Recent Use of Oral Contraceptives and the Risk of Multiple Sclerosis

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Background: Exogenous estrogens affect the onset and clinical course of experimental allergic encephalomyelitis. Oral contraceptives, a frequent source of exogenous estrogens in humans, could have a role in the development of multiple sclerosis (MS).

Objective: To examine whether recent oral contraceptive use and pregnancy history are associated with the risk of MS.

Design and Setting: A case-control study nested in the General Practice Research Database. This database contains prospective health information (drug prescriptions and clinical diagnoses) on more than 3 million Britons who are enrolled with selected general practitioners.

Participants: One hundred six female incident cases of MS, younger than 50 years, with at least 3 years of continuous recording in the General Practice Research Database before the date of first symptoms (index date), identified between January 1, 1993, and December 31, 2000,

and 1001 controls matched on age, practice, and date of joining the practice.

Main Outcome Measure: Incidence of first symptoms of MS, confirmed through medical records.

Results: The incidence of MS was 40% lower (odds ratio, 0.6; 95% confidence interval, 0.4-1.0) in oral contraceptive users compared with nonusers during the previous 3 years. The risk of MS increased in the 6 months after pregnancy (odds ratio, 2.9, 95% confidence interval, 1.2-6.6), but it was not otherwise related to parity.

Conclusions: The hormonal changes that occur during oral contraceptive use and pregnancy may be associated with a short-term reduction in the risk of MS, and the postpartum period may be associated with a short-term increase in the risk of MS.

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E STROGENS AFFECT IMMUNE response[1] and, thus, may affect the development of multiple sclerosis (MS). Exogenous estrogens delay the onset and ameliorate the clinical course of experimental allergic encephalomyelitis in mice,[2-4] and it is therefore possible that oral contraceptives (OCs) could have a role in the development of MS. Pregnancy and puerperium, 2 states associated with profound hormonal changes, alter the clinical course of MS[5] and could affect the risk of developing the disease.

Previous prospective studies[6-8] assessed the association between OC use and MS risk. Overall, their findings are consistent with a null effect, but they included few cases of MS[6,7] or were not appropriately designed to study the short-term effects of OC use.[8] Therefore, little is known about the potential short-term effects of

use of OCs on the risk of developing MS. We evaluated the association of recent OC use and pregnancy with the risk of MS in a prospectively followed up population of British women.

METHODS

STUDY POPULATION

The General Practice Research Database (GPRD) contains prospective health information on more than 3 million Britons who are enrolled with selected general practitioners.[9] These physicians have been trained to record their patients' medical and demographic information in a standard manner and have agreed to supply it anonymously for research purposes. In addition, practices used in this study agree to collaborate in specific research projects by providing photocopies of their patients' paper medical records after personal identifiers have been removed. Drug prescriptions were computer generated by the physi-

cians and automatically recorded in the database using a coded drug dictionary. This computerized information has been found to be of satisfactory quality for drug safety studies.[10,11] Because the date of menopause is not systematically recorded in the GPRD, we restricted our study to women younger than 50 years.

CASE ASCERTAINMENT

The assessment of incident cases of MS in the GPRD has been described previously.[12] Briefly, we identified individuals having a new diagnosis of MS (*International Classification of Diseases, Ninth Revision*, code 340.0) recorded in the GPRD between January 1, 1993, and December 31, 2000. We then requested photocopies of all their MS-related medical records available in their general practitioner's office. Review of medical records confirmed that 242 (63.9%) of 379 women younger than 50 years had definite or probable MS according to standardized criteria.[13,14] The other 137 participants were excluded because they were prevalent cases of MS, they had a diagnosis of possible MS, their medical records could not be obtained because of transfer into another general practice or death, or they did not have MS. The estimated incidence of MS in women younger than 50 years was 10.5 cases per 100 000 person-years of follow-up, which is similar to the incidence in the cohort studies[6,7] conducted in the United Kingdom.

Among the 242 cases, 180 had their first symptoms after the date of their first computer-recorded medical information. To ensure at least 3 years of exposure information, our primary analysis included only the 106 cases with at least 3 years of continuous information in the GPRD before the date of first symptoms.

EXPOSURE ASSESSMENT

Oral contraceptive use during the 3-year period before the index date was determined from the computerized medical records. The most frequently used OCs in our study population were a combination of an estrogen (usually ethinyl estradiol) and a progestogen. A woman was classified as a current OC user if she had a prescription period that included the index date and as a past OC user if no prescription period included the index date. Periods of OC use were added together to calculate the duration of use. For past OC users, the time since last use was also determined. These calculations were made for any OC use and separately for second-generation OCs (containing levonorgestrel), third-generation OCs (containing gestodene or desogestrel), and other OCs.

Pregnancy data are recorded in the GPRD as the date of end of pregnancy and the pregnancy outcome. We imputed the duration of pregnancy as 270 days for full-term deliveries, 210 days for preterm deliveries, 180 days for miscarriages, 270 days for stillbirths, and 120 days for induced abortions. Other realistic imputations of the duration of pregnancy yielded results similar to those presented herein.

STUDY DESIGN

We conducted a case-control study nested in the GPRD cohort. Cases were defined as women younger than 50 years having a confirmed diagnosis of MS between January 1, 1993, and December 31, 2000, and with at least 3 years of continuous recording in the GPRD before first symptoms. Up to 10 control subjects per case were selected, matched by age (±1 year), practice, and date of joining the practice (±1 year). Controls had to be alive, be free of having an MS diagnosis, be presently listed in the database at the date of first symptoms of their corresponding case (the index date), and have at least 3 years of continuous recording in the database before the index date. We

Table 1. Characteristics of Multiple Sclerosis (MS) Cases and Control Subjects*

Characteristic	MS Cases (n = 106)	Control Subjects (n = 1001)
Age, y		
Mean ± SD	33.4 ± 8.1	33.7 ± 8.0
<30	39.6	38.5
30-39	34.9	35.7
40-49	25.5	25.7
Ever smokers	40.2	39.4
Course of the disease		
Relapsing remitting	82.1	. . .
Primary progressive	8.5	. . .
Secondary progressive	9.4	. . .

*Data are given as percentages unless otherwise indicated. Ellipses indicate not applicable.

used conditional logistic regression to compute odds ratios (ORs) and their 95% confidence intervals (CIs), adjusted for the matching factors.

RESULTS

Our analyses included 106 incident cases of MS and 1001 matched controls (**Table 1**). The incidence of MS in OC users was 40% lower than in nonusers (OR, 0.6; 95% CI, 0.4-1.0). The OR was also 0.6 (95% CI, 0.4-1.1) when we excluded women with at least 1 pregnancy in the previous 3 years. Smoking was associated with increased OC use among controls (47% of current OC users were smokers vs 38.4% of past OC users and nonusers). However, when we adjusted for smoking status, the OR of MS for OC users compared with nonusers remained unchanged (OR, 0.6; 95% CI, 0.4-1.1). Additional adjustment for body mass index (calculated as weight in kilograms divided by the square of height in meters) did not materially affect the OR estimate.

There was no clear trend with longer duration of use or time since last OC use (**Table 2**), but our results suggest that the highest risk reduction occurred among women who used OCs in the year before the index date compared with nonusers (OR, 0.4; 95% CI, 0.2-0.7). Compared with nonusers, the ORs were 0.6 (95% CI, 0.3-1.0) for use of third-generation OCs, 0.9 (95% CI, 0.5-1.5) for use of second-generation OCs, and 0.7 (95% CI, 0.3-1.4) for use of other OCs. The ORs for any OC use compared with nonuse were 0.6 (95% CI, 0.3-0.9) for a relapsing-remitting course at MS clinical onset (97 cases) and 1.2 (95% CI, 0.2-6.7) for primary progressive MS (9 cases). Repeated use of emergency contraception (available in the United Kingdom as a combination of estrogen and progestogen and, since 1999, as a progestogen-only regimen) was nonsignificantly associated with a higher risk of MS (OR for ≥2 uses compared with nonuse, 2.8; 95% CI, 0.8-10.6).

Parity in the 3 years before the index date was not associated with the risk of MS (**Table 3**). Women had a higher risk of developing first symptoms of MS in the 6 months following a pregnancy (OR, 2.9; 95% CI, 1.2-6.6) and a nonsignificant lower risk during pregnancy (OR,

Table 2. Association Between Oral Contraceptive Use and Multiple Sclerosis (MS) Incidence*

3 Years Before the Index Date	MS Cases (n = 106)	Control Subjects (n = 1001)	Odds Ratio (95% Confidence Interval)
Oral contraceptive use			
No	50 (47.2)	396 (39.6)	1.0 (Referent)
Yes	56 (52.8)	605 (60.4)	0.6 (0.4-1.0)
Past	46 (43.4)	479 (47.9)	0.6 (0.4-1.0)
Current	10 (9.4)	126 (12.6)	0.5 (0.3-1.2)
Duration of use, mo			
No use	50 (47.2)	396 (39.6)	1.0 (Referent)
≤12	39 (36.8)	394 (39.4)	0.7 (0.3-1.1)
>12†	17 (16.0)	211 (21.1)	0.6 (0.3-1.1)
Time since last use, mo			
No use	50 (47.2)	396 (39.6)	1.0 (Referent)
>24	14 (13.2)	129 (12.9)	0.7 (0.3-1.4)
>12 to 24	17 (16.0)	92 (9.2)	1.3 (0.7-2.6)
≤12	15 (14.2)	258 (25.8)	0.3 (0.2-0.6)
Current user‡	10 (9.4)	126 (12.6)	0.5 (0.2-1.1)

*Data are given as number (percentage) unless otherwise indicated.
†P = .09 for trend, modeling the exposure as a continuous variable, with nonusers as zero. P = .51 for trend, modeling the exposure as a continuous variable, after excluding nonusers.
‡P = .008 for trend, modeling the exposure as a continuous variable, with nonusers as zero. P = .08 for trend, modeling the exposure as a continuous variable, after excluding nonusers.

Table 3. Association Between Pregnancy History and Multiple Sclerosis (MS) Incidence*

3 Years Before the Index Date	MS Cases (n = 106)	Control Subjects (n = 1001)	Odds Ratio (95% Confidence Interval)
No. of pregnancies			
0	83 (78.3)	784 (78.3)	1.0 (Referent)
1	14 (13.2)	152 (15.2)	0.8 (0.5-1.6)
≥2†	9 (8.5)	65 (6.5)	1.3 (0.6-2.8)
Time since last pregnancy, mo			
No pregnancy	83 (78.3)	784 (78.3)	1.0 (Referent)
>6	12 (11.3)	133 (13.3)	0.8 (0.4-1.6)
≤6	9 (8.5)	32 (3.2)	2.9 (1.2-6.6)
Currently pregnant	2 (1.9)	52 (5.2)	0.3 (0.1-1.4)

*Data are given as number (percentage) unless otherwise indicated.
†P = .78 for trend.

0.3; 95% CI, 0.1-1.4), compared with those with no pregnancy. Restricting the analysis to women without previous use of OCs (50 cases) did not materially change the results for parity, but the few pregnant cases prevented estimating the effect of time since last pregnancy.

Analyses not restricted to women with at least 3 years of information in the database (180 cases and 1738 controls) yielded similar results. The ORs of MS were 0.6 (95% CI, 0.4-0.9) for OC use compared with nonuse, 1.8 (95% CI, 0.9-3.5) for postpartum state at the index date vs no pregnancy in the previous 3 years, and 0.4 (95% CI, 0.1-1.1) for pregnancy at the index date vs no pregnancy in the previous 3 years. When we added possible cases and their controls to our main analysis (122 cases and 1149 controls), the OR of MS for OC users vs nonusers was 0.7 (95% CI, 0.4-1.1).

COMMENT

We found that recent use of OCs was associated with a 40% reduction in the incidence of MS. This result cannot be explained by recall bias because data on OC use were recorded before first symptoms of MS, or by bias in the selection of controls because our study was nested in a well-defined prospective cohort.

Our finding can be interpreted in several ways. First, OC use may decrease the incidence of MS by reducing the number of women who will ever develop the disease. Second, OC use may affect the incidence of MS by delaying the onset of symptoms. Third, the association between recent OC use and MS might be the result of confounding by unknown factors. As described herein, the overall epidemiological and experimental evidence favors the second interpretation over the first one and suggests that confounding cannot fully explain our results. Fourth, an alternative explanation is that unrecognized symptoms of MS may induce women to stop taking OCs, but this seems unlikely because factors associated with OC discontinuation would be discussed with a woman's physician and, hence, would be recorded in the GPRD.

Previous cohort studies have assessed the relationship between OC use and risk of MS. The Oxford Family Planning Association Study found a lower incidence rate of MS in OC users compared with those who never used OCs (relative rate, 0.7; 95% CI, 0.4-1.1).[6] The Royal College of General Practitioners' Oral Contraception Study detected a slightly increased rate of MS in OC users compared with those who never used OCs (relative rate, 1.2; 95% CI, 0.8-1.8).[7] A similar result (relative rate, 1.2; 95% CI, 0.9-1.6) was found in a pooled analysis of the Nurses' Health Study and the Nurses' Health Study II.[8] The Nurses' Health Studies biennially collected approximate times of OC use and of MS first symptoms and are more helpful to evaluate the long-term effects of OC use than its short-term effects. On the other hand, our study design is expected to provide more accurate estimates of the short-term effects of OC use because the time of recent use of OCs and the time of the first symptoms of MS were precisely determined based on computerized prescription records and on complete medical records, respectively. Therefore, the epidemiological evidence is consistent with a delay in the onset of MS in some OC users, followed by a lack of long-term effects of OC use on the overall risk of MS. Animal models of MS also support this hypothesis.[3] These observations could be explained by the estrogens' ability to modulate the immune response and their potential neuroprotective effect.[15-18]

Our findings also suggest that the risk of MS onset may decrease during pregnancy and is increased in the 6 months after pregnancy. This is consistent with studies on the effect of pregnancy in patients with MS[5] and the immunological changes associated with pregnancy.[19] Like previous studies,[6-8,20,21] ours did not find any relationship between parity and the risk of MS, which gives ad-

ditional support to the hypothesis of a delay in MS on-set caused by high levels of estrogens: MS cases who would have had their first clinical attack during pregnancy did not experience it until the postpartum period, so that over-all there was no effect of parity on MS risk.[19]

CONCLUSIONS

Recent OC use and, possibly, current pregnancy are associated with a lower risk of developing MS. On the contrary, the postpartum period confers a higher risk of MS onset. Our findings suggest that high levels of exogenous estrogens from OC use and of endogenous estrogens during pregnancy may delay the first clinical attack of MS.

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