Therapeutics and Clinical Risk Management

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ORIGINAL RESEARCH

Meta-analysis of oral contraceptives and rheumatoid arthritis risk in women

This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management
4 November 2014
Number of times this article has been viewed

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Background and objectives: Epidemiological investigations of the relationship between oral contraceptives and rheumatoid arthritis (RA) risk have reported controversial results. Therefore, a meta-analysis of case-control or cohort studies was performed to evaluate the role of oral contraceptives in relation to risk of developing RA.

Methods: Eligible studies were identified from databases PubMed and EMBASE by searching and reviewing references. Random effect models were utilized to summarize the relative risk (RR) estimates with 95% confidence intervals (CIs).

Results: A total of 12 case-control studies and five cohort studies were eligible for our analysis. No statistically significant association was observed between oral contraceptives and RA risk (RR=0.88, 95% CI=0.75–1.03). In the subgroup of geographic area, a decreased risk of borderline significance was observed for oral contraceptive users in European studies (RR=0.79, 95% CI=0.62–1.01), but this association did not emerge in the North American studies group (RR=0.99, 95% CI=0.81–1.21). No evidence for publication bias was detected (*P* for Egger's test =0.231).

Conclusion: Our results of meta-analysis do not support the hypothesis of a protective effect of oral contraceptives on the risk for RA in women.

Keywords: rheumatoid arthritis, oral contraceptive, hormone, meta-analysis

Introduction

Rheumatoid arthritis (RA) is a common chronic systemic inflammatory autoimmune disorder of the synovial tissues and joints, which affects approximately 1% of the adult population all over the world.[1–3] Although the etiology of RA remains elusive, an increasing body of evidence suggests that sex hormones may play a role in RA pathogenesis. RA occurs approximately twice to thrice as often in women as in men.[4] In addition, RA symptoms tend to diminish during pregnancy and aggravate postpartum.[5,6] Owing to this background, recent epidemiological studies evaluated the risk of RA in users of oral contraceptives (OCs) versus nonusers.[4,7–42] However, a conflicting picture on this issue was presented in these studies. Given that the vast majority of studies were of small sample size and characterized by low statistical power, these findings may be detected by chance. Therefore, we performed a meta-analysis of case-control and cohort studies to summarize the evidence and provide an accurate estimation of association between OCs use and RA risk.

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Material and methods

Search strategy

Studies assessing the relationship between RA risk and OCs were identified in PubMed and EMBASE databases using the following search terms: ("oral contraceptives" OR

"exogenous hormones" OR "hormone") AND ("rheumatoid arthritis" OR "RA") AND ("risk" OR "risk factor"). The latest date for this search was June 13, 2014. The bibliographies of relevant articles were checked by a manual search for additional publications of interest.

Inclusion criteria

We adopted the following inclusion criteria: (1) the report described a case-control or cohort study; (2) the report provided the relative risk (RR) or odds ratio with corresponding 95% confidence interval (CI), or sufficient information to calculate them (ie, the distribution of exposure); (3) when multiple reports involved the same study population, only the most informative one was identified for this analysis. We excluded the conference abstracts, case series, letter to editors, reviews, meta-analysis, and cross-sectional studies and we also excluded those studies that involved family cases in their subjects.

Data collection

We extracted information on the first author, sites where the study was performed, age of study population, number of subjects (cases, controls, or cohort size), study design, years of case diagnosis or cohort enrollment, length of follow-up for cohort studies, the method of OCs exposure assessment, the adjusted RR estimates with corresponding 95% CIs from multivariable model, match factors, and covariates adjusted for in the analysis.

Statistical analysis

Analyses were conducted using STATA version 12 (STATA Corporation, College Station, TX, USA). The measure of interest was the RR. ORs were directly considered as RRs, because the prevalence of RA was rare.[43] A random-effect model with the method of DerSimonian and Laird, which incorporates the heterogeneity across studies, was employed to calculate the pooled RR.[44] We evaluated the heterogeneity using the Cochran's Q and I^2 statistics.[45,46] Significant heterogeneity was found as P-value for heterogeneity <0.10 or $I^2>50\%$. Stratified analyses were performed according to study design (case-control vs nested case-control vs cohort studies), source of control (population-based vs hospital-based case-control studies), and geographic area (European vs North American studies). Also, a sensitivity analysis was performed to investigate the influence of potential confounding (ie, age, smoking, parity/pregnancy, age at menarche, body mass index (BMI), social class, and marital status) on RA risk. We conducted a sensitivity analysis to assess the impact of individual studies on the overall results by excluding one study at a time. Potential publication bias was evaluated using Begg's funnel plots and quantified by the Egger's test (a P-value of <0.05 was considered statistically significant).[47,48]

The unit of the meta-analysis was a single comparison of OCs users versus nonusers. When a study presented separate RRs for different duration of OCs use versus nonuse, the overall risk estimate for OCs use versus nonuse was calculated from these separate RRs with the method proposed by Hamling et al.[49] This method is utilized to combine estimates using the same reference category. Also, the association between estimates is taken into account. In the analyses on duration of OCs use, we define short-term use as <5 years, and long-term use ≥ 5 years. Among the included studies, two studies that reported long-term use as ≥ 4 years were also included in this meta-analysis. Then, we performed an analysis that excluded those two studies to investigate the robustness of the results of long-term OCs use.

Results

Search results and study characteristics

Based on our search terms, a total of 1,116 publications were identified in PubMed and EMBASE databases. Figure 1 shows the flowchart of literature inclusion and exclusion. We identified 47 publications for full-text evaluation, of which 30 publications were further excluded because they did not fulfill the inclusion criteria (ie, conference abstracts,[34–42] meta-analyses/reviews,[50–58] letters to editor/comments,[59] cross-sectional studies,[29,30] providing insufficient data,[28] involving the same study population or overlapped data,[8,31–33] involving family cases,[13,17] reporting the relationship between noncontraceptive hormones and RA among perimenopausal and postmenopausal women,[11] and using OCs users with less than one patient as reference[9]). Therefore, our meta-analysis was based on 17 publications, including 12 case-control and five cohort studies published between 1982 and 2010.[4,7,10,12,14–16,18–27] All studies were published in English. The other characteristics of included studies are listed in Table 1.

Overall association of OCs use and RA risk

Figure 2 presents the study-specific and pooled RRs and 95% CIs of RA for OCs users versus nonusers. The summary estimates were 1.02 (95% CI=0.90–1.15, I^2=0.0%, P for heterogeneity =0.688), 0.81 (95% CI=0.63–1.05, I^2=66.4%, P for heterogeneity <0.001), and 0.88 (95% CI=0.75–1.03,

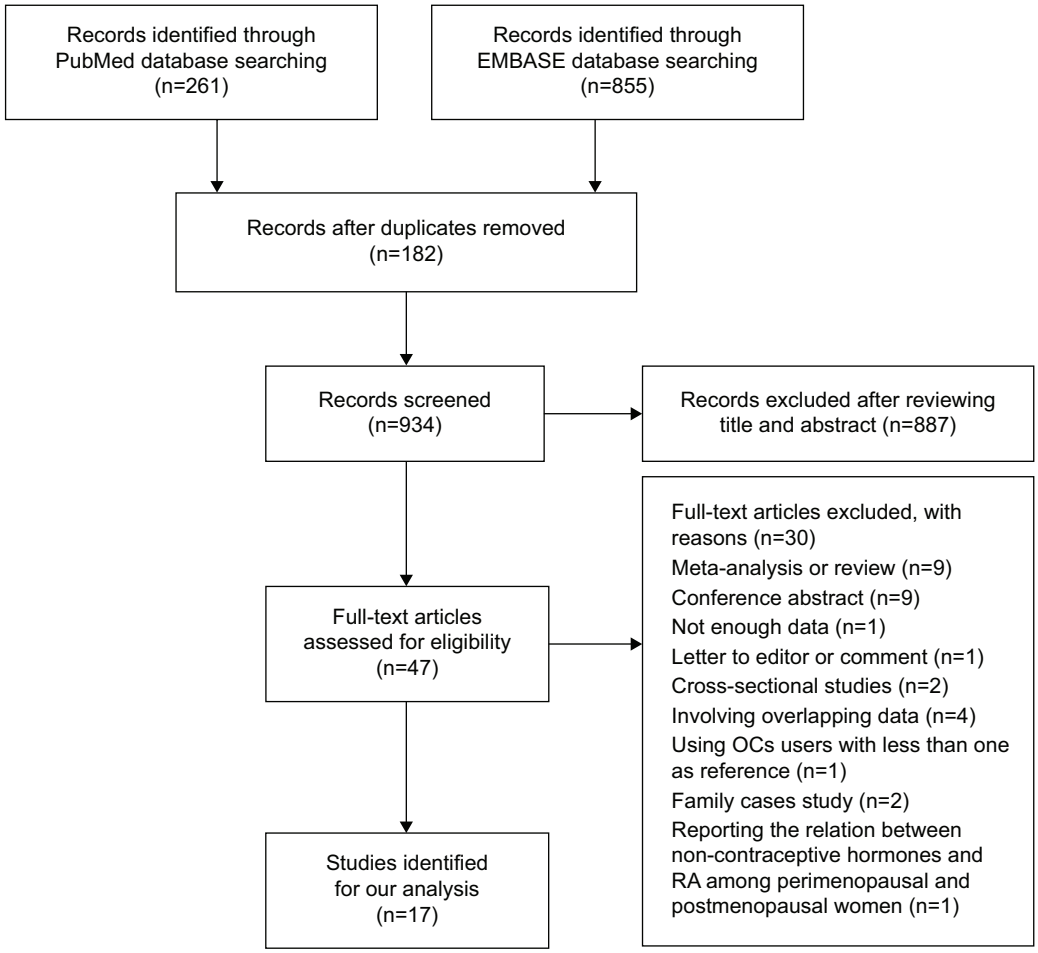

Figure 1 The flowchart of literature selection.
Abbreviations: OC, oral contraceptive; RA, rheumatoid arthritis.

I^2=61.1%, *P* for heterogeneity =0.001) for cohort studies, case-control studies, and all studies, respectively. In further analysis, according to the type of controls for the case-control studies, similar trends with the overall result were observed in population-based case-control studies (RR=0.87, 95% CI=0.65–1.17, I^2=47.1%, *P* for heterogeneity =0.093) and hospital-based case-control studies (RR=0.78, 95% CI=0.51–1.18, I^2=77.3%, *P* for heterogeneity =0.001). Considering subgroups of geographic area, the combined estimate was 0.79 (95% CI=0.62–1.01, I^2=67.6%, *P* for heterogeneity =0.001) in European studies and the corresponding estimate was 0.99 (95% CI=0.81–1.21, I^2=37.7%, *P* for heterogeneity =0.155) in North American studies. Considering subgroups of matching or adjusted factors, the correlation of OCs use related with RA risk was not significantly modified by age, smoking, parity/pregnancy, age at menarche, BMI, social class, or marital status (Table 2). In the analyses on duration of OCs use, the pooled RRs were 0.84 (95% CI=0.56–1.27, I^2=80.0%, *P* for heterogeneity <0.001) for short-term use and 0.84 (95% CI=0.64–1.10, I^2=52.8%, *P* for heterogeneity =0.048) for long-term use.

Sensitivity analysis and publication bias

In the sensitivity analysis, we removed one study at a time to assess robustness of the overall results. The results of the sensitivity analysis are shown in Table 3. The Begg's funnel plot does not show any asymmetry (Figure 3). Also, no publication bias was ascertained by Egger's test (*P* for Egger's test =0.231).

Discussion

Female hormones have long been considered to play a role in human disease. Many epidemiologic studies that evaluated the relationship between OCs use and RA have yielded conflicting results, with inverse and positive correlations reported. To clarify this issue, five system reviews or meta-analyses have been published between 1989 and 1996.[52–55,57] However, the results from previous meta-analysis remain

Table 1 Descriptive characteristics of 17 included studies of RA risk with OCs use

Study	Site	Age (years)	Cases, n	Control, n	Study design	Years of case diagnosis	OC assessment	RR with 95% CI (ever vs never)	Matching or adjustment
Vandenbroucke et al[7]	the Netherlands	25–56	228	302	HB	1963–1979	Questionnaire	0.42 (0.27–0.65)	Age, marital status, menopause status, date of diagnosis, outpatient clinic
del Junco et al[10]	USA	17–49	182	182	HB	1960–1983	Medical records	1.1 (0.7–1.7)	Age, age at first marriage, date of diagnosis
Darwish and Armenian[12]	Lebanon	30–70	100	100	HB	1970–1985	Questionnaire	1.29 (0.64–2.58)	Age
Hazes et al[14]	the Netherlands	20–50	135	378	HB	1982–1986	Interview	0.40 (0.23–0.66)	Age, marital status, age at symptom onset, age at menarche, pregnancy, menopausal status, smoking, drinking
Moskowitz et al[15]	USA	17–45	71	280	HB	1977–1986	Medical records	1.46 (0.80–2.68)	Age, pregnancy, date of diagnosis
Spector et al[16]	UK	35–70	270	245	PB	1986–1987	Questionnaire	0.60 (0.30–1.17)	Age, marital status, parity, age at menarche
Jorgensen et al[18]	France	25–84	176	145	HB	1994	Questionnaire	0.74 (0.52–1.08)	Age, breast feeding, parity
Brennan et al[21]	UK	16–70	115	115	PB	1994–1995	Questionnaire	0.88 (0.47–1.64)	Age, social class, parity, marital status
Doran et al[19]	USA	≥18	455	455	PB	1955–1994	Medical records	0.56 (0.34–0.92)	Age, smoking
Pedersen et al[20]	Denmark	18–65	366	478	PB	1998–2003	Interview	1.24 (0.91–1.71)	Age, age at onset of disease
Pikwer et al[22]	Sweden	44–74	136	544	PB	1991–1996	Questionnaire	1.03 (0.63–1.67)	Age
Berglin et al[23]	Sweden	23–73	70	280	PB	NA	Questionnaire	0.79 (0.45–1.38)	Age, residence
Cohort studies									
Study	**Site**	**Age (years)**	**Cases, n**	**Cohort, n**	**Follow-up**	**Years of recruitment**	**OC assessment**	**RR with 95% CI (ever vs never)**	**Matching or adjustment**
Vessey et al[24]	England, Scotland	25–39	78	17,032	12–15	1968–1974	Interview or Medical records	1.12 (0.79–1.79)	NA
Hannaford et al[25]	UK	≥16	283	46,000	1–20	1968–1969 (14 months)	Interview or Medical records	0.90 (0.71–1.14)	Parity, smoking, social class
Hernandez-Avila et al[26]	USA	30–55	217	116,799	8	1976–1984	Questionnaire	0.9 (0.6–1.4)	Age, follow-up cycle, age at menarche, parity, time since menopause, BMI
Merlino et al[4]	USA	55–69	158	31,366	1–10	1986	Questionnaire	1.00 (0.67–1.50)	Age
Karlson et al[27]	USA	30–55	674	121,700	Up to 2002	1976	Questionnaire	1.1 (0.9–1.3)	Age, smoking, BMI, age at menarche, age at first birth, breast-feeding, menstrual cycle regularity, parity, and PMH use

Abbreviations: BMI, body mass index; CI, confidence interval; HB, hospital-based case-control study; OC, oral contraceptive; PB, population-based case-control study; PMH, postmenopausal hormone; RA, rheumatoid arthritis; RR, relative risk; vs, versus; NA, not available.

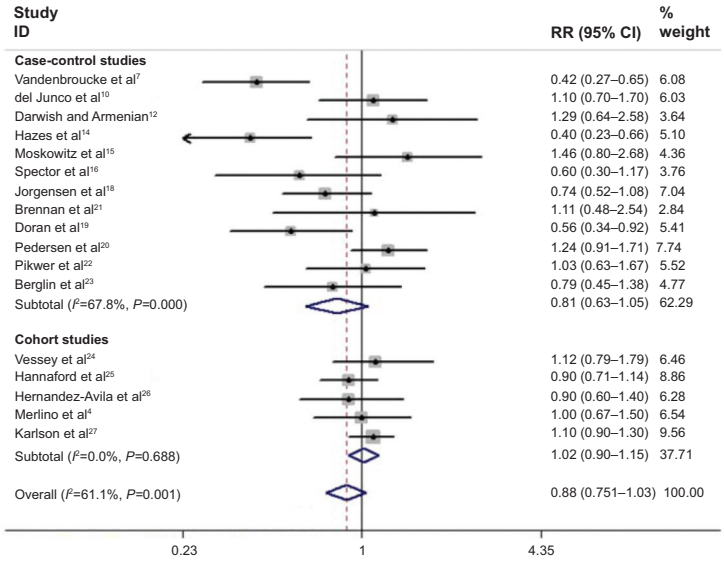

Figure 2 Forest plots of RA risk and OCs use.
Abbreviations: OC, oral contraceptive; RA, rheumatoid arthritis; RR, relative risk; CI, confidence interval.

Table 2 Subgroup analyses of RRs for the association between RA risk and OCs use

Group	Number of studies	Pooled RR (95% CI)	Heterogeneity	
			I^2	*P*
Overall	17	0.88 (0.75–1.03)	61.1%	0.001
Study design				
Case-control studies	12	0.81 (0.63–1.05)	67.8%	<0.001
Cohort studies	5	1.02 (0.90–1.15)	0.0%	0.688
Source of control				
PB	6	0.87 (0.65–1.17)	47.1%	0.093
HB	6	0.78 (0.51–1.18)	77.3%	0.001
Geographic area				
Europe	10	0.79 (0.62–1.01)	67.6%	0.001
North America	6	0.99 (0.81–1.21)	37.7%	0.155
Matching or adjustment factor				
Age				
Yes	15	0.86 (0.71–1.04)	65.2%	<0.001
No	2	0.95 (0.77–1.17)	0.0%	0.364
Smoking				
Yes	4	0.90 (0.72–1.14)	57.0%	0.073
No	13	0.88 (0.70–1.10)	64.1%	0.001
Parity or pregnancy				
Yes	8	0.86 (0.68–1.08)	62.3%	0.010
No	9	0.90 (0.70–1.16)	64.6%	0.004
Age at menarche				
Yes	4	0.74 (0.46–1.16)	79.5%	0.002
No	13	0.92 (0.76–1.10)	54.6%	0.009
Social class				
Yes	2	0.91 (0.73–1.15)	0.0%	0.635
No	15	0.87 (0.72–1.05)	65.8%	<0.001
BMI				
Yes	2	1.07 (0.90–1.25)	0.0%	0.394
No	15	0.85 (0.71–1.03)	61.8%	0.001
Marital status				
Yes	5	0.64 (0.40–1.02)	71.4%	0.007
No	12	0.98 (0.87–1.11)	24.9%	0.200

Abbreviations: BMI, body mass index; CI, confidence interval; HB, hospital-based case-control study; OC, oral contraceptive; PB, population-based case-control study; RA, rheumatoid arthritis; RR, relative risk.

Table 3 Results of sensitivity analysis for RA risk with OCs use

Study omitted	Pooled RR (95% CI)	Heterogeneity	
		I^2	*P*
Vandenbroucke et al[7]	0.93 (0.80–1.07)	46.5%	0.021
del Junco et al[10]	0.87 (0.73–1.03)	63.0%	<0.001
Darwish and Armenian[12]	0.87 (0.73–1.02)	62.7%	<0.001
Vessey et al[24]	0.86 (0.73–1.03)	62.7%	<0.001
Hazes et al[14]	0.92 (0.79–1.07)	51.7%	0.009
Hannaford et al[25]	0.87 (0.73–1.05)	63.5%	<0.001
Hernandez-Avila et al[26]	0.88 (0.74–1.04)	63.5%	<0.001
Moskowitz et al[15]	0.86 (0.73–1.01)	61.4%	0.001
Spector et al[16]	0.89 (0.76–1.05)	62.0%	0.001
Jorgensen et al[18]	0.89 (0.75–1.06)	62.1%	0.001
Brennan et al[21]	0.87 (0.74–1.03)	63.4%	<0.001
Merlino et al[4]	0.87 (0.73–1.04)	63.4%	<0.001
Doran et al[19]	0.90 (0.77–1.06)	59.5%	0.001
Karlson et al[27]	0.86 (0.71–1.02)	59.1%	0.001
Pedersen et al[20]	0.85 (0.72–1.01)	60.1%	0.001
Pikwer et al[22]	0.87 (0.73–1.03)	63.45%	<0.001
Berglin et al[23]	0.88 (0.74–1.05)	63.2%	<0.001

Abbreviations: CI, confidence interval; OC, oral contraceptive; RA, rheumatoid arthritis; RR, relative risk.

controversial. Romieu et al in their meta-analysis of nine case-control studies found no significant association between OCs use and RA risk (RR=0.79, 95% CI=0.58–1.08).[54] Spector and Hochberg reported that OCs use was associated with a decreased risk of RA (RR=0.73, 95% CI=0.61–0.85).[55] In 1996, Pladevall-Vila et al summarized the evidence of seven case-control and three cohort studies published before 1993.[57] The combined results showed that OCs use cannot decrease the risk of RA (RR=0.95, 95% CI=0.81–1.21).[57] Since 1993, more than ten original studies have proven or denied those findings.[17–34] Therefore, an updated meta-analysis was undertaken. Specifically, in our study, we (1) included the studies published to date, (2) excluded the overlapped data, (3) analyzed the variables (ie, study design, source of control, geographic area, and matching or adjustment factors) across studies, (4) investigated how the RA risk changed with the dose effect of duration of OCs use, and (5) conducted sensitivity analyses and publication bias.

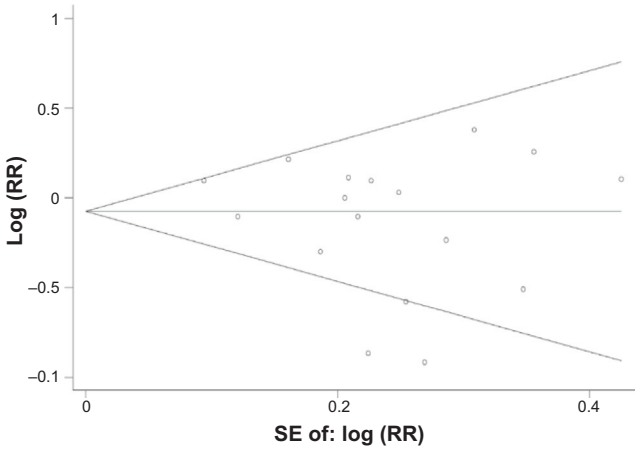

Figure 3 Begg's funnel plot (with pseudo 95% confidence limits) analysis to detect publication bias.
Abbreviations: RR, relative risk; SE, standard error.

Our current meta-analysis of 12 case-control and five cohort studies suggested that use of OCs was not significantly associated with RA risk. The association was not significantly affected by study design, source of control, or matching/adjustment factors. However, subgroup meta-analyses of geographic area based on limited numbers of studies indicated that compared with nonusers, a decreased risk of borderline significance was observed for OCs users in European studies, but this association did not emerge in the North American studies group.

Another problematic OCs variable (ie, current use) has been evaluated by three case-control and two cohort studies.[7,15,21,24,26] All studies showed that there was a nonsignificant increase or decrease in RA risk emerged except in one hospital-based case-control study with 228 cases and 302 controls.[7] Vandenbroucke et al found a 55% reduction in RA risk among current users. However, the number of current users was small, and we cannot exclude the possibility that the finding, of a significant decreased risk for RA among current users, is a chance finding and should be interpreted with caution. Given that "current use" measures different time points with respect to the date of diagnosis (or date of interview for controls) in case-control versus prospective cohort studies, risk estimates of this variable cannot be pooled across study designs.

Heterogeneity is often a concern in a meta-analysis. In our meta-analysis, evidence of substantial heterogeneity across studies of the associations of OCs use with RA risk was observed. This finding was consistent with a previous meta-analysis published in 1996, which showed that the source of controls was the most important characteristic in accounting for the strong heterogeneity.[57] In our subgroup analyses by study design and source of controls, no significant heterogeneity was detected in cohort (I^2=0.0%) or population-based case-control studies (I^2=47.1%), but substantial heterogeneity was observed in hospital-based case-control studies (I^2=77.3%). In hospital-based case-control studies, the choice of control populations differed markedly. The controls were women with a diagnosis of soft tissue rheumatism (bursitis, tenosynovitis, shoulder-hand syndrome, carpal tunnel

syndrome, low back pain, etc) or osteoarthritis (localized to knee, hip, or vertebrae) recruited from outpatient clinics of university hospitals or private clinics. Moreover, the included studies were conducted in different countries, where people may share little in terms of genetic background, lifestyles, and RA incidence. Thus, the characteristics of subjects and study design likely contributed to the observed heterogeneity.

To evaluate the effect of exposure duration, short-term use of OCs was defined as duration of <5 years, and long-term use as duration of ≥5 years. We found that no significant reduction in RA risk was associated with short-term or long-term use. Moreover, the relationship between dose of OCs use and RA risk has been addressed in a hospital-based case-control study with 135 cases and 378 controls.[14] Hazes et al defined the use of low-dose OCs as dose of <0.05 mg estrogen and high dose as dose of ≥0.05 mg estrogen, and found that the dose did not moderate the RR estimates. Evaluation of dose effect lends support for a causality of an association between exposure and disease, therefore, further investigation of OCs use with RA risk is needed with particular attention to duration and dose of OCs use.

Potential limitations of the present meta-analysis need to be addressed. First, because our analysis was mainly based on retrospective case-control studies, the observed null association may be masked by the recall and select biases originating from primary studies. Moreover, unmeasured or residual confounding is always a subject of major concern in observational studies. Although the results of subgroup analyses showed that the relationship between OCs use and RA risk was not influenced by the confounders such as age, smoking, parity/pregnancy, age at menarche, BMI, social class, or marital status, the likelihood that our finding resulted from other unmeasured confounders cannot be excluded. Second, we were unable to evaluate the components of OCs with RA risk. During the 1980s, OCs markedly differed from the ones used later on, eg, low estrogen, triphasic.[60] Therefore, the formulation of OCs with RA risk remains open to discussion. Third, the RA case identification was based on different diagnosis criteria. Both 1958 American College of Rheumatology (ACR) and 1987 ACR criteria for RA were adopted in included studies. Thus, misclassification of subjects was possible and the relationship between OCs use and RA risk may be underestimated or overestimated. Furthermore, nowadays, RA classification criteria are updated by 2010 ACR classification criteria. Further evaluation of the relationship between OCs use and RA risk should adopt the new ACR classification criteria. Finally, publication bias could be a problem because studies with null effects are less likely to be published than those providing statistically significant results. Although no evidence of publication bias was detected by Egger's test and Begg's funnel plots in our meta-analysis, the estimation may not be accurate enough as the number of the included studies is relatively small.

In summary, findings of the present meta-analysis of 17 observational studies indicate that OC use cannot reduce the risk of RA. Yet, many questions still need to be addressed. Further large-scale prospective studies with emphasis on strict case definition based on the 2010 ACR classification criteria, formulation of OCs, duration of OCs use, dose of OCs use, and confounders are warranted to validate our findings.

Disclosure

The authors report no conflicts of interest in this work.

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