ORAL CONTRACEPTIVES AND RHEUMATOID ARTHRITIS: FURTHER EVIDENCE FOR A PREVENTIVE EFFECT

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Summary To investigate a reported negative association between the use of oral contraceptives (OC) and the development of rheumatoid arthritis, a case-control study was undertaken to compare the histories of OC use between 228 women with a diagnosis of probable or definite rheumatoid arthritis and 302 women with the diagnosis of soft-tissue rheumatism and/or osteoarthritis. The use of OCs before the onset of joint complaints was acknowledged by 31·1% of the rheumatoid arthritis patients and by 55·6% of the controls. After adjustment for possible confounding variables, the rate ratio for ever use became 0·42 (95% confidence interval 0·27–0·65), while it was 0·40 (0·22–0·72) for ex-users and 0·45 (0·28–0·75) for current users. These findings confirm the finding from the Royal College of General Practitioners Oral Contraceptive Study that the incidence rate of rheumatoid arthritis among OC users was halved.

Introduction

A HALVING of the incidence rate of rheumatoid arthritis among users of oral contraceptives (OC) was an unexpected finding in the Oral Contraceptive Study of the Royal College of General Practitioners.[1] Until now this negative association has only been supported by the description of a decreasing secular trend in rheumatoid arthritis incidence rates among women living in Rochester, Minnesota.[2] On the basis of these two reports, the study of the association between oral contraceptives and rheumatoid arthritis has been accorded priority status in rheumatic disease epidemiology.[3]

We undertook a case-control study in which we compared young women with rheumatoid arthritis with young women with soft-tissue rheumatism and/or osteoarthritis. The aim of the study was to see whether inquiry into OC use before and at the time of onset of rheumatic complaints would indeed yield a rate-ratio around one-half.

Patients and Methods

Diagnoses

All cases and controls were women, born between 1926 and 1956, who were drawn at random from those attending five rheumatology outpatient clinics in the Netherlands (Leiden University, Utrecht University, Arnhem Municipal Hospital, Ziekenzorg Hospital Enschede, and Stadsmaten Hospital Enschede). The cases were women with seropositive or seronegative rheumatoid arthritis and the controls were women with a diagnosis of soft tissue rheumatism (bursitis, tenosynovitis, shoulder-hand syndrome, carpal tunnel syndrome, vertebral disc herniation, low back pain) and/or primary osteoarthritis (localised to knee, hip, or vertebrae, or generalised). In four of the five clinics the women were selected from a nationwide rheumatology diagnostic registry with which these clinics had participated in 1978 and 1979. At the Utrecht University clinic this procedure could not be used, and women were selected from the 1980–81 outpatient records. The diagnoses were recorded as possible, probable or definite rheumatoid arthritis.[4] Both the registry and the Utrecht patients included new patients and patients attending for follow-up.

Selection

Cases and controls were selected by computerised random number drawing from among clinic attenders who met the diagnostic and age criteria. To spread the workload over the different clinics we varied the probability of enrolment according to the clinic and to case or control status, from 30 to 100%, up to a maximum number of about 100 cases or controls per clinic. The diagnoses were reviewed by the attending rheumatologists in three of the clinics and by one of us (J. P. V.) in two clinics. Women with major concurrent diseases (cardiovascular or cancer) were excluded.

Questionnaire

We invited 386 cases and 465 controls to participate in the study. All women were approached between October, 1981, and April, 1982, by their attending rheumatologists through a postal questionnaire, followed by one reminder. The covering letter was the same for cases and controls, and referred to the scientific and the social need to know more about the association between hormones and joint diseases. The questionnaire, which was also the same for cases and controls, started with a question about the duration of the

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general practitioner's (GP) treatment before specialist opinion was sought (number of weeks, months, or years), followed by a memory refresher about initial rheumatic symptoms, and the date of first specialist referral. It proceeded to questions about the menopause and its nature (surgical or natural) and ended by asking about OC use during adult life and about the reasons for use (avoidance of pregnancy or heavy or irregular menses or otherwise). Year of birth and marital status were known from the clinical records.

The response rate to the questionnaire was uniformly high, ranging between 82·2% and 88·3%, with a median of 85·2%; it was similar for cases and controls. 9·4% of questionnaires were not usable because they were unclear or lacked information on duration of GP treatment, date of specialist referral, or dates of OC use.

Analysis

In the analysis, we discarded the records of the women whose rheumatic complaints had started before 1960, when OC use in the Netherlands was almost non-existent. We also excluded the cases whose rheumatoid arthritis was labelled as only "possible" after review of the diagnoses; most of these were seronegative cases. For analysis, there remained 228 cases with probable or definite rheumatoid arthritis (80 seronegative and 148 seropositive), and 302 controls (168 soft tissue rheumatism, 107 osteoarthritis, and 27 "miscellaneous" after the review).

We classified the patients by OC exposure as follows: "never users" with no history of OC use before the first GP visits for rheumatic complaints; "ex-users" whose OC use had started and ended before the first GP visit; "current users", who were still taking OCs at the time of the first GP visit; and "ever users", a category that combines "ex" and "current" (i.e., the complement of "never"). For the ever users, we also calculated the duration of OC use up to the time of the first GP visit.

Statistics

Rate ratios (odds ratios) and their 95% confidence limits were calculated by maximum likelihood estimation in a logistic model.[5] Rate ratios were estimated relative to the category of never users; therefore, the indicator variables for ex-use and current use were always entered into the model together, while the rate ratio for ever use was estimated in a separate model. When the 95% confidence interval of the rate ratio does not include unity, the rate ratio is different from unity at a significance level of 5% or less. Crude rate ratios were obtained by entering only the indicator variables for the categories of the exposure in the model. Possible confounders of the association between OCs and rheumatoid arthritis upon which we had information were: year of birth, year of onset of rheumatism (i.e., initial GP visit), marital status, menopausal status (calculated back to the time of the first GP visit), and rheumatology clinic (due to our sampling procedure). Adjustment for these possible confounders was accomplished by entering indicator variables for the categories of the confounders into the model.

Results

Table I gives the main characteristics of cases and control patients. Several differences emerge, which can have bearing on the frequency of the use of OCs. These are potential confounders, and should be controlled for in the analysis. Cases tended to be more chronic: they had an earlier calendar year for the first GP visit. The controls tended to be more recent patients. By contrast, the cases were somewhat younger than the controls, while the controls had been seen longer by the GP before specialist referral. The latter finding was a major reason for confining the categorisation of the exposure to OC use before or at the time of the first GP visit. Other differences are marital status and menopausal status. Finally, there is a difference in the reasons for OC use between cases and controls: the cases used these agents more often for contraceptive purposes.

Table II gives the crude percentages of the different categories of OC use for cases and controls.

TABLE I—CHARACTERISTICS OF 228 CASES AND 302 CONTROL PATIENTS

Characteristic	Centiles		
	10th	50th	90th
Year of birth			
Cases	1927	1935	1948
Controls	1927	1933	1946
First GP visit:			
Cases	1963	1973	1978
Controls	1968	1977	1979
Months between GP and specialist referral:			
Cases	0·5	3	24
Controls	0·75	6	48
	%		
Married:			
Cases		86·8	
Controls		96·3	
*Menopausal:**			
Cases		6·3	
Controls		18·2	
Pregnancy avoidance as reason for pill use:			
Cases		93·7	
Controls		85·0	

*Calculated back to time of first GP visit.

TABLE II—FREQUENCY OF ORAL CONTRACEPTIVE EXPOSURE CATEGORIES AMONG CASES AND CONTROLS

Exposure category*	Cases	Controls
Never users:	157 (*68·9%*)	134 (*44·4%*)
Ever users:		
Ex-users	25 (*11·0%*)	83 (27·5%)
Current users	46 (*20·1%*)	85 (*28·1%*)
Total	228	302

*Definition: see Patients and Methods.

Table III gives for the different categories of OC use the crude rate ratio and the rate ratio adjusted for all potential confounders.

Because of the differences in the reason for OC use between cases and controls, we also did an analysis in which the exposure was restricted to pill use for contraceptive purposes only. This slightly weakened the association, though the adjusted rate ratio estimate for ever use stayed at 0·56 (95% confidence interval 0·36 to 0·87); likewise the rate ratio estimates for former and current use increased slightly, but remained significant.

To explore a dose-response relationship, we did analyses by duration of OC use before the initial GP visit. The negative

TABLE III—RATE-RATIO ESTIMATES FOR DIFFERENT CATEGORIES OF ORAL CONTRACEPTIVE USE RELATIVE TO NEVER USE

	Never use	Ex-use	Current use	Ever use
Crude	1	0·26 (0·16–0·42)*	0·46 (0·30–0·70)	0·36 (0·25–0·52)
Adjusted†	1	0·40 (0·22–0·72)	0·45 (0·28–0·75)	0·42 (0·27–0·65)

*95% confidence interval of rate ratio.

†Adjustment for: year of birth, year of first GP visit, marital status, menopausal status, and outpatient clinic.

TABLE IV—RATE RATIO (AND 95% CONFIDENCE INTERVAL) ESTIMATES OF EVER USE FOR DIFFERENT CONTRASTS BETWEEN SUBGROUPS OF CASES AND CONTROLS

Group	Rate ratio*
Seropositive RA *vs* soft tissue rheumatism	0·37 (0·21–0·66)
Seropositive RA *vs* osteoarthritis	0·38 (0·20–0·76)
Seronegative RA *vs* soft tissue rheumatism	0·61 (0·31–1·19)
Seronegative RA *vs* osteoarthritis	0·56 (0·24–1·30)

*Adjusted for year of birth, year of first GP visits, marital status, menopausal status, and outpatient clinic.

association proved somewhat stronger for pill use of more than two year's duration than for pill use of less than one year; this difference was not significant, however.

As a final test of the consistency of the findings, we split the case-group into seropositives and the seronegatives, and likewise split the control group into those with soft tissue rheumatism and those with osteoarthritis, thus omitting the control patients whose diagnoses had been labelled "miscellaneous" in the review process. This permitted four different case-control analyses: seropositive rheumatoid arthritis *vs* soft tissue rheumatism, seropositive rheumatoid arthritis *vs* osteoarthritis, seronegative rheumatoid arthritis *vs* soft tissue rheumatism, and seronegative rheumatoid arthritis *vs* osteoarthritis. Table IV shows the results for ever use: in all contrasts the negative association persists, though the confidence intervals become wider, the numbers involved being smaller. The results also show that the negative association of pill use with rheumatoid arthritis is somewhat stronger in seropositive patients than in seronegatives.

Discussion

At face value, our results confirm the findings of the Oral Contraceptive Study of the Royal College of General Practitioners:[1] OC use is associated with a halving of the incidence rate of rheumatoid arthritis. In consequence, our results also support the explanation for the secular trend in rheumatoid arthritis incidence among women in Rochester, Minnesota.[2] One major difference is that in the R.C.G.P. study the OC effect was confined to current users, while we found it to be at least as strong for ex-users. As we had not expected a confirmatory result when planning this study, we carefully checked all possible biases.

A first point in the evaluation of a case-control study is the selection of the cases and controls. Both groups of patients were sampled from existing files. Thus, all represent prevalent states of disease at the time of our inquiry. We opted for prevalent cases because an incident case of rheumatism is hard to define when sampling from a specialist outpatient clinic: most patients will already have been treated by their GPs and by other specialists before coming to a particular clinic. In principle, prevalent cases can yield valid rate-ratio estimates, on condition that the survival of cases and controls is not affected differentially by the exposure of interest.[6] It is unlikely that this condition would not be met in this investigation. The control group was chosen as a clinical series of patients from two major and frequent rheumatic diagnoses, soft-tissue rheumatism and osteoarthritis, which cover a wide variety of illnesses in kind, severity, and duration. This variety was taken as a safeguard against unknown associations of these control diagnoses with OC use.[7] In addition, we were in the fortunate position during the planning of the study, to check in another setting the frequency of OC use among women with soft tissue rheumatism and/or osteoarthritis in comparison with the general population. During a cross-sectional population survey on 10 532 persons, conducted earlier by one of us (H. A. V.), data had been collected both on the use of OC and on the prevalence of clinical rheumatic conditions. Information about these two items had been collected in different parts of the survey because the OC/rheumatoid arthritis hypothesis had not been proposed at that time. These population survey data permitted us to compare the frequency of pill use in young women with the more common soft tissue rheumatisms and/or osteoarthritis with that in young women who did not have any of these conditions. No differences emerged (tables available from J. P. V. upon request). Furthermore, in the analysis of the present case-control study, we have shown that splitting the control group in its two major components (soft-tissue rheumatism and osteoarthritis) did not affect the rate-ratio estimates. Nevertheless, the reasons for OC use did differ between cases and controls: cases more often indicated pregnancy avoidance as reason for pill use. This could indicate that cases and controls were women of a somewhat different type: maybe women who consult for soft-tissue rheumatism and osteoarthritis have a higher complaint rate in general, which could lead to higher frequencies of OC use for heavy or irregular menses. However, we found significant rate-ratios of the same order of magnitude after redefining the exposure as pill use for contraceptive purposes only.

A second major point in the evaluation of a case-control study is the quality of the information—bias and misclassification. Since all our control patients also had rheumatic complaints, it was very natural to inquire into dates of onset of rheumatism and dates of OC use in a questionnaire accompanied by a covering letter which were the same for cases and controls. Cases and controls thus were blind to the hypothesis involved. A further guarantee against differential bias between cases and controls is the uniformly high response rate. To control observer bias, all codings of the exposure were checked upon by a computer algorithm. The use of prevalent cases and controls might have a drawback relating to the accuracy of the information: cases and controls had to recall dates of first visits to doctors and dates of OC use from a more or less distant past. Inevitably, this will induce some misclassification between the OC exposure categories, in cases and controls alike. Misclassification in case-control studies tends to dilute associations that are real.[8] Thus, if there was much misclassification, the true rate ratio gradients between the categories of OC use would be stronger than the ones we found. Obviously, misclassification is least likely in the distinction between never and ever users. By contrast, some degree of misclassification might account for the absence of a clear dose-response relationship and for the difference between our findings and those of the R.C.G.P. study group on the effect of past use of the pill.

A third point in the evaluation of a case-control study is the control of confounding. Differences emerged between cases and controls which could themselves lead to higher or lower frequencies of exposure in one of the groups: year of birth, year of first GP visit (due to secular trends in OC use[9]), menopausal status, and marital status. Control for those potential confounders together with control for outpatient clinic increased the rate ratio estimates, but for all exposure categories it stayed around or below one-half, and remained significant. The rate ratio estimate was influenced most by adjustment for year of birth and for time of the first GP visit; adjustment for clinic did not have any material influence.

A more general concern about a study that tries to confirm or to refute a specific hypothesis, is statistical power. With

228 cases and 302 controls, the power to reject the null hypothesis of no difference in ever use at a level of 0·05, given an expected rate ratio of one-half and an ever-use frequency of 55·6% among the controls, is more than 95%.[10]

Finally, our concern is not only with associations and their statistical tenability, but also with the biological plausibility of the proposed effects. It is difficult to devise a biologically plausible model for a preventive effect of OC use on rheumatoid arthritis. There is the old clinical dictum that patients with rheumatoid arthritis do better during pregnancy;[11] this could be compatible with a pseudopregnancy effect of OCs. However, the mechanisms by which some immunological diseases are altered during pregnancy are far from resolved, and it is not at all certain that these mechanisms are necessarily hormonal.[12] Of additional interest is our finding of a larger effect of OC use on seropositive than on seronegative rheumatoid arthritis. This could reflect differences in pathogenesis. An alternative explanation, however, is that among seronegative rheumatoid arthritis patients there are more uncertain diagnoses (the patients are lacking one diagnostic criterion from the start), so that some misclassified patients could weaken the association.

Our study was intended as a quick check on a major new hypothesis. Although our data are confirmatory, we think that more information is needed before a preventive effect of OC on rheumatoid arthritis can be accepted. We would welcome further information about types of OCs (the OC use described in this study was mainly that of the early 1970s and may be of historical interest only), about other oestrogens (especially oestrogen replacement after the menopause), and the clinical effects of pregnancies and OC in the same women. Finally, our results and previous studies call for further elaboration of biological models of hormonal influences on autoimmune phenomena. If OCs really do prevent rheumatoid arthritis, a condition with a prevalence of about 2% in adult females, this could be an important factor in off-setting the negative image of OCs due to their association with cardiovascular disease. It also could have a profound impact on society's need to care for the disabling consequences of rheumatoid arthritis.

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ROLE OF N-ACETYLTRANSFERASE PHENOTYPES IN BLADDER CARCINOGENESIS: A PHARMACOGENETIC EPIDEMIOLOGICAL APPROACH TO BLADDER CANCER

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Summary A large excess of patients with bladder cancer who have previously been exposed to N-substituted aryl compounds as a result of the production of dyestuff intermediates have the slow phenotype of the enzyme N-acetyltransferase. Among bladder-cancer patients in general, those presenting with T3 or T4 disease or carcinoma-in-situ also show an excess of the slower subtypes. Either N-substituted aryl compounds more frequently produce tumours with this invasive potential if linked with slow acetylation or slow acetylators are more susceptible to tumour production when exposed to some N-substituted aryl compounds. It is suggested that acetylator status could be used to identify susceptible individuals in potentially hazardous occupations.

Introduction

ACETYLATION has been linked both to activation of carcinogens inducing liver tumours and to carcinogenic detoxification in aromatic-amine-induced bladder cancer. These systems have been investigated in animals.[1,2] Interspecies enzymic differences have been linked to different sites of malignant disease[3] and, as a result of these studies, it has been postulated that the human liver-bound enzyme group, N-acetyltransferase, might play a significant part in the control of the detoxification of the carcinogenic substances metabolised from N-substituted aryl compounds.[4]

The rates of acetylation in both man and rabbit vary considerably between individuals, who may be categorised as fast and slow acetylators.[5] This heterogeneity is controlled genetically by two autosomal alleles at a single locus, the trait for rapid acetylation being dominant and that for slow acetylation recessive. An intermediate, possibly heterozygous, phenotype can now be distinguished.[6] Although not conclusively proven, the physiological determinant of acetylator status is probably the total hepatic N-acetyltransferase activity.[7]

The clinical consequences of this polymorphism are extensive,[8] having been linked both to an increased

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