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Oral contraceptives use and the risk of myocardial infarction: a meta-analysis

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Abstract

This meta-analysis of oral contraceptive use in relation to myocardial infarction is based on 19 case-control studies and 4 cohort studies that met pre-stated inclusion criteria. A comprehensive literature search was performed using the MEDLINE computerized database (for studies from January 1966 through October 2002). In addition, a manual search was performed for references cited in published original and reviewed articles. Current oral contraceptive (OC) users have an overall adjusted odds ratio (OR) of myocardial infarction (MI) of 2.48 [95% confidence interval (CI): 1.91–3.22] compared to never-users. The risk of MI for past OC users is not significantly different from that for never-users, overall OR = 1.15 (95% CI: 0.98–1.35; p = 0.096).

Keywords: Cardiovascular diseases; Meta-analysis; Myocardial infarction; Oral contraceptives; Estrogen

1. Introduction

Soon after oral contraceptives (OCs) were first marketed in the 1960s, case reports linked their use to the occurrence of myocardial infarction (MI) [1]. Over the past several decades, numerous studies examined the cardiovascular complications associated with OC use and reached conflicted conclusions [2–25].

Some studies indicated that OC use was not associated with incidence of MI [8–10,13,14,18,22], while others found an increased risk of MI among women who used OCs [3–7,11,12,15,16,20,25].

We conducted a meta-analysis to examine the relationship between use of OCs and risk of MI in the observational studies. By pooling information from individual studies, we were able to obtain more precise and accurate statistical estimates of the effect of OCs on the risk of MI and to explore the basis for heterogeneity in the study findings.

2. Methods

A comprehensive literature search was performed using the MEDLINE computerized database (for studies from January 1966 through October 2002) with medical subject headings "oral contraceptives/side effects, complications" and "myocardial infarction" or "cardiovascular disease." Only full-length original journal articles were considered; no attempt was made to include abstracts or unpublished studies. The search was restricted to studies published in English-language journals, conducted on human subjects and classified as case-control or cohort studies in the MEDLINE database. In addition, a manual search was performed for references cited in published original and reviewed articles. The contents of full-text articles that were identified during the literature search were reviewed to determine whether they met the criteria for inclusion.

Two investigators (Y. K. and O. A.) independently reviewed the studies and decided which ones should be included based on pre-stated eligibility criteria, and disagreements were resolved through discussion with additional input from a third investigator (J. R.). Inclusion criteria are: (a) cohort or case-control design that provides a risk estimate of MI associated with OC use or sufficient information to calculate it, (b) cases defined as women with fatal or nonfatal MI, (c) exposure defined as current or past use of

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OCs, (d) inclusion of at least 20 cases of MI and (e) control for age in study design or analysis.

Of 822 references identified, 95 were considered potentially relevant and 72 studies failed to meet one or more of the inclusion criteria. In total, 19 case-control studies and 4 cohort studies were included in this analysis.

Major reasons for exclusion of studies were case series, case reports, reviews, letter to editors, inadequate definition of MI cases, reporting the same data in other reports, failure to control for age in study design or analysis, insufficient information to determine or calculate odds ratio (OR), relative risk (RR) or their confidence intervals (CI).

Using a standard protocol, three investigators extracted information on the name of the journal, name of authors, year and location of study, characteristics of the study population, sample size, study design, measure of risk factors, measure of outcome of interest, covariates adjusted or matched and risk estimates or raw numbers for calculation of them. Areas of disagreement or uncertainty were adjudicated by discussion between the three abstractors and in some instances with input from another author. Definitions of current, past and ever use of OCs were taken directly from included articles. Definitions of past and ever use were consistent among studies, while current use varied somewhat, with last use ranging from 1 week to 1 year prior to the onset of MI. Variables were considered controlled in studies when they were used to exclude or restrict subjects, match controls, calculate standardized or stratified estimates or were included in multivariable analysis. Estrogen dosages, type and generation of OCs were abstracted only when they were defined in original publications. MI diagnosis was confirmed by symptoms, cardiac enzymes and electrocardiogram in most studies.

The strength of the relationship between OC use and MI was assessed by RR or OR, which were used as surrogate measures of the RR. Because the absolute risk of MI was low in menstruating women, the relative odds provided a good approximation of RR. OR and RR were obtained directly from the study or calculated using the available data. Before pooling the data, ORs or RRs from individual studies were transformed to their natural logarithms or log (OR), to stabilize the variances and to normalize the distributions [26]. For calculation of the pooled OR, each study was assigned a weight equaling the reciprocal of the variance of the log (OR) in that study. Because the variances of log OR were not reported directly in most manuscripts, they were calculated from CIs, t-statistics, p-values or from the standard formula [27].

Estimates of the overall OR and the corresponding 95% CI were calculated by using both fixed-effects and random-effects models [28]. Homogeneity of effect size across studies was tested by Q-statistics [28]. Because there was significant variation across studies, we present the results obtained using random-effects models as developed by DerSimonian and Laird [28] and Kleinbaum, Kupper, and Morgenstern [29]. A sensitivity analysis was conducted to assess the robustness of our findings with respect to different exclusion criteria. The z-statistics were calculated, and a two-tailed p-value ≤ 0.05 was considered statistically significant. To explore the effects of the covariates on the overall effect, we conducted a series of pre-stated subgroup analyses on the basis of plausibility and knowledge of the literature.

The potential for publication bias was examined by plotting log ORs against their variance [30]. In addition, the association between variance and log OR was analyzed by rank correlation using the Kendall's tau method. In the absence of a publication bias, no significant correlation between the variance and log relative OR would be evident [30].

3. Results

Nineteen case-control studies and 4 cohort studies are included in our meta-analysis of the relation between OC use and risk of MI. Twelve studies compared past OC use to never use [5–11,13,14,16,17,22], 13 studies compared current use to never use [2,3,5–9,13–17,22] and 6 studies compared current use to noncurrent use [4,6,11,14,16,24].

3.1. Participant characteristics and study design

Selected participants and study design characteristics of the 19 case-control studies and 4 cohort studies included in our meta-analysis are presented in Tables 1 and 2, respectively. Six studies were conducted in the US, 5 studies in England and Wales and 12 studies in other European, African and Asian countries. The number of cases enrolled in these studies ranged from 26 to 910, and the number of controls ranged from 63 to 3120. The age of participants in these studies ranged from 15 to 55 years. Matching and adjustment were performed in most of the studies for a variety of potential confounders. The most common confounders controlled for in these studies were age, diabetes, hypertension, smoking, body mass index and abnormal lipids. The outcome for these studies was acute MI, nonfatal MI or fatal MI.

3.2. Current OC use

The risk of MI in current OC users compared to never users was explored in 13 studies [2,3,5–9,13–17,22]. Twelve of the 13 studies found that current OC users have a higher risk of MI compared to never users after adjusting for possible confounders, but this difference was significant in eight studies only [2,3,5–7,16,17]. One study found an OR <1, but it was not significant [22]. Significant adjusted ORs in these studies range from 1.70 to 5.64 (Fig. 1).

Current OC users have overall adjusted odds ratio of MI of 2.48 (95% CI: 1.91–3.22; $p < 0.0005$) compared to never users (Fig. 1). There is heterogeneity among the studies in

Table 1
Studies and participant characteristics in 19 case-control studies of the effect of oral contraceptives on myocardial infarction

Study	Year and location	Cases/ controls	Diagnosis of MI	Age (Years)	Variables controlled for
Inman et al. [2]	1968, UK	84/998	Fatal coronary thrombosis	20–44	
Mann JI et al. [3]	1975, England and Wales	63/189	WHO	<45	Smoking, hypertension, obesity
Jick et al. [4]	1978, US	30/63	ICD 410	27–45	Age
Shapiro et al. [5]	1979, US	234/1742	WHO	25–49	Age, smoking, diabetes, lipid, hypertension,
Rosenberg et al. [6]	1980, US	156/3120	MI	<50	Smoking, hypertension, diabetes, elevated cholesterol
Adam et al. [7]	1981, England and Wales	139/276	WHO	15–44	Matched for age and marital status
La Vecchia et al. [8]	1987, Northern Italy	168/251	WHO	<55	Geographic region, marital status, education, social class, smoking, alcohol and coffee consumption, diabetes, hypertension, obesity, hyperlipedemia, history of ischemic heart disease
Ananijevic-Pandey et al. [10]	1989, Belgrade	58/174	ICD 410 (9th revision)	≤50	Hypertension, smoking, history of angina cholesterol (stratification)
Rosenberg et al. [11]	1990, US	910/1760	WHO	25–64	Age, region, interview year, smoking, hypertension, diabetes, elevated cholesterol, BMI, exercise, education, coffee consumption
Thorogood et al. [12]	1991, England and Wales	161/309	Fatal MI	<40	Medical risk factors and surgical sterilization
D'Avanzo et al. [13]	1994, Italy	251/475	First episode of acute MI	17–54	Smoking, history of angina, hypertension BMI, hyperlipedemia, diabetes
Sidney et al. [14]	1996, US	130/339	AHACE	15–44	Smoking, hypertension, hypercholesterolemia, BMI, diabetes
Lewis et al. [15]	1997, UK, Germany, Switzerland, Austria, France	182/635	ICD 410, WHO	16–44	Smoking, hypertension, hypercholesterolemia, diabetes, family history of MI
WHO Collaborative[a] [16]	1997, Africa, Asia, Europe	368/941	Symptoms, ECG, enzymes	20–44	Diabetes, abnormal blood lipid level, smoking, hypertension
Lidegaard. [17]	1999, Denmark	94/1041	First acute MI	15–44	Smoking, hypertension, BMI, diabetes, family history of MI, education
Dunn et al. [18]	1999, England, Scotland, and Wales	448/1728	ICD 410 (9th revision)	16–44	Smoking, hypertension, hypercholesterolemia, diabetes, family history of MI
Frits et al. [19]	2001, Nationwide	248/925		18–49	Adjustment used but factors are unknown
Rosenberg et al. [20]	2001, US	627/2947	Symptoms, enzymes, ECG	<45	Age, region, interview year, smoking, hypertension, diabetes, elevated cholesterol, BMI
Tanis et al. [21]	2001, Netherlands	248/925	Symptoms, cardiac enzymes, ECG	24–49	Smoking, diabetes, hypercholesterolemia, hypertension, obesity, family history of CVD, education, alcohol intake

MI = myocardial infarction; WHO = World Health Organization (criteria); ICD = International Classification of Diseases; BMI = body mass index; AHACE = American Heart Association Council on Epidemiology; ECG = electrocardiogram; CVD = cardiovascular disease.
[a] WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception.

the overall OR estimate ($p = 0.035$), suggesting that differences in study results are not due to chance alone. Sensitivity analysis shows that the adjusted overall OR ranges from 2.30 to 2.75, and the lower limits of the 95% confidence intervals do not cross 1 (2.08–2.12). When current OC use is compared to noncurrent OC use (past or never use), the overall adjusted OR is elevated to 3.00 (95% CI: 1.70–5.28; $p < 0.0005$).

3.3. Past OC use

The relationship between past OC use and the risk of MI after adjusting for important confounders was explored in 12 studies [5–11,13,14,16,17,22]. Adjusted ORs in these studies range from 0.70 to 2.42 (Fig. 2). Overall, the risk of MI for past OC users is not significantly different from that for never users, overall OR = 1.15 (95% CI: 0.98–1.35; $p = 0.096$).

3.4. Subgroup analysis

A series of pre-stated subgroup analyses based on reports in the literature were conducted to examine their influences on the relationship between OC use and risk of MI (Table 3).

Table 2
Studies and participant characteristics in four cohort studies of the effect of oral contraceptives on myocardial infarction

Study	Year and location	Population	Diagnosis	Follow-up (years)	Variables controlled for
Croft et al. [9][a]	1989	158 cases and 474 controls were included in the analysis	ICD 4100–4109 (8th revision)		Social class, smoking
Petitti et al. [22]	1979, US	16759 women aged 18–54 years	Symptoms, ECG, enzymes		Adjustment used but no information about confounders
Salonen et al. [23]	1982, Finland	2653 women aged 35–49 years	ICD 410–411	7 years	No adjustment
Mant et al. [24]	1998, England and Scotland	17032 women aged 25–39 years	(ICD-8th revision) code 410	Annual follow-up until the age of 45 years	Age, parity, social class, smoking, Quetelet Index, hypertension, hyperlipedemia, diabetes

ECG = electrocardiogram; ICD = International Classification of Diseases.
[a] Croft et al. is a cohort study analyzed using the nested case-control approach.

3.4.1. Location of the study

Stratifying studies by location shows that the overall adjusted OR for current OC use varies very little; OR = 2.46 (95% CI: 1.79–3.37; $p < 0.0005$) for studies conducted in the US [5,6,14,22] and OR = 2.62 (95% CI: 2.10–3.26; $p < 0.0005$) for studies conducted in Europe [2,3,7–9,13,15–17] (Table 3). On the other hand, the overall adjusted OR associated with past OC use for studies conducted in Europe increases, OR = 1.20 (95% CI: 0.98–1.46; $p = 0.080$), while it decreases for studies conducted in the US, OR = 1.02 (95% CI: 0.84–1.24; $p = 0.827$), but both remain nonsignificant.

3.4.2. Generations of oral contraceptives

Stratifying by generation of OCs shows that first and second-generation OC users have a significantly higher risk of MI compared with nonusers, and the overall ORs are 2.21 (95% CI: 1.30–3.76; $p = 0.004$) and 2.17 (95% CI: 1.76–2.69; $p < 0.0005$), respectively. On the other hand, third generation OC users are not significantly different from nonusers in relation to the risk of MI, OR = 1.27 (95% CI: 0.96–1.67; $p = 0.094$) (Table 3).

3.4.3. Dosage of estrogen

Subgroup analysis based on the dose of estrogen shows a dose–response relationship. The overall OR is 3.62 (95% CI: 2.22–5.90; $p < 0.0005$), 1.97 (95% CI: 1.43–2.71; $p < 0.0005$) and 0.92 (95% CI: 0.21-4.08; $p = 0.918$) for estrogen dose preparations ≥50 μg, 30–49 μg and 20 μg, respectively (Table 3).

3.4.4. Oral contraceptives use by age

Among women who are younger than 35 years, the overall OR of having MI for OC users compared to nonus-

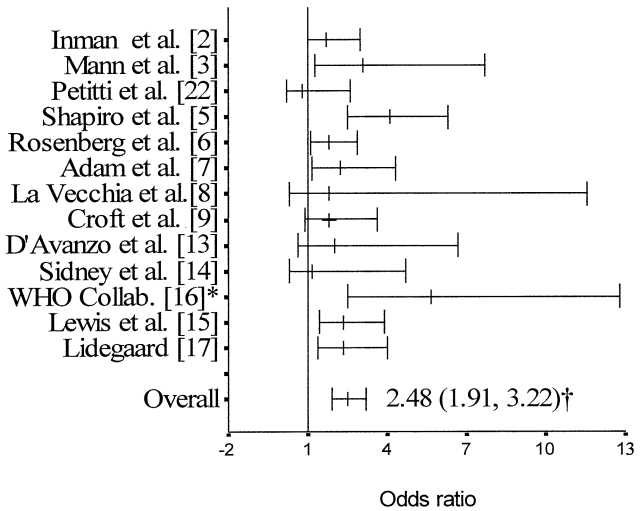

Fig. 1. Odds ratios and their 95% confidence intervals of myocardial infarction associated with current oral contraceptive use from individual studies and overall. The horizontal lines (—) represent the 95% confidence intervals from the random effect model. *WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception; †overall odds ratio and its 95% confidence interval.

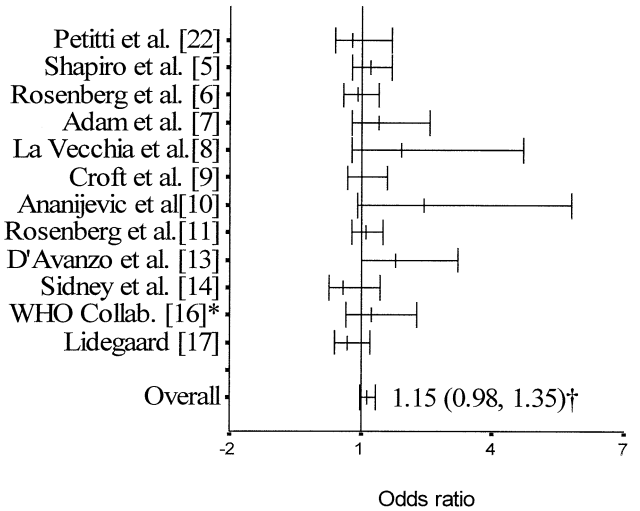

Fig. 2. Odds ratios and their 95% confidence intervals of myocardial infarction associated with past oral contraceptive use from individual studies and overall. The horizontal lines (—) represent the 95% confidence intervals from the random effect model. *WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception; †overall odds ratio and its 95% confidence interval.

Table 3
Combined odds ratio (OR) of myocardial infarction (MI) associated with oral contraceptives (OCs) use in subgroups by study characteristics

Subgroups	No. of studies	OR	95% CI	p-value*
OCs Exposure				
Past vs. never use [5–11,13,14,16,17,22]	12	1.15	0.98, 1.35	0.0965
Current vs. never use [2,3,5–9,13–17,22]	13	2.48	1.91, 3.22	<0.0005
Current vs. noncurrent use [4,6,11,14,16,24]	6	3.00	1.70, 5.28	<0.0005
Study location				
Past use (US) [5,6,11,14,22]	5	1.02	0.84, 1.24	0.8268
Past use (Europe) [7–10,13,16,17,24]	8	1.20	0.98, 1.46	0.0801
Current use (US) [5,6,14,22]	4	2.46	1.79, 3.37	<0.0005
Current use (Europe) [2,3,7–9,13,15–17]	9	2.62	2.10, 3.26	<0.0005
Type of OC				
First generation [14,15,17,18,20,21]	6	2.21	1.30, 3.76	0.0036
Second generation [15–21]	7	2.17	1.76, 2.69	<0.0005
Third generation [15–21]	7	1.27	0.96, 1.67	0.0940
Estrogen dose				
20 μg [17,18]	2	0.92	0.21, 4.08	0.9179
30–49 μg [17,18,20,21]	4	1.97	1.43, 2.71	<0.0005
≥50 μg [7,16,17,20,21]	5	3.62	2.22, 5.90	<0.0005
Cigarette smoking				
No [3,5,9,10,12,14,18,20,21,24]	10	1.84	1.32, 2.57	<0.0005
Yes [3,5,6,10–12,14,16,18,20,22–24]	13	1.90	1.38, 2.62	<0.0005
Combined effect of OCs and one of another risk factors compared with absence of both				
Smoking [5,6,9,12,13,15,16,20,21,23]	10	9.52	5.41, 16.72	<0.0005
Hypertension [9,13,16,21]	4	9.30	3.89, 22.23	<0.0005
Hypercholesterolemia [13,21]	2	9.90	1.83, 53.53	0.0078
Prothrombin mutation [20,21]	2	2.08	1.50, 2.90	<0.0005

CI = confidence interval.
* Two-tailed.

ers is 2.69 (95% CI: 1.35–5.39; p = 0.005). For women who are 35 years or older, the overall OR is 2.15 (95% CI: 1.30–3.56; p = 0.003).

3.4.5. Cigarette smoking

Independent effect of OC use compared to nonuse among smokers and nonsmokers was analyzed. The overall OR of having MI for OC users compared to nonusers is 1.90 (95% CI: 1.38–2.62; p < 0.0005) among smokers and 1.84 (95% CI: 1.32–2.57; p < 0.0005) among nonsmokers.

3.4.6. Combined effect of oral contraceptives and other cardiovascular disease risk factors

The combined effect of OC use and one of the other cardiovascular disease risk factors as compared with the reference category of women who have not used OCs and who do not have the given risk factor was explored. The overall OR of having MI is 9.52 (95% CI: 5.41–16.72; p < 0.0005) for women who use OCs and smoke compared to women who do not use OCs and do not smoke; OR = 9.30 (95% CI: 3.89–22.23; p < 0.0005) for those who use OCs and have a history of hypertension compared to women who do not use OCs and do not have a history of hypertension; OR = 9.90 (95% CI: 1.83–53.53; p = 0.0078) for those who use OCs and have a history of hypercholesterolemia compared to women who do not use OCs and do not have a history of hypercholesterolemia; OR = 2.08 (95% CI: 1.5–2.90; p < 0.0005) for those who use OCs and have factor V Leiden or a G20210A mutation in the prothrombin gene compared to women who do not use OCs and do not have that factor or mutation (Table 3).

3.4.7. Testing for publication bias

The possibility of publication bias was explored by plotting the log ORs against their variances of studies included in the main analysis (Fig. 3). This plot showed a symmetrical distribution about the mean effect size, as would be

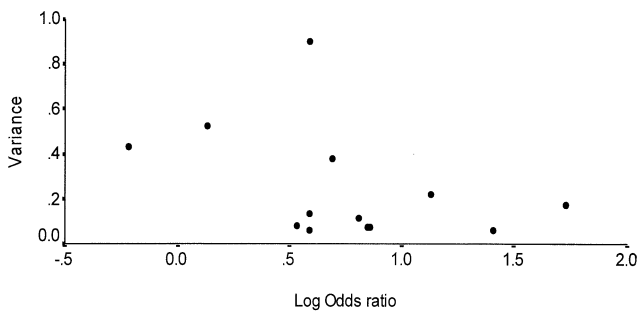

Fig. 3. Plot of log odds ratios by their variances of studies included in the main analysis to test for publication bias. Kendall's correlation coefficient between variance and standardized log odds ratios is 0.326 (p = 0.146).

expected in the absence of publication bias. Kendall's correlation coefficient between variance and standardized log ORs was 0.326 ($p = 0.146$). Thus, the totality of the evidence failed to support the presence of publication bias.

4. Discussion

Interpretation of the results from this meta-analysis study should consider that the studies pooled in this analysis vary in the formulations, doses and generations of OCs. Prescribing patterns have changed over the years, following recognition that OCs raise blood pressure and pose additional risk in older women who smoke cigarettes [7,31]. These changes in products and their use would be expected to reduce cardiovascular risks associated with OCs. Obviously, only recent case-control studies can quantitate risks associated with current formulations and prescribing practices.

A meta-analysis depends on the quality of the studies included. Observational studies on this topic are susceptible to bias [32–34], including healthy user bias, recency of introduction bias, duration of use of OCs, diagnostic suspicion and referral bias and prescribing and switching bias. Sometimes it was difficult to determine the characteristics of subjects in a study. If a study of MI was reported to have excluded events that occurred in women with a history of this problem or during or soon after surgery or pregnancy, we assumed that it studied an apparently healthy group of women. While the random-effects model of meta-analysis attempts to encompass nonrandom variation between study results, the source of these differences must be examined to understand the role of characteristics and design in study outcomes.

It is difficult to study the influence of study design on the relationship between OC use and the risk MI because the main analysis included two cohort studies only [9,22]. Stratifying studies by location changed the overall OR very little, suggesting that this aspect of study location was unimportant. The risk of MI decreases as estrogen dosages decrease, falling from an OR of 3.62 with 50 μg or more to an OR of 1.97 with 30–49 μg to an OR of 0.92 with 20 μg. Analysis of progesterone type suggested that the third-generation OCs are not associated with the risk of MI, while second- and third-generations OCs are significantly associated with elevated risk of MI when compared with nonusers. The definition of second- and third-generation OCs was not fully consistent across reports. However, definitions did not affect the results materially. The summary risk estimates within different subgroups do not adjust for the different preparations or changes in clinical practice over time which could be confounding comparisons between products. While attempts to allow for confounding across strata is possible within a study, meta-analyses of published data cannot make such adjustments and this is one reason why reanalyses of original data from observational studies need to be done.

We did not give quality scores to included studies because of their inherent subjectivity and potential to result in diverging summary estimates [35]. We assessed appropriate adjustment for confounding by comparing adjusted and unadjusted odds ratios and by presenting stratified analyses. The presence of confounding is unlikely for the past OC use on the risk of MI because the pooled adjusted OR was almost equal to the pooled unadjusted OR.

In our systematic review of the literature, the overall adjusted risk estimate for MI among current OC users was 2.48 (95% CI: 1.91–3.22). On the other hand, the overall adjusted risk estimate for MI among past OC users was 1.15 (95% CI: 0.98–1.35). We analyzed results from studies separately examining the effect of OC use among smokers and nonsmokers. OC use appeared to impart a similar MI risk among nonsmokers and smokers. This suggests that the MI risk of OC use is independent of smoking. However, current prescribing practices may have resulted in unbalanced levels of additional risk factors, such as fewer pack-years in OC users who smoke, and inadequate control of level of smoking could obscure an interaction between smoking and OC use. Also, since this risk factor increases baseline risk of MI, a greater absolute increase in MI risk with OC use would be anticipated.

Some studies found greater MI risk among OC users who had additional risk factors, such as hypertension, smoking, diabetes, hypercholesterolemia. Assuming that OC use and other risk factors act synergistically to elevate MI risk, it has been suggested that OC use in women with these risk factors is riskier than for those without them. This has led to recommendations to avoid OC prescriptions for smokers and those with hypertension. In our systematic review of the literature, the overall adjusted risk estimate for MI is highly increased if women use OCs and have an additional cardiovascular disease risk factors compared with women who have not used OCs and who do not have the given risk factor. The ORs reach 9.25 (95% CI: 5.41–16.72), 9.30 (95% CI: 3.89–22.23), 9.90 (95% CI: 1.83–53.53) and 2.08 (95% CI: 1.5–2.90) for smoking, having hypertension, having hypercholesterolemia and having mutation in the prothrombin gene as additional risk factors, respectively.

This meta-analysis suggests that current OC use, but not the past use, is a risk factor for MI. Clinical decisions on these associations should consider that the absolute risk of MI is very low especially at the age when most women use OCs, even among those with other risk factors.

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