The Effect of Oral Contraceptives and Estrogen Replacement Therapy on the Risk of Rheumatoid Arthritis: A Population Based Study

MICHELE F. DORAN, CYNTHIA S. CROWSON, W. MICHAEL O'FALLON, and SHERINE E. GABRIEL

ABSTRACT. ***Objective.*** Epidemiologic evidence for a protective effect of exogenous female sex hormones on the development of rheumatoid arthritis (RA) is contradictory. We examined whether exposure to either oral contraceptives (OC) or postmenopausal estrogen replacement therapy (ERT) is associated with the development of RA in women.

Methods. We separately examined the relationship between use of OC and ERT on the risk of RA in a population based case-control study. Case patients, including all female residents of Rochester, Minnesota, ≥ 18 years of age, who first fulfilled 1987 American College of Rheumatology criteria for RA between 1955 and 1994 (n = 445), were compared with age matched female controls from the community. Multivariable conditional logistic regression models were used to determine whether OC or ERT exposure had an effect on RA development after controlling for potential confounders.

Results. We observed an inverse association between ever-use of OC and the risk of RA, which persisted after adjusting for potential confounders in multivariate analyses (OR 0.56, 95% CI 0.34, 0.92). Earlier calendar-year of first exposure to OC was associated with lower OR for RA. We found no evidence of a significant association of ERT with RA risk (adjusted OR 1.11, 95% CI 0.69, 1.78).

Conclusion. Exposure to OC, but not ERT, significantly reduces the risk of development of RA. The risk of developing RA is lower when OC exposure occurred in earlier years, which suggests that the higher doses of estrogens and progestins contained in earlier OC preparations may have a stronger protective effect against developing RA. While this protective effect is strong, it only explains a small portion of the observed decrease in RA incidence over the past few decades because the proportion of Rochester women exposed to OC is quite small. (J Rheumatol 2004;31:207–13)

Key Indexing Terms:
ORAL CONTRACEPTIVES ESTROGEN REPLACEMENT THERAPY
RHEUMATOID ARTHRITIS

Observational and epidemiologic evidence suggests that sex hormones may play a role in the etiology and course of rheumatoid arthritis (RA). First, there is the recognized female preponderance among individuals with RA. Second, such a role is suggested by the documented reduction in both incidence and disease activity in RA during pregnancy[1]. Third, an increased risk of RA development and of disease exacerbations in the postpartum period has been reported[2]. Fourth, nulliparity has been found to be a risk factor for RA development in some studies[3,4]. Finally, both men and women with RA have been shown to have reduced testosterone concentrations[5,6], further supporting the evidence for a role for gonadal hormones in the etiology of RA.

Given the suggested role of endogenous sex hormones in RA, it is possible that exposure to preparations containing exogenous gonadal hormones, such as oral contraceptives (OC) or estrogen replacement therapy (ERT), may also influence RA development. A number of epidemiological investigations investigated whether exogenous estrogens in the form of OC have a protective effect on RA development, with conflicting results (Figure 1)[2,7-23]. A smaller number of studies that examined the risk of RA development in women who used postmenopausal ERT were also inconclusive (Figure 2)[13,24-27]. Methodological issues and biases inherent in these studies have been blamed for these disparate results[18,28]. It thus remains unclear whether exposure to exogenous gonadal hormones, through either OC or ERT, decreases the risk of RA.

We investigated whether exposure to either OC or ERT is associated with the development of RA. We separately examined the relationship between use of OC and of ERT on risk of RA in a retrospective population based matched case-

From the Department of Rheumatology, Mater Misericordiae University Hospital, Dublin, Ireland; and the Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota, USA.

Supported in part by a grant from the Immunex Corporation and the National Institutes of Health (AR-30582), US Public Health Service.

M.F. Doran, MB, MRCPI, Department of Rheumatology, Mater Misericordiae University Hospital; C.S. Crowson, BS; W.M. O'Fallon, PhD; S.E. Gabriel, MD, MSc, Department of Health Sciences Research, Mayo Clinic.

Address reprint requests to Dr. S.E. Gabriel, Department of Health Sciences Research, Mayo Clinic, 200 First Street SW, Rochester, MN 55905. E-mail: gabriel.sherine@mayo.edu

Submitted February 10, 2003; revision accepted July 22, 2003.

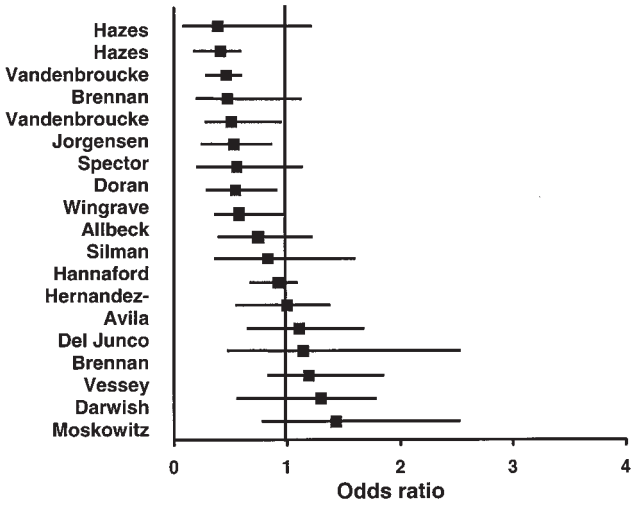

Figure 1. Results of studies that investigated OC use and RA.

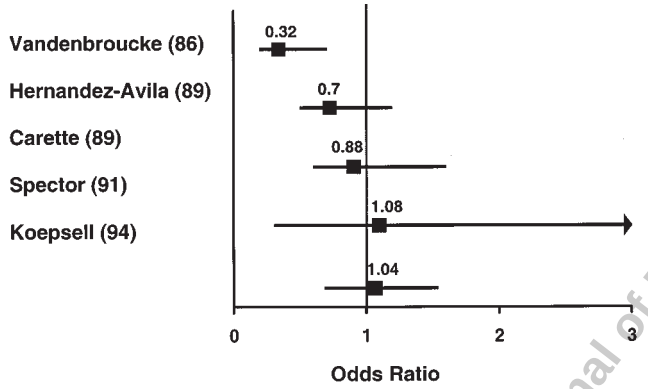

Figure 2. Results of studies that have investigated ERT use and RA.

control study specifically designed to overcome many of the methodological limitations of previous studies. Such limitations include differences in the populations sampled and in case ascertainment, lack of information regarding doses used in OC and ERT preparations, and referral, response, recall and protopathic biases. We also examined whether the reported decline in RA incidence in women might be explained by the increasing frequency of OC use in the community.

MATERIALS AND METHODS

Epidemiologic research in Rochester, Minnesota, is possible because of its relative geographical isolation from other urban centers and because nearly all medical care is delivered to local residents by a small number of providers. Each provider uses a comprehensive medical record system, whereby all data collected on an individual are assembled in one data resource. The Rochester Epidemiology Project, a diagnostic indexing and medical records-linkage system that exists at the Mayo Clinic, affords access to medical records from all sources of care for community residents. The potential of this data retrieval system for population based studies has been described[29,30]. This study was approved by the Mayo Clinic Institutional Review Board.

Identification of cases and controls. As cases, we included all female members of a population based inception cohort[31,32]. This cohort comprised all residents of Rochester, Minnesota, ≥ 18 years of age, who first fulfilled 1987 American College of Rheumatology (ACR) criteria for RA between 1955 and 1994[33]. To identify these cases, all potential cases of RA were identified by searching the computerized diagnostic index of the Rochester Epidemiology Project for any diagnosis of arthritis (excluding degenerative arthritis or osteoarthritis) made any time between January 1, 1955, and December 31, 1994, among Rochester residents ≥ 18 years of age. The index date assigned to each case was the first date of RA diagnosis according to the ACR criteria. To select controls, each case was individually matched to one randomly selected Rochester resident with no diagnosis of inflammatory arthritis, of the same age (± 3 yrs) and sex, and who had a similar length of enrollment (± 1 yr) in the records-linkage system. This ensured that controls had a similar duration of contact with the system prior to incidence date to that of cases, and were thus matched with the RA patients by calendar year. Controls were assigned an index date corresponding to that of their matched case.

We chose the 1:1 case:control ratio on the basis of an a priori power estimate. Given our sample size of 445 case-control pairs, and expected rates of OC and ERT use in the community[34,35], we calculated that we would have 80% power to detect a 50% reduction in risk of developing RA.

Data collection. Data were collected according to a prespecified and pretested detailed protocol. The entire (inpatient and outpatient) community medical records were reviewed for the period prior to the incidence/index date of the cases and controls, respectively, using a pretested data collection form. Confirmation of the diagnosis of RA was based on fulfillment of 4 of the 7 ACR criteria. The study team, including 3 trained nurse abstractors, the principal investigator (MFD), and coinvestigator (SEG) met weekly throughout the abstraction period to ensure accuracy and consistency in data collection, interpretation of definitions, and application of study criteria. Reliability testing was carried out at the outset of the abstraction process, and again at a point midway through the data collection, where a sample of medical records was reviewed by all abstractors to ensure good interobserver and intraobserver agreement. After data abstraction for all study subjects, we performed an extensive series of checks for data consistency, proper sequences of dates, and an evaluation of missing or incomplete data. Where necessary, medical records were reviewed again, and questions were resolved at team meetings.

OC use was defined as any medical record documentation of prescription of combined (containing both estrogen and progestin) OC in premenopausal women before the index date. ERT exposure was defined as commencement of any form of oral or transdermal ERT in a postmenopausal woman before index date. Data on topical estrogen preparations was not collected.

Information on form, dose, and duration of OC/ERT use was collected from the medical records, as were details regarding several potential confounders. Cigarette smoking was classified as ever or never before index date. Menopausal status (pre- or postmenopausal) was determined for cases and controls at their index dates. Menopause was defined as not having had menstrual periods for 6 months before the index date in the absence of pregnancy. Surgical menopause was defined as having had either a bilateral oophorectomy or a pelvic radium treatment before the index date. Age at onset of menstruation and other reproductive variables including gravidity, parity, numbers of stillbirths and miscarriages, and age at first pregnancy were recorded. Height and weight closest to incidence/index date were also recorded to enable estimation of body mass index (BMI).

Data analysis. Univariate conditional logistic regression models were used to investigate the roles of potential confounders. These potential confounders included BMI, smoking status, marital and menopausal status at index date, nulliparity, and history of surgical menopause prior to index date (Table 1). For each case-control comparison, an odds ratio (OR) and 95% confidence interval (CI) were calculated. Any potential confounder with missing data (e.g., smoking status) was also tested using logistic

Table 1. General characteristics at baseline of RA patients and non-RA controls.

Characteristic	Cases		Controls		
	Missing Values	Mean (SD) or N (%)	Missing Values	Mean (SD) or N (%)	OR (95% CI)
Age at index date, mean (SD) yrs	0	57.5 (15.5)	0	57.7 (15.5)	NA*
Length of medical history prior to index date, yrs, mean (SD)	0	27.1 (17.0)	0	27.0 (17.1)	1.00 (0.98, 1.03)
BMI, mean (SD)	3	25.3 (5.0)	2	25.8 (5.0)	0.98 (0.96, 1.01)
Married prior to index date, n (%)	0	376 (84.5)	2	382 (86.2)	0.84 (0.55, 1.27)
Smoker, n (%)	30	185 (44.6)	17	156 (36.5)	1.43 (1.06, 1.93)
Postmenopausal at index date, n (%)	1	307 (69.1)	1	308 (69.4)	0.95 (0.52, 1.76)
Nulliparous, n (%)	3	117 (26.5)	2	103 (23.2)	1.23 (0.89, 1.72)
Surgical menopause prior to index date, n (%)	21	29 (6.8)	10	42 (9.7)	0.65 (0.39, 1.08)

* Odds ratio not computed because age was a matching variable for controls.

regression on unmatched pairs to verify that that elimination of matched pairs with missing data did not bias the results. For the 2 primary analyses, we defined exposure as any documentation of use of OC or ERT prior to incidence date. Similar analyses for OC or ERT exposure for at least 6 months' duration and for current OC or ERT exposure at index date were also performed.

The backwards stepwise selection procedure was used to define a best multivariable conditional logistic regression model of potential confounding covariates, adjusting for the influence of age. OC and ERT exposure were then added to the best model of confounders to determine whether they had an effect on RA development. Interactions between covariates and with other measures of OC/ERT use (such as total duration of therapy, time from first use to index date, date of first use, and current compared to past or never use on index date) were investigated. For each model, an estimate of the OR for each exposure and for covariates was obtained along with 95% CI for the estimate. All tests were 2-sided and a result was considered statistically significant if the p value was less than 0.05. We also examined whether the OC exposure had a different effect on the development of rheumatoid factor (RF) positive (as compared to RF negative) RA.

The effect of calendar year of initial OC exposure was assessed by calculating for selected time points, t, the OR and 95% CI for patients exposed prior to time t compared with never users, adjusting for patients exposed after time t.

Estimates of population attributable-risk (AR) were obtained using the formula established by Miettinen[36] commonly used for case-control studies. The formula is AR = P(FID)*(OR – 1)/OR, where P(FID) is the prevalence of the risk factor among those with the disease and OR is the odds ratio for the risk factor. Since OC exposure is a protective factor and the AR formula requires a risk factor, the OR used in this analysis is the conditional logistic regression OR associated with a lack of OC exposure. Similarly, P(FID) is the prevalence of no OC exposure in the cases. Bootstrap sampling was used to estimate CI for attributable risk estimates.

RESULTS

The study population consisted of 445 RA cases and 445 age matched female Rochester residents without RA. The general characteristics of cases and controls at baseline are shown in Table 1. Marital status, mean BMI, and mean duration of medical history within the system were similar among cases and controls. Cases were significantly more likely than controls to have been cigarette smokers (OR 1.43, 95% CI 1.06, 1.93, p = 0.02).

Of those women exposed to OC before index date, a somewhat higher proportion of controls than cases had been exposed in the 1960s (51.4% controls vs 38.8% cases). The date of first documented OC exposure in a study subject was April, 1961. When we examined exposure to low, medium, and high doses of estrogen, defined as < 0.05 mg, 0.05 mg, and > 0.05 mg, respectively, exposure to high dose OC was twice as common in controls than in cases (26.6% controls vs 13.3% cases). Among women who took postmenopausal estrogens, and for whom type and dosage information was available, the most common preparation was oral conjugated equine estrogens (68% cases, 63% controls). A further 23% of cases and 26% of controls were exposed to stilboestrol. Transdermal estrogen (patches) was rarely used (0 cases, 2 controls). The majority of women receiving ERT were prescribed unopposed estrogen therapy without concomitant progestins (82% cases and 78% controls).

Univariate analyses showed a statistically significant protective association between ever-use of OC and the risk of RA, where 50 cases and 70 controls were exposed to OC (OR 0.57, 95% CI 0.35, 0.91) (Table 2). Examining only women with more than 6 months of OC revealed nearly identical results. We did not observe an association between current OC use and RA development (OR 1.0, 95% CI 0.4, 2.52), but this analysis included only 10 cases and 10 controls receiving OC at index date. Earlier calendar year of first OC exposure, if exposure occurred in the first 10 years following introduction of OC, was associated with still lower OR for later RA development (Figure 3).

Adjusting for age and smoking status, OC exposure remained a significant predictor of RA development in multivariable models (OR 0.56, 95% CI 0.34, 0.92). When further adjusted for ERT use in addition to these variables, the OR for OC exposure was unchanged. The protective effect of OC exposure on the development of RF positive (compared to RF negative) RA was more pronounced (OR 0.36, 95% CI 0.18, 0.72) than the effect of OC exposure on RF negative RA (OR 0.982, 95% CI 0.46, 2.10), although not quite statistically significant (p = 0.06).

A significant association between ERT exposure and RA development was not observed (OR 1.26, 95% CI 0.81,

Table 2. Univariate analyses* of oral contraceptive (OC) and estrogen replacement therapy (ERT) exposures among 445 RA patients and 445 non-RA controls.

Characteristic	Cases, n (%)	Controls, n (%)	Odds Ratio (95% CI)	p
OC exposure, ever use	50 (11.2)	70 (15.7)	0.57 (0.35, 0.91)	0.02
OC exposure, > 6 mo	46 (10.3)	66 (14.8)	0.56 (0.34, 0.91)	0.02
OC exposure, current at RA incidence	10 (2.2)	10 (2.2)	1.00 (0.40, 2.52)	1.00
ERT exposure, any duration	55 (12.4)	46 (10.3)	1.26 (0.81, 1.96)	0.31
ERT exposure, > 6 mo	52 (11.7)	39 (8.8)	1.42 (0.90, 2.25)	0.14
ERT exposure, current at RA incidence	22 (4.9)	14 (1.67)	1.67 (0.81, 3.41)	0.16

* Cases and controls were matched on age and calendar year.

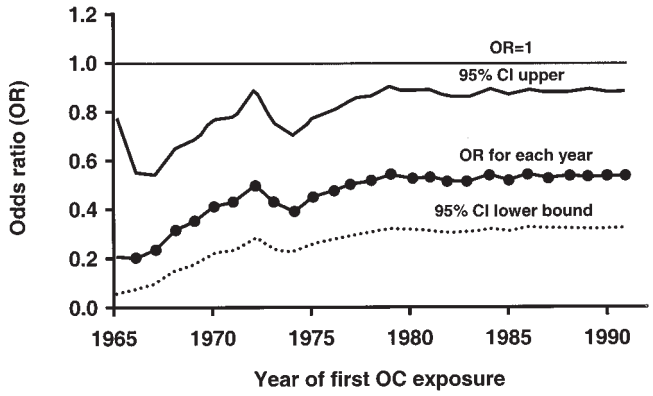

Figure 3. Risk of development of RA according to calendar year of first exposure to oral contraceptives.

1.96) (Table 2), including separate analyses for women with at least 6 months of exposure and current ERT users at index date. However, there is a suggestion of a possible protective effect, particularly in the subjects with > 6 months exposure (OR 1.42, 95% CI 0.90, 2.25) and those exposed at time of RA incidence (OR 1.67, 95% CI 0.81, 3.41). Exclusion of women who first commenced ERT after initial onset of RA symptoms, but before index date, did not change the observed result (OR 1.17, 95% CI 0.75, 1.84). When only women with nonsurgical menopause were included in a subanalysis, the absence of a significant effect persisted (OR 1.36, 95% CI 0.81, 2.28).

Multivariable modeling with adjustment for age, smoking status, and OC use did not change the OR for ERT use significantly (OR 1.11, 95% CI 0.69, 1.78).

To quantify the influence of OC exposure on the decline in RA incidence in the population, population attributable-risk (AR) estimates were computed. This estimate is based on the OR for nonexposure to OC as a risk factor (1/0.57 = 1.77) and the prevalence of no OC exposure among the RA cases (89%). The estimated AR for any exposure to OC is 38.6% (95% CI 13.5%, 63.6%). In other words, if the entire female population (age ≥ 18) of Rochester had OC exposure, the number of women in the population who develop RA would drop by roughly 38.6%. While the proportion of Rochester women exposed to OC has increased over time, it is still quite small. Only 1% of the RA cases diagnosed from 1955 to 1969 were exposed to OC prior to diagnosis, while 26% of the RA cases diagnosed in 1985 to 1994 had OC exposure. The prevalence of OC exposure among the controls was similar (2% in 1955 to 1969 and 35% in 1985 to 1994). Based on the protective effect of OC exposure, we would expect that this increase in exposure would lead to a decrease in the number of women in the population diagnosed with RA. If the amount of OC exposure had remained constant over time, then using our estimated attributable risk, we estimate an additional 18 cases of RA in our population in the 1985 to 1994 time period. These additional cases would have increased the incidence from 40/100,000, as reported[31], to 48/100,000. The majority of the decrease in incidence from an incidence of 72/100,000 to the estimated 48/100,000 is still unaccounted for. Therefore, the protective effect of OC exposure on the development of RA can only explain a small portion of the dramatic decrease in RA incidence over the past few decades.

DISCUSSION

This study found an inverse association between OC exposure and development of RA, such that women experience a 44% reduction in the risk for RA following OC exposure, after controlling for potential confounders (OR 0.56, 95% CI 0.34, 0.92). Exposure to OC in earlier calendar years, when higher doses of estrogen and progestins were used in the formulations, is associated with a further lowering of risk, such that women who received OC prior to 1970 have only one-quarter the risk of unexposed women. We did not find a similar reduction in risk for postmenopausal use of ERT.

In addition to its etiologic interest, the question addressed here is of potential public health importance as OC and ERT are now widely used in the community. Rates for OC use of up to 80% of women born since 1945 have been reported[35], and rates for ERT range from 12% to 32% in population surveys in the United States[34]. The incidence of RA in the population has been reported to be decreasing in a number

of epidemiologic studies, and this decline appears to be more marked in women than in men[31,37-39]. To determine how much of the observed decline in RA incidence in women can be attributed to increasing use of OC, we calculated attributable risks and found that a protective effect of OC exposure on the development of RA can only explain a small portion of the dramatic decrease in RA incidence over the past few decades.

Studies examining the risk of RA following exposure to OC and ERT have yielded disparate results. In the case of studies examining OC use, 14 case-control studies and 4 cohort studies have been published (Figure 1). Our findings concur with those of 4 of these case-control studies, which found a significant protective effect for ever-use of OC, with risk ratios ranging from 0.37 to 0.6[10,13,20,23]. Three further case-control studies found a suggestion of a protective effect, but did not reach statistical significance[12,19,21]. Contrasting results are reported, however, from other case-control studies, including 2 earlier studies performed at this center[11,15]. Of the 4 cohort studies examining this question, only one found a protective effect for OC use on RA development[8]. Our findings concur with the majority of studies examining ERT and RA in not finding a protective effect[13,24-27](Figure 2).

There are a number of possible reasons for these discrepant results, many of which relate to methodological challenges and potential biases inherent in these studies[18,28]. We sought to overcome most of these biases to clarify this issue.

The first of these relates to the population sampled in the various studies. We included all incident cases of RA in a geographically defined region and selected controls randomly from the population. Most previous case-control studies were hospital based and may have been affected by referral and/or incidence-prevalence bias. The subjects for the cohort studies were recruited from a contraceptive clinic in one case[9], general practitioners in 2 cases[8,17], and from the Nurses Health Study in the other[25]. All the women included in these studies were married, and may not be representative of the general population.

The second possible limitation of previous studies relates to case ascertainment. Of the cohort studies, 2 relied principally on self-report of RA diagnosis[9,25], and the criteria used in the other case-control and cohort studies for RA were variable. The different composition of RA cases in older studies, compared to ours, where the 1987 ACR criteria for RA were used, may explain some of the conflicting results in these studies. For ascertainment of exposure, previous case-control studies largely relied on questionnaire or interview techniques, which can predispose to both recall and response biases. In our study, exposure information was obtained through review of each subject's complete (inpatient and outpatient) medical history, including medical record data from all healthcare providers, avoiding these potential biases.

Two further methodological issues that may explain the conflicting results of the 5 studies that examined the question of ERT and RA relate to women who underwent surgical menopause and protopathic bias. Since women who undergo surgical menopause at an earlier age are subject to reduced endogenous estrogen exposure, and are also very likely to receive treatment with replacement hormones, a true association between ERT and RA could be masked. We examined this possibility by excluding those women with surgical menopause in a subanalysis. While the resulting odds ratio (OR 1.36, 95% CI 0.81, 2.28) increased slightly, it remained statistically insignificant. Protopathic bias could occur if physicians were to prescribe ERT for menopausal women with musculoskeletal symptoms and those symptoms eventually turned out to be an early manifestation of RA rather than symptoms of menopause. If ERT were commenced during the time between onset of musculoskeletal symptoms and actual RA incidence date, RA cases would be more likely to be prescribed ERT than controls and a true association could thus be obscured. For this reason, we performed the analysis excluding all study cases with any documented musculoskeletal symptoms and their matched controls. The result was unchanged (OR 1.17, 95% CI 0.75, 1.84).

Our findings concur with those of most previous case-control studies examining OC use in revealing an important and statistically significant protective effect for OC use on RA risk. However, in the case of ERT, the weight of the available evidence is against such a protective effect. There are several plausible biological reasons for these apparently conflicting findings.

It has been suggested, on the basis of laboratory evidence, that the reported immunomodulatory effects of estrogen are dose-related, where lower physiological doses have immunostimulatory effects, and high doses are immunosuppressive[40]. This could explain our finding of a stronger protective effect in earlier years following the introduction of OC, as OC contained considerably higher doses of estrogen at that time[41]. It would also explain the lack of protection from ERT, as most estrogen supplements used for postmenopausal replacement have less than one-sixth the potency of low dose OC[42].

Another possible explanation for the protective effect of OC (in contrast to ERT) is that it is not the estrogen, but rather the progestin component of the OC, that exerts the protective effect. Progesterone has been shown to have immunosuppressive effects *in vivo*[43]. It has been suggested that the elevated concentration of progesterone during pregnancy is, in part, responsible for the immunosuppression necessary to prevent fetal homograft rejection[43]. A possible protective effect afforded by progestins in OC preparations could also relate to their androgenic effects. Androgens are thought to have a number of immunosuppressive effects[40], and both men and women with RA have been shown to have

lower serum levels of androgens, suggesting that androgens may protect against RA[5,6,44,45]. Since the majority of women prescribed ERT in this study did not receive concomitant progestins (82% cases, 78% controls), such a protective effect of progesterone could help explain why we found that OC preparations, all of which contain a progestin component, are protective. Our finding of even greater protection for women exposed during the initial years after introduction of OC would also support this theory, as progestin doses contained in OC preparations were at least 10-fold higher prior to 1970[41].

It should also be noted, when considering explanations for a protective effect of OC but not for ERT, that these are very different types of preparations with different biological effects. They are generally prescribed for very different reasons and are used at different times in life. It has been speculated that aspects of behavior associated with OC use, such as smoking, pregnancy, and recurrent genital tract infections, may confer a higher risk of RA[4,20,46]. In this study, the protective effect of OC remained unchanged even after controlling for smoking and pregnancies.

One potential limitation of this study is that the data on OC and ERT routinely documented in medical records may be incomplete. Incomplete documentation regarding exposure can lead to bias if such documentation errors were different in cases compared to controls (better documentation in cases, for example). However, the exposures of interest were those occurring before the development of RA, and were recorded prospectively in the medical record without knowledge of subsequent disease outcome. Thus, there is no reason to believe that documentation would be differential in cases compared to controls. Ascertainment for the variables of interest was generally excellent (Table 1) and the number of missing data elements was likely too small to cause significant confounding.

Another potential study limitation was incomplete blinding of the data collection. It was not possible to keep the abstractors unaware of the case or control status of the study subjects. However, with the exception of the principal investigator (MFD), who abstracted only a minority of cases, the abstractors were not aware of the hypotheses being tested, and reliability testing revealed no differences in data collection patterns among abstractors. We did not have information regarding other possible confounding factors, such as socioeconomic status and education level, which may be important. Finally, some racial and ethnic groups are underrepresented in Rochester, MN, where the population was 96% white in 1990 (US census data). Thus, the results of our population based study are not necessarily generalizable to the entire US population.

Evidence from observational studies regarding the influence of OC and ERT on the risk of RA has been controversial. Our study, the design of which minimized many of the biases of previous case-control studies that examined this question, finds evidence for a strong protective effect of OC exposure on the development of RA. However, this effect does not appear to explain the declining incidence of RA in women. Our findings are consistent with most of the evidence regarding ERT use, which fails to find a similar protective effect. Further research, including both clinical studies and laboratory studies in the field of immunoendocrinology, may help to explain the complex relationship between estrogen, progestins, and RA.

ACKNOWLEDGMENT

Thanks to Denise Herman, RN, Deanne Stiebner, RN, and Patricia Hartkopf, RN for their work on data abstraction for this study, and Deborah Fogarty for assistance in the preparation of the manuscript.

REFERENCES

1. Da Silva JA, Spector TD. The role of pregnancy in the course and aetiology of rheumatoid arthritis. Clin Rheumatol 1992;11:189-94.
2. Silman A, Kay A, Brennan P. Timing of pregnancy in relation to the onset of rheumatoid arthritis. Arthritis Rheum 1992;35:152-5.
3. Hazes J, Dijkmans B, Vandenbroucke J, de Vries R, Cats A. Pregnancy and the risk of developing rheumatoid arthritis. Arthritis Rheum 1990;33:1770-5.
4. Spector TD, Roman E, Silman AJ. The pill, parity, and rheumatoid arthritis. Arthritis Rheum 1990;33:782-9.
5. Cutolo M, Balleari E, Giusti M, Monachesi M, Accardo S. Sex hormone status of male patients with rheumatoid arthritis: evidence of low serum concentrations of testosterone at baseline and after human chorionic gonadotropin stimulation. Arthritis Rheum 1988;31:1314-7.
6. Masi AT, Chatterton RT, Comstock GW, Malamet RL, Kochberg MC. Decreased serum dehydroepiandrosterone sulphate (DHEAS) levels before onset of RA in younger, premenopausal women: a controlled, prospective study [abstract]. Arthritis Rheum 1994;37 Suppl:S315.
7. Moskowitz MA, Jick SS, Burnside S, et al. The relationship of oral contraceptive use to rheumatoid arthritis. Epidemiology 1990;1:153-6.
8. Wingrave SJ, Kay CR. Reduction in incidence of rheumatoid arthritis associated with oral contraceptives. Lancet 1978;2:569-71.
9. Vessey MP, Villard-Mackintosh L, Yeates D. Oral contraceptives, cigarette smoking and other factors in relation to arthritis. Contraception 1987;35:457-64.
10. Vandenbroucke JP, Valkenburg HA, Boersma JW, et al. Oral contraceptives and rheumatoid arthritis: further evidence for a preventive effect. Lancet 1982;2:839-42.
11. Linos A, Worthington JW, O'Fallon WM, Kurland LT. Case-control study of rheumatoid arthritis and prior use of oral contraceptives. Lancet 1983;1:1299-300.
12. Allebeck P, Ahlbom A, Ljungstrom K, Allander E. Do oral contraceptives reduce the incidence of rheumatoid arthritis? A pilot study using the Stockholm County medical information system. Scand J Rheumatol 1984;13:140-6.
13. Vandenbroucke JP, Witteman JC, Valkenburg HA, et al. Noncontraceptive hormones and rheumatoid arthritis in perimenopausal and postmenopausal women. JAMA 1986;255:1299-303.
14. Darwish MJ, Armenian HK. A case-control study of rheumatoid arthritis in Lebanon. Int J Epidemiol 1987;16:420-4.
15. del Junco DJ, Annegers JF, Luthra HS, Coulam CB, Kurland LT. Do oral contraceptives prevent rheumatoid arthritis? JAMA 1985;254:1938-41.

16. Hernandez-Avila M, Liang MH, Willett WC, et al. Exogenous sex hormones and the risk of rheumatoid arthritis. Arthritis Rheum 1990;33:947-53.
17. Hannaford PC, Kay CR, Hirsch S. Oral contraceptives and rheumatoid arthritis: new data from the Royal College of General Practitioners' oral contraception study. Ann Rheum Dis 1990;49:744-6.
18. Spector TD, Hochberg MC. The protective effect of the oral contraceptive pill on rheumatoid arthritis: an overview of the analytic epidemiological studies using meta-analysis. J Clin Epidemiol 1990;43:1221-30.
19. Hazes J, Silman A, Brand R, Spector TD, Walker DJ, Vandenbroucke J. Influence of oral contraception on the occurrence of rheumatoid arthritis in female sibs. Scand J Rheumatol 1990;19:306-10.
20. Hazes JM, Dijkmans BC, Vandenbroucke JP, de Vries RR, Cats A. Reduction of the risk of rheumatoid arthritis among women who take oral contraceptives. Arthritis Rheum 1990;33:173-9.
21. Brennan P, Silman A. An investigation of gene-environment in the etiology of rheumatoid arthritis. Am J Epidemiol 1994;140:453-60.
22. Brennan P, Bankhead C, Silman A, Symmons D. Oral contraceptives and rheumatoid arthritis: results from a primary care-based incident case-control study. Semin Arthritis Rheum 1997;26:817-23.
23. Jorgensen C, Picot MC, Bologna C, Sany J. Oral contraception, parity, breast feeding, and severity of rheumatoid arthritis. Ann Rheum Dis 1996;55:94-8.
24. Koepsell TD, Dugowson CE, Nelson JL, Voigt LF, Daling JR. Non-contraceptive hormones and the risk of rheumatoid arthritis in menopausal women. Int J Epidemiol 1994;23:1248-55.
25. Hernandez-Avila M, Liang MH, Willett WC, et al. Oral contraceptives, replacement oestrogens and the risk of rheumatoid arthritis. Br J Rheumatol 1989;28 Suppl 1:31;discussion 42-5.
26. Spector TD, Brennan P, Harris P, Studd JW, Silman AJ. Does estrogen replacement therapy protect against rheumatoid arthritis? J Rheumatol 1991;18:1473-6.
27. Carette S, Marcoux S, Gingras S. Postmenopausal hormones and the incidence of rheumatoid arthritis. J Rheumatol 1989;16:911-3.
28. Pladevall-Vila M, Delclos GL, Varas C, Guyer H, Brugues-Tarradellas J, Anglada-Arisa A. Controversy of oral contraceptives and risk of rheumatoid arthritis: meta-analysis of conflicting studies and review of conflicting meta-analyses with special emphasis on analysis of heterogeneity. Am J Epidemiol 1996;144:1-14.
29. Kurland LT, Molgaard CA. The patient record in epidemiology. Sci Am 1981;245:54-63.
30. Melton LJ 3rd. History of the Rochester Epidemiology Project. Mayo Clin Proc 1996;71:266-74.
31. Doran MF, Pond GR, Crowson CS, O'Fallon WM, Gabriel SE. Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a 40-year period. Arthritis Rheum 2001;46:625-31.
32. Gabriel SE, Crowson CS, O'Fallon WM. The epidemiology of rheumatoid arthritis in Rochester, Minnesota, 1955-1985. Arthritis Rheum 1999;42:415-20.
33. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315-24.
34. Scalley EK, Henrich JB. An overview of estrogen replacement therapy in postmenopausal women. J Women's Health 1993;2:289-94.
35. Dawson DA. Trends in the use of oral contraceptives. Data from the 1987 National Health Interview Survey. Family Planning Perspec 1990;22:169-72.
36. Miettinen OS. Proportion of disease caused or prevented by a given exposure, trait, or intervention. Am J Epidemiol 1974;99:325-32.
37. Dugowson CE, Koepsell TD, Voigt LF, Bley L, Nelson JL, Daling JR. Rheumatoid arthritis in women. Incidence rates in a group health cooperative, Seattle, Washington, 1987-1989. Arthritis Rheum 1991;34:1502-7.
38. Kaipianen-Seppanen O, Aho K, Isomaki H, Laakso M. Incidence of rheumatoid arthritis in Finland during 1980-1990. Ann Rheum Dis 1996;55:608-11.
39. Hochberg MC. Changes in the incidence and prevalence of rheumatoid arthritis in England and Wales, 1970-1982. Semin Arthritis Rheum 1990;19:294-302.
40. Cutolo M. Do sex hormones modulate the synovial macrophages in rheumatoid arthritis? Ann Rheum Dis 1997;56:281-4.
41. Gerstman BB, Gross TP, Kennedy DL, Bennett RC, Tomita DK, Stadel BV. Trends in the content and use of oral contraceptives in the United States, 1964-88. Am J Pub Health 1991;81:90-6.
42. Lobo RL. Estrogen and cardiovascular disease. Ann NY Acad Sci 1990;592:286-94.
43. Grossman CJ. Regulation of the immune system by sex steroids. Endocrin Rev 1984;5:435-55.
44. Feher KG, Feher T, Merety K. Interrelationship between the immunological and steroid hormone parameters in rheumatoid arthritis. Exp Clin Endocrinol 1986;87:38-42.
45. Spector T, Perry L, Tubb G, Silman A, Huskisson E. Low free testosterone levels in rheumatoid arthritis. Ann Rheum Dis 1988;47:65-8.
46. Silman AJ, Newman J, MacGregor AJ. Cigarette smoking increases the risk of rheumatoid arthritis. Results from a nationwide study of disease-discordant twins. Arthritis Rheum 1996;39:732-5.