ORIGINAL ARTICLE: CONTRACEPTION

Long-term influence of combined oral contraceptive use on the clinical course of relapsing–remitting multiple sclerosis

Giulia Gava, M.D.,[a] Ilaria Bartolomei, M.D., Ph.D.,[b] Antonietta Costantino, Ph.D.,[a] Marta Berra, M.D.,[a] Stefano Venturoli, M.D.,[a] Fabrizio Salvi, M.D., Ph.D.,[b] and Maria Cristina Meriggiola, M.D., Ph.D.[a]

[a] Gynecology and Physiopathology of Human Reproduction, University of Bologna and S. Orsola-Malpighi Hospital, Bologna; and [b] Center for Rare and Neuroimmunological Diseases, Scientific Institute for Research, Hospitalization and Health Care (IRCCS), Istituto delle Scienze Neurologiche di Bologna, Bellaria Hospital, Bologna, Italy

Objective: To assess the long-term effects of combined oral contraceptives (COCs) on the clinical course of relapsing–remitting multiple sclerosis (RRMS), focusing on disability progression and evolution to secondary-progressive multiple sclerosis (SPMS).
Design: Retrospective and exploratory study.
Setting: Academic medical center.
Patient(s): A total of 174 women with clinically confirmed MS; of these, 33 had evolved to SPMS at the time of enrollment in the study, whereas 141 still had a relapsing–remitting form of disease.
Intervention(s): Women were interviewed to obtain gynecologic and obstetric history.
Main Outcome Measure(s): Expanded Disability Status Scale (EDSS); Multiple Sclerosis Severity Score (MSSS); annualized relapse rate; evolution to SPMS.
Result(s): Mean ± SD duration of disease was 14.3 ± 9.8 years. Compared with non-users of COCs, COC users had lower EDSS scores and MSSS only in the subset of the population with prior or current immunomodulatory treatment. Nonuse of COCs was a predictor of disease evolution in SPMS, whether treated or not with immunomodulatory drugs. The annualized relapse rate was not influenced by COC use. No differences in EDSS scores and evolution to SPMS depending on COC formulation were detected.
Conclusion(s): Our results suggest that COC use is associated with a less severe disease and less severe evolution. Whether different doses or types of progestin may have different effects remains to be defined. (Fertil Steril® 2014;■:■–■. ©2014 by American Society for Reproductive Medicine.)
Key Words: Disability, multiple sclerosis, neurologic outcome, oral contraceptives, sex steroids

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Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system characterized by damage to myelin sheaths (demyelination) and secondary axonal degeneration. Approximately 50% of patients first diagnosed with relapsing–remitting multiple sclerosis (RRMS) develop secondary-progressive MS (SPMS) within 10 years, and this form of disease is the primary cause of disability (1). Several sex differences in brain damage and clinical evolution indicate a potential role of sex hormones (2). Females have an incidence of RRMS two to three times higher than males, and the disease usually affects women during their reproductive years (3). However, women reach disability milestones at an older age than men, and the male sex is associated with a more rapid progression and worse outcome (4). Blood levels of sex steroid hormones seem to be related to the frequency of relapse: during the third trimester of pregnancy a reduction of relapse rate and clinical symptoms of MS is observed, with a temporary rebound of disease activity in the

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Reprint requests: Maria Cristina Meriggiola, M.D., Ph.D., Gynecology and Physiopathology of Human Reproduction, University of Bologna and S. Orsola-Malpighi Hospital, Via Massarenti 13, Bologna, Italy 40138 (E-mail: cristina.meriggiola@unibo.it).

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3 months postpartum (5, 6). Childbearing seems to have a possible favorable long-term effect on the course of MS (7), and women with at least two pregnancies have reduced disability progression compared with nulliparous women (8). In a trial involving 10 female MS patients estriol administration was shown to be beneficial (9). There are several phase II trials underway to evaluate the efficacy of estrogen (E) treatment in MS (10). In the animal model of MS, experimental autoimmune encephalomyelitis (EAE), E and progesterone (P) treatments reduce demyelination, neuronal dysfunction, and clinical severity in EAE mice (10–12). Combined oral contraceptives (COCs) are a source of exogenous sex steroid hormones widely used among women during the years in which they are most susceptible to MS. Most existing epidemiologic evidence does not clarify whether long-term use of COCs influences the risk of developing MS (13) or affects the age of onset. In two prospective cohort studies conducted in Britain OC use was not associated with an increased risk of MS (14, 15); the Nurses' Health Study did not find an overall correlation between MS incidence and OC use but indicated a possible increased risk in long-term users (16). The General Practice Research Database study suggests a reduced risk of MS in some OC users (17), whereas other studies found a higher age of onset in OC users (18).

There is little information in the literature about the long-term effects of COCs on the clinical course of MS. In one cross-sectional survey of 675 women with RRMS there was no influence of COC use on progression of disability (8), whereas a retrospective study associated OC use with a milder clinical course of disease in a cohort of 132 women with RRMS not taking disease-modifying therapies and with a mean ± SD duration of disease of 6.2 ± 5.1 years (19).

The present retrospective and exploratory study was designed to assess the cross-sectional association of COCs with the clinical course of RRMS, especially with regard to the annualized relapse rate, disability progression, and evolution in SPMS. The influence of possible confounders, such as disease-modifying therapies (DMTs) and childbearing, was also investigated.

MATERIALS AND METHODS

The present study was approved by the Medical Ethics Committee of the Bellaria Hospital, and all patients gave written informed consent. In this retrospective study women with clinically and magnetic resonance imaging–confirmed RRMS, according to the revised McDonald criteria (20), and a disease course of >1 years since initial symptoms, were recruited at the time of their routine clinical visit at the Center for Rare and Neuroimmunological Diseases at the Bellaria Hospital in Bologna, Italy. The recruitment lasted 4 months. Demographic and clinical information was collected by consulting patients' medical records. The clinical neurologic data analyzed included age at onset of MS (age at which first neurologic symptoms of MS appeared), disease duration, annualized relapse rate, DMTs, progression of disability, and evolution to SPMS. Secondary-progressive MS is defined as an "initial relapsing remitting disease course followed by progression with or without occasional relapses, minor remissions, and plateaus" (21). Concomitant diseases and concomitant medications, other than those used for MS, were also recorded. The degree of disability was assessed by the same operators using the Expanded Disability Status Scale (EDSS) and the Multiple Sclerosis Severity Score (MSSS) (22). The EDSS quantifies disability with a scale from 0 to 10 (higher scores are associated with higher disability; e.g., EDSS 6 is defined as the loss of ability to walk 100 m without constant assistance) (23). Multiple Sclerosis Severity Score is defined as the median deciles rank of each EDSS grade in the population of patients with similar disease durations (22); it adds the element of disease duration to the EDSS, and it is a method by which to compare disease progression and disease severity in groups of patients (24).

Clinical relapse is the presence of a neurologic deficit typical of MS detected by the neurologist and lasting at least 24 hours. The annualized relapse rate is defined as the number of relapses divided by the number of years of disease. All neurologic evaluations were performed by the same neurologist. Patients were interviewed to obtain gynecologic and obstetric history: age at menarche, age at start of COC use, duration of COC use, formulation of COC, dates and number of full-term deliveries, number of miscarriages, and current sexual activity (number of sexual intercourse in the last month and use of nonhormonal contraception in the past 5 years). Women were considered COC users if they had taken COCs for at least 1 year continuously. From a pilot study conducted on a sample of 28 COC users and 19 non-users, EDSS score standard deviations were 1.41 and 2.34, respectively, and assuming a minimum clinically significant difference of 1, error $\alpha = 0.05$, and a power of at least 0.8, the minimum number of cases to analyze considering EDSS as a primary endpoint was determined as 120 (60 COC users and 60 non-users).

All continuous data were expressed as mean and standard deviation of the mean, and all categoric data were expressed by frequency rate and percentage. The Kolgomorov-Smirnov test was used to assess the normality of the distributions. One-way analysis of variance was performed to assess differences between groups when data were normally distributed and the Levene test for homogeneity of variances was not significant ($P < .05$); otherwise, the Mann-Whitney test (two groups) or the Kruskal-Wallis test (more than two groups) were used. The Scheffè test was used as post hoc pairwise comparisons of one-way analysis of variance. The Mann-Whitney test with Bonferroni correction for multiple comparisons was used as post hoc pairwise comparisons of Kruskal-Wallis test. Pearson's nonparametric χ^2 test (more than two groups) or Fisher's nonparametric χ^2 test (two groups) was performed to investigate the relationships between categoric variables. Spearman's rank correlation was used to assess the correlation between continuous variables. The Kaplan-Meier survival analysis was used to assess the influence of categoric variables on disease evolution. The Cox regression survival analysis was used to assess the influence of continuous variables on disease evolution and as multivariate analysis to find the combined influence of predictors and eventual