-analyses of the literature concluded that there was a higher MI risk among women using OC (11, 12) compared with nonusers. Regarding the interaction with environmental and demographical factors, MI risk among OC users is increased by smoking, especially for women over 35 yr old (8).

Although the original development of OC focused on progestogen-only products, progestogen-only contraceptives (POC) were introduced in family planning later than combined OC (13). The number of POC users is estimated to more than 20 million people worldwide (14), and using progestogen-only products as a contraceptive method may be an attractive option for women with or without cardiovascular risk factors. Nevertheless, the occurrence of MI related to POC has rarely been studied so far, because of the low event rate among childbearing age women as well as the lack of statistical power to assess the risk.

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Abbreviations: CI, Confidence interval; CRP, C-reactive protein; DMPA, depot medroxyprogesterone acetate; HDL, high-density lipoprotein; MI, myocardial infarction; OC, oral contraceptive; POC, progestogen-only contraceptive; OR, odds ratio; WHO, World Health Organization.

Based on these observations, we conducted a meta-analysis of epidemiological studies to examine the relationship between POC use and risk of MI.

Materials and Methods

Selection of studies

We reviewed the literature published since the early sixties after the introduction of OC. Potentially eligible articles were identified from MEDLINE and EMBASE using the following heading terms: "*myocardial infarction*," "*cardiovascular disease*," "*progestogen-only pill*," "*minipill*," "*progestin*," "*coronary event*," "*Provera*," and "*contraceptives*." We only retrieved studies published in English. They were all screened based on their abstract. We also identified original articles by back references from general reviews. We excluded publications which were not related to the topic, on postmenopausal hormone therapy, and biological studies. The selected articles were reviewed, and we excluded general reviews and articles that did not address MI risk.

Data extraction

All relevant articles were consensually selected by the two investigators (Z.C. and G.P.-B.). We assessed the quality of studies using a specific checklist, and we only included studies that fully completed theses inclusion criteria (15). To be included, cohort or case-control studies had to be controlled at least for age. Nonfatal cases of MI were identified based on chest pain and changes in electrocardiogram and/or cardiac enzyme elevation. Fatal MI cases based on these criteria were also accepted if patients underwent a necropsy that confirmed the diagnosis. Regarding hormone exposure, OC users and nonusers (former and/or never) were clearly defined. We considered all type of POCs and delivery devices (oral, implant, or injectable). Sufficient data ought to be provided to assess relative risks or odds ratios (OR) with their 95% confidence intervals (CI). When several articles reported results of the same study, we used the most updated data.

Statistical analysis

For each study, we used the most adjusted OR with its 95% CI and we estimated variance of OR from the 95% CI. We weighted OR by the inverse of their variance to obtain a pooled measurement of the OR. The combined OR was obtained using both fixed effect model (16) and random effect model (17) according to the homogeneity between studies (18). In the fixed effect model, it is assumed that the effect is the same in all pooled studies and that the variations observed between studies only correspond to random measurement errors. On the contrary, the random effect model acknowledges the fact that the variations observed between studies correspond to a combination of a specific true effect and measurement errors. Homogeneity between studies was tested using the Cochrane test. We assessed publication bias graphically by using a funnel plot and statistically by using a linear regression test of funnel plot asymmetry. We used R statistical software package (meta) version 2.10.1 for all analyses.

Results

The systematic retrieval process to identify eligible studies is summarized in Fig. 1. Among the 28 selected articles, 22 were excluded because the MI risk associated with POC use could not be assessed. These 22 excluded articles included 14 case-control studies, two nested case-control studies, and six cohort studies. We included six case-control studies mentioning the MI risk in relation to POC or presenting a subgroup of women using POC (5, 10, 19–22). There was no cohort study which met the inclusion criteria for the meta-analysis. Characteristics of these studies are shown in the Table 1. Three of the studies were set-up in Europe (5, 19, 22), two in the United-States (10, 20), and one worldwide (21). Participants' age in these included articles ranged from 15 to 44 yr old, and cases and controls were matched for age. In all of them, MI event was clearly defined and diagnosed with clinical, biological, and/or radiological tools. Two publications dealt with fatal MI only (5, 19), two gave only data on nonfatal MI (10, 21), and two studied all types of MI (20, 22). Controls were differentially selected from a study to the other one. The World Health Organization (WHO) study and the study by Rosenberg only included hospital controls (10, 21), whereas Heinemann recruited the controls from both hospital and general population (22) and two studies were selected from general practice (5, 19). The number of cases and controls ran from 127 to 592 and from 264 to 2711, respectively. Subjects were exposed to oral POC in four studies (5, 10, 19, 22), to oral and injectable POC in one other (21), and to Norplant in the last one (20). In each study, cardiovascular risk factor, including especially age,

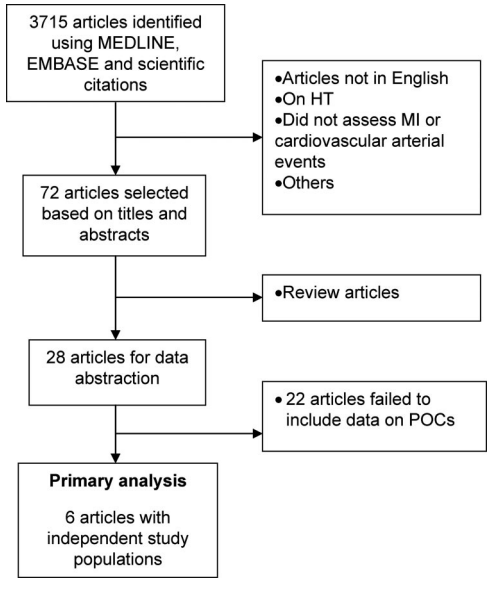

FIG. 1. Flowchart of eligible studies. HT, postmenopausal hormone therapy.

TABLE 1. Characteristics of studies evaluating Progestogen-only contraceptive use and the risk of myocardial infarction

Case-control study, year	Region	Years of study	Age (yr)	Control type	Number of cases/ controls	No of cases/controls exposed to POC	POC type	Event definition	Matching or adjustment variables
Thorogood 1991 (19)	UK	1986–1988	16–39	General practitioner	127/264	3/12	Oral	Fatal MI	Age and marital status
Petitti 1998 (20)	USA	1990	18–44	Population controls	307/1048	1/1	Implant	All MI	Age
WHO 1998 (21)	Worldwide	1989–1993	20–44	Hospital	263/809	4/14	Oral and injectable	Nonfatal MI	Age, HBP, diabetes, smoking
Heinemann 1999 (22)	Europe	1993–1996	16–44	H and P	133/474	7/17	Oral	All MI	Age, HBP, diabetes, smoking, education
Dunn 1999 (5)	UK	1993–1995	16–44	General practitioner	395/1516	9/49	Oral	Fatal MI	Age, smoking, BMI, HBP, diabetes, family history of MI
Rosenberg 2001 (10)	USA	1985–1998	> 45	Hospital	592/2711	1/1	Oral	Nonfatal MI	Age, residence area, HBP, diabetes, smoking, BMI, high cholesterol, family history of MI

H, hospital; P, population controls; All, fatal and nonfatal MI; BMI, body mass index; HBP, high blood pressure.

smoking, hypertension, and diabetes, were taken into account for the analyses.

The pooled OR for MI event between POC users *vs.* POC nonusers was 1.07 (95% CI: 0.62–1.83) (Fig. 2), which did not reach the statistical significance. The test for homogeneity did not underline great differences between studies (P value = 0.57). Information on progestogen type used and its dose was not available for all studies. However, the pooled estimated OR for the MI risk associated with oral POC users (5, 10, 19, 21, 22) was 1.05 (95% CI: 0.60–1.85) (test for heterogeneity: $P = 0.55$). When injectable progestogen was excluded, no difference in estimated OR was found. Finally, two studies provide the information on the type of progestogen and showed no significant increase in MI risk among users of either Levonorgestrel implant or medroxyprogesterone acetate injectable (8, 20).

We did not find evidence for publication bias from the funnel plot, which showed a symmetrical distribution of the individual study ORs around the overall OR (Fig. 3). The linear regression test of funnel plot asymmetry was also not significant ($P = 0.22$).

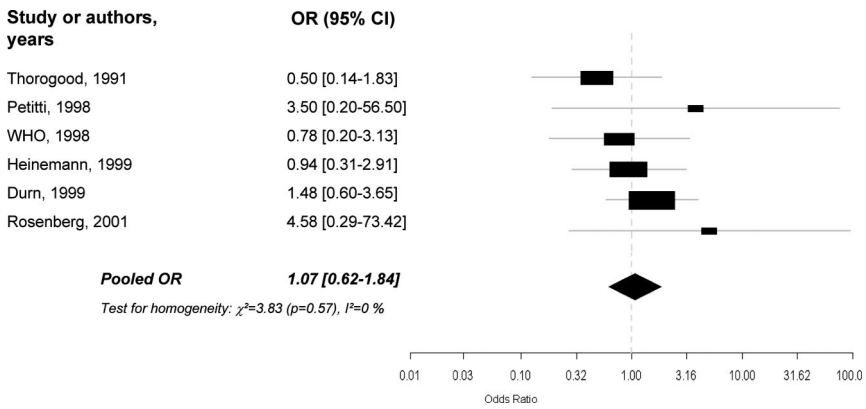

FIG. 2. OR and their 95% CI of MI associated with POC use from individual studies and overall.

Discussion

POC was introduced on the market after the combined pills in 1973. While the prevalence of its use varied widely around the world, POC assured effective contraceptive for millions of women. The aim of our work stood on elucidating whether POC use was safe with respect to MI risk. To our knowledge, this meta-analysis is the first assessing the association between POC and MI risk. No significant association was apparent between POC use and MI with an overall OR of 1.07 (95% CI: 0.62–1.84).

This meta-analysis has several methodological limitations. First, because of the low incidence of MI among young women, no cohort study was adequately designed to evaluate the MI risk associated with POC, and all selected studies were case-control studies. Such studies are more susceptible to recall bias than cohort studies. A survival bias could also explain null findings, and we cannot exclude an increased risk of fatal MI associated with the first year of POC use. Second, the meta-analysis only included six studies, and all individual study OR were assessed on small population samples. We cannot therefore exclude that the absence of association between POC use and MI in each study was attributable to a lack of statistical power. However, the power of our meta-anal-

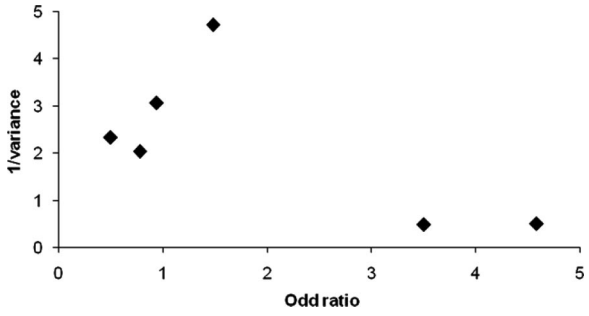

FIG. 3. Funnel plot of the studies of POC use and MI risk.

ysis to detect an OR of two for users of POC *vs.* nonusers was 95% at the 5% significance level. An OR of two is based on the results of two previous meta-analyses relating MI risk and OC (11, 12). Third, the magnitude of the association between POC and MI could be affected by two distinct parameters: 1) the selection of an hospitalized control group—which were more likely to be at high cardiovascular risk—could underestimate this relationship (*vs.* a population control group), and 2) the determination of POC users and nonusers varied from 0 to 3 months before the inclusion date, which could classify a participant into one or the other category depending in each study. Moreover, because of the lack of information on dose and type of oral POC, we cannot exclude an increased MI risk for the use of a specific molecule. Finally, although almost all studies were controlled for appropriate confounders, some important other risk factors might be unbalanced between POC users and nonusers, especially the healthy user characteristics. Women who used contraceptives were more likely than nonusers to be in better health and to participate to the health maintenance and disease screenings. This discrepancy between users and nonusers might underestimate the magnitude of the association between POC use and MI risk.

The association between MI and important cardiovascular risk factors, such as high blood pressure, was shown in two studies. The WHO study found an OR of 8.05 (95% CI: 4.89–13.3) for all MI among hypertensive women, and POC use did not confer an additional MI risk to these women (21). Moreover, the Transnational Study confirmed that the greater MI risk related to high blood pressure (OR = 8.34, 95% CI: 3.76–18.51) was not further increased by POC use (22). Nevertheless, these data must be interpreted with caution, because the number of women with a history of hypertension and POC use was very small. POC currently remains a contraceptive option for women with hypertension as long as it is well controlled and monitored (23). Hall *et al.* (24) established, in a U.S. prospective controlled study comparing women using POC for at least 6 months and matched control population using copper intrauterine device, that there was no significant rise in systolic and diastolic blood pressure. In addition, Wilson *et al.* (25) determined the same results with their Scottish population with oral and injectable POC over a 2-yr period.

Similar data regarding smoking were reported. In the WHO study, the adjusted OR for MI which was 4.96 (95% CI: 3.38–7.29) among OC nonuser smokers did not significantly rise among smokers with oral POC use. Moreover, the Transnational Study showed an elevated OR associated with smoking (OR = 10.20, 95% CI: 5.04–20.61), which was very similar to additional oral POC use (OR = 10.41, 95% CI: 1.10–98.83).

Progestogens as a contraceptive method have been assessed on lipid parameters. On one hand, lipoproteins have been measured in several studies before and after insertion of Norplant, and most of these publications showed a lowering in triglycerides, total cholesterol, and low-density lipoprotein concentrations. On the other hand, lipid profile has been studied among POC users, and data remain controversial. While one study found that high-density lipoprotein (HDL) cholesterol was slightly diminished or even increased (26), a Norwegian cross-sectional survey showed that depot medroxyprogesterone acetate (DMPA) and all oral POCs—except oral levonorgestrel—were linked with lower concentrations of HDL cholesterol compared with hormone nonusers (27). In addition, this latter study exhibited that total cholesterol and triglycerides were higher with oral and DMPA use. In both studies, there was little change in the total cholesterol/HDL cholesterol ratio, which might imply that POC should not aggravate risk factors for atherosclerosis, but this hypothesis still remains to be confirmed.

Numerous papers on DMPA reported a significant elevation of insulin concentration compared with baseline after sequential oral glucose tolerance test (28) and iv glucose tolerance test (29). Despite the reduced insulinosensitivity, most of the studies did not find any effect of POC on glucose concentrations in lean women. Increased glucose involved in heavier DMPA users or long treatment duration users (29). Other studies also observed an increase in insulin area under the curve with etonogestrel implants after oral glucose tolerance test and in Norplant users, an elevation of glucose concentrations which is intensified with greater implant use period and returned to baseline after removal (30, 31). This presumption of insulin resistance was supported by a finding of increased free fatty acids after glucose challenge among DMPA users (32). One other mechanism might be weight gain. Cross-sectional and longitudinal studies of DMPA users generally found increased mean weight (33), which appeared to be associated with changes in adipose mass (34). About 30% of implant users noted either weight gain or weight

loss, the former being more frequent in developing countries (35, 36).

Regarding blood coagulation, POC could have no deleterious effect on hemostasis. Indeed, in the study by Winkler *et al.* (37), desogestrel and levonorgestrel induced a reduction of factor VII activity and fragment 1 + 2 concentration. In addition, these progestogens had no effect on antithrombine and protein C, whereas protein S increased notably. Authors also noticed a nonsignificant decrease in D-dimers. Concordant results were found in a phase III trial focusing on DMPA, which reported steady antithrombin and factor VIIIc levels coupled with lowered D-dimers and C-reactive protein (CRP) (38). Decreases in both D-dimers and CRP support a potential reduced risk of venous and/or arterial thrombosis. D-dimers are a marker of procoagulant and subsequent fibrinolytic activity, which was established as an indicator of venous and sometimes arterial thrombotic risk (39, 40). Likewise some studies reported a link between high CRP levels and the risk of MI and stroke (41, 42).

Finally, in the Transnational Study, POC users tended to be older, had a higher body mass index, were more often smokers, more frequently had hypertension or diabetes, and more often had a family history disease than users of combined OC (22). Some of these differences in the risk factor profile were also observed in the WHO study, even if they were less consistent (21). These differences in the POC characteristics users between Transnational and WHO studies could be explained by a selection bias. The latter study included a large population from developing countries where POCs are frequently prescribed in first line because of their cheapness and effectiveness. By contrast, women recruited in the Transnational Study came mainly from industrial countries where POCs are often used as an alternative to OC for women with cardiovascular risk factors. Despite this discrepancy, no change in MI risk between these two studies was noted. One explanation could be that these women were narrowly monitored to correct these cardiovascular risk factors.

In conclusion, this meta-analysis suggests that POC use might be safe with respect to MI risk. However, further investigation regarding this topic is needed, especially among women with cardiovascular risk factors, and POCs must still be cautiously used for these women.

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