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Contraceptive use among women with multiple sclerosis: a systematic review☆,,☆☆

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Abstract

Background: Contraception is an important consideration for women with multiple sclerosis (MS); however, little is known about the possible effects of hormonal contraception on disease progression or other adverse outcomes (e.g., thrombosis, low bone mineral density).

Objective: To evaluate the evidence on the safety of contraceptive use among women with MS.

Search strategy: We searched the PubMed database for peer-reviewed articles published in any language from database inception through July 2015.

Selection criteria: We included studies that examined health outcomes among women diagnosed with MS initiating or continuing a contraceptive method. We excluded case reports and case series but included all other study designs.

Results: From 111 articles, we identified four studies (from 5 articles) that met our inclusion criteria. Evidence from one randomized controlled trial, two retrospective cohort studies, and one cross-sectional study suggests that use of combined oral contraceptives (COCs) or oral contraceptives (OCs) (type not specified) among women with MS does not worsen the clinical course of disease, defined as *disability level, disease severity or progression, relapse or number of new brain lesions on magnetic resonance imaging* (body of evidence grading Level I, fair to Level II-3, poor). No studies were identified that examined the safety of other contraceptive methods or examined other outcomes of interest (venous thromboembolism, changes in bone mineral density) related to contraceptive use among women with MS.

Conclusions: Limited evidence suggests that COC or OC use after MS onset does not worsen the clinical course of disease.

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Keywords

Multiple sclerosis; Contraception; Combined oral contraceptives; Oral contraceptives; Systematic review

1. Introduction

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system in which the immune system attacks the myelin, disrupting communication between the brain and the rest of the body. Symptoms of MS vary widely over time and among individuals, depending on the amount of damage and which nerves are affected. Symptoms may include optic neuritis, sensory and gait disturbances, muscle weakness, tremor, spasticity, vertigo, bladder dysfunction and fatigue [1].

The course of MS has been categorized into several disease patterns based on disease activity and progression [2,3]. Clinically isolated syndrome (CIS) is the first clinical presentation of a disease compatible with MS that has yet to fulfill diagnostic criteria. Relapsing remitting MS (RRMS) is characterized by clearly defined relapses with no disease progression in between. Secondary progressive MS (SPMS) is characterized by an initial RRMS disease course followed by progression with or without acute relapses. The last disease pattern is primary progressive MS (PPMS), characterized by disease progression from onset with occasional plateaus or temporary minor improvements, with or without acute relapses. PPMS accounts for approximately 10–20% of cases at onset [4]. The nonrelapsing patterns are associated with greater neurological disability.

Although data are not available on the prevalence of MS among women of reproductive age in the United States, estimates suggest that 135 persons per 100,000 in the United States have MS [5], which translates to roughly 435,000 people [6]. As women are affected 2.4 times as often as men [7], we estimate that roughly 307,000 women in the United States have MS. Contraception is an important consideration for women with MS because the peak age of onset for women is during the childbearing years [8], and the disease does not impair fertility [9]. Further, since use of disease-modifying therapies to treat MS is generally not recommended for women seeking to achieve pregnancy and some are known teratogens [10], use of effective contraception is important to prevent unintended pregnancies among women using these treatments.

Most epidemiological evidence suggests no association between oral contraceptive (OC) use and risk of developing MS [11]; however, these data do not provide information on possible effects of hormonal contraception in women with MS, including disease progression or other adverse outcomes. MS patients have increased risk for venous thromboembolism (VTE) due to disability, immobility and autoinflammatory processes [12,13], which may be further increased with combined hormonal contraceptive use. MS patients may also have compromised bone health [14], so use of progestin-only injectables may be of concern. On the other hand, endogenous and exogenous hormonal exposures have been shown to stabilize MS [15,16]; thus, hormonal contraceptive use may positively affect the MS disease course.

The U.S. Centers for Disease Control and Prevention (CDC) publishes the U.S. Medical Eligibility Criteria for Contraceptive Use (US MEC) [17], which provides evidence-based guidance on the safety of contraceptive methods for women with certain characteristics or medical conditions. Currently, the US MEC does not include recommendations for contraceptive use by women with MS. As part of a process to update the US MEC, the objective of this systematic review was to evaluate the evidence on the safety of contraceptive use among women with MS.

2. Materials and methods

We conducted this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18]. Our key question was whether women of reproductive age with MS using a specific contraceptive method are at increased risk for adverse outcomes (e.g., relapse, disease progression, VTE, change in bone mineral density) compared with women using a different method or no method of contraception.

2.1. Literature search

We searched the PubMed database for peer-reviewed articles published in any language from database inception through June 2015 on the safety of using any contraceptive method among women with MS, using the following search strategy:

((((((((((contracept* OR mirena) OR ((((“Norpregnanes”[Mesh] OR (“Contraceptive Agents”[Mesh] OR “Contraceptive Agents “[Pharmacological Action])) OR “Contraceptive Devices”[Mesh]) OR “Contraception” [Mesh]))))) OR ((((((progest*)) OR ((((“Progestins” [Mesh] OR “Progesterone Congeners”[Mesh])) OR “Progesterone”[Mesh])))) AND (((contracept*) OR ((((“Norpregnanes”[Mesh] OR (“Contraceptive Agents”[Mesh] OR “Contraceptive Agents “[Pharmacological Action])) OR “Contraceptive Devices”[Mesh]) OR “Contraception” [Mesh])))))) OR (((((((((dmpa)) OR ((depo-provera))) OR ((norethisterone enanthate)))) OR ((“Medroxyprogesterone 17-Acetate”[Mesh])))) AND (((contracept*) OR ((((“Norpregnanes”[Mesh] OR (“Contraceptive Agents”[Mesh] OR “Contraceptive Agents “[Pharmacological Action])) OR “Contraceptive Devices”[Mesh]) OR “Contraception” [Mesh])))))) OR ((((iud)) OR ((“Intrauterine Devices” [Mesh])))))) OR ((((emergency contraception)) OR ((“Contraception, Postcoital”[Mesh] OR “Contraceptive Agents”[Mesh])))))) OR ((((nuvaring)) OR (((“Desogestrel”[Mesh] OR “Contraceptive Agents, Female”[Mesh]) OR “Contraceptive Devices, Female”[Mesh])))))) OR (((((hormonal patch)) OR ((ortho evra))) OR (((“Norges- trel”[Mesh] OR “Contraceptive Devices, Female” [Mesh]) OR “Contraceptive Agents, Female”[Mesh])))))))) AND (((“Multiple Sclerosis” [Mesh] OR “Multiple Sclerosis, Relapsing–Remitting”[Mesh] OR “Multiple Sclerosis, Chronic Progressive”[Mesh])) OR “multiple sclerosis”)

In addition, we hand-searched reference lists from articles identified by the search and key review articles.

2.2. Selection criteria

We reviewed titles as well as abstracts to identify studies examining the safety of using any contraceptive method among women with MS. We included studies that examined health outcomes among women diagnosed with MS initiating or continuing a contraceptive method. We excluded case reports and case series but included all other study designs.

2.3. Study quality assessment and data synthesis

The evidence was summarized and systematically assessed using standard abstraction forms. The quality of each individual piece of evidence was assessed using the grading system developed by the United States Preventive Services Task Force [19]. We focused on several study factors when assessing quality, including study design, diagnostic criteria for MS, assessment of contraceptive use, outcome assessment, adjustment for potential confounders, timing of contraceptive use relative to outcome assessment and participation and follow-up (FU) rates. We did not compute summary measures of association due to heterogeneity across the included studies related to study population, study design, classification of exposure and outcomes reported.

3. Results

The search strategy identified 111 articles, of which four studies [20–23] (from five articles [20–24]) met our inclusion criteria. Two articles are described together as a single piece of evidence since both reported findings from the same project and included overlapping samples of women [21,24]. Excluded studies were mainly review papers and papers not relevant to our key question. Three studies were excluded because it was unclear if contraceptive use occurred after MS diagnosis [25–27].

Each of the four included studies examined OCs, two of which specified the type as combined oral contraceptives (COCs) [20,22]. One study examined the effect of COCs as an add-on therapy in patients taking interferon β−1a [22]. We did not identify studies that examined the safety of other contraceptive methods among women MS.

Of the four included studies, one was a randomized controlled trial (RCT) rated as having fair quality [22], two were retrospective cohort studies rated as having fair quality [20,23] and one was a cross-sectional study rated as having poor quality [21]. All studies examined some aspect of the clinical course of MS (e.g., disability, severity/disease progression, annualized relapse rate, brain lesions). Sample sizes in the four studies ranged from 132 [23] to 512 [21]. Study participants had different types of MS including RRMS [22,23] and RRMS at onset, some of which had progressed to SPMS [20]. One study did not specify the type of MS [21]. No studies were included among women with PPMS or CIS. Table 1 describes the details of each study.

The RCT examined the effect of COCs as an add-on therapy in 149 women with RRMS taking interferon β−1a subcutaneously [22]. Women were randomized into one of three study groups: (a) no COC; (b) low-dose COC [20-mcg ethinyl estradiol (EE)]; or (c) higher dose COC (40-mcg EE). The sample was recruited from five MS medical centers, and women had a mean age of ~30 years with a mean disease duration of ~3–4 years; baseline

disability was fairly low. The primary outcome of interest was the cumulative number of combined unique active lesions (CUALs), an accepted marker of inflammation, on brain magnetic resonance imaging (MRI) at 96 weeks. Secondary outcomes included the number of CUALs at 48 weeks, the annualized relapse rate from week 0–96, the proportion of women with sustained disability progression and adverse events. Overall, 99% of women completed 96 weeks of FU. The treatment completion rate for interferon β−1a was 90%, 88% and 92% for Groups 1, 2 and 3, respectively. The treatment completion rate for COC use was 76% for Group 2 and 73% for Group 3. The time at which treatment was discontinued was also comparable between study groups. The mean (median) duration of interferon β−1a treatment was 23.1 (24), 21.9 (24) and 23.8 (24) months in Groups 1, 2 and 3, respectively; and the mean (median) duration of COC use was 20.6 (24) months in Group 2 and 19.3 (24) months in Group 3. Reasons for interferon β−1a discontinuation included adverse events, disease progression, loss to FU and pregnancy; similar information on reasons for COC discontinuation were not reported for all discontinuers. The primary outcome only was analyzed using the intention-to-treat subgroup, which included all patients treated with at least one dose of interferon β−1a. Results showed the cumulative number of CUALs (*defined as new nonenhancing T2-weighted lesions or new gadolinium-enhancing T1-weighted lesions*) at week 96 varied by study group (0.98, 0.85 and 0.72 for Groups 1, 2 and 3, respectively), representing a relative reduction of 14.1% comparing Group 2 (20-mcg COC) versus 1 (no COC) (p= .24) and 26.5% comparing Group 3 (40-mcg dose COC) versus 1 (no COC) (p=.04); these findings were adjusted for age, number of gadolinium-enhancing lesions and baseline disability. No significant differences were observed at week 48. Further, no significant differences in the annualized relapse rate from week 0–96 or in sustained disability progression were observed between study groups after adjustment for confounders. Of note, although the incidence of interferon β−1a-related adverse events was similar between study groups as was the incidence of COC-related adverse events among the 20-mcg and 40-mcg COC groups (no details provided), one woman in the 20-mcg COC group prematurely discontinued COC use due to an episode of deep venous thrombosis (DVT); no other details about the woman or DVT episode were provided.

The first retrospective cohort study examined the effect of at least 1 year of continuous OC use (type not specified) before or after disease onset (DO) on disability, severity and annualized relapse rates among 132 women with RRMS before receiving disease-modifying treatment (DMT) [23]. Disability at the time of the study was measured by the Expanded Disability Status Scale (EDSS) [28], which ranges from 0 (*normal neurologic exam*) to 10 (*death due to MS*), and severity at the time of the study was measured by the MS Severity Score (MSSS) [29], which is based on the EDSS score but adjusted for disease duration. The sample included women from an outpatient clinic at a university hospital first examined in 1995–2010. All women had at least 2 years of disease duration (mean of 6.2 years), and none had been treated with steroids for at least 1 month. Women were categorized as never OC users (n=52), OC users only before DO (n=26) or OC users after DO (n=54), 83% of whom began OC use before DO. After adjustment for confounders (i.e., age at DO, disease duration, smoking status, age at menarche), OC users after DO had significantly (p<.05) lower EDSS and MSSS values versus never OC users. MSSS values were dichotomized, and

women with values <2.5 were considered to have a more benign disease course. After adjustment for confounders, OC users after DO had significantly (p<.05) increased odds of having a benign disease course versus never OC users and OC users only before DO combined [adjusted odds ratio (AOR)=2.97, 95% confidence interval (CI)=1.24, 6.54]. No association was found between OC group and annualized relapse rates.

The second retrospective cohort study also examined the effect of at least 1 year of continuous OC use before or after DO on disability, severity and annualized relapse rates among women with RRMS at onset [20]. The study specifically examined the effect of COCs and additionally included progression to SPMS as an outcome. Disability at the time of the study was measured by the EDSS [28], and severity at the time of the study was measured by the MSSS [29]. The sample included 174 women from an academic medical center with at least 1 year of disease duration (mean of 14.3 years); 59% had ever used DMT. Women were categorized as never COC users (n=63), COC users only before DO (n=33), COC users before and after DO (n=44) or COC users only after DO (n=34). Among COC users, the median duration of use was 7 years ranging from 1 to 32 years. COC users before and after DO had significantly (p<.05) less disability versus never users (EDSS=2.3±1.6 vs. 3.4±2.2, respectively). COC users only after DO also had lower disability scores (EDSS=2.5±1.6) versus never users, but findings were not statistically significant. Survival analysis adjusted for a wide range of confounders (i.e., age, disease duration, DMT use, age at menarche, parity) found a significantly lower probability of progression to SPMS in COC users before and after DO versus never COC users (p=.015) and in COC users only after DO versus never COC users (p=.008). Disease severity and annualized relapse rates did not significantly differ between groups. Last, among COC users before and after DO and only after DO combined (n=78), total duration of COC use after onset was significantly (p=.0005) associated with lower disability but not severity.

The cross-sectional study examined the effect of at least 3 months of OC use (type not specified) after DO on MS disease course [21]. The type of MS was not specified. Outcomes included self-reported worsening of symptoms and severity/disease progression calculated by dividing the level of disability measured by the Kurtzke scale (the predecessor of the EDSS) [30] by years of disease duration. The sample included 512 women from an outpatient clinic. Among OC users after DO (n=151), 14% reported worsening of symptoms; the proportion of non-OC users after DO reporting worsening of symptoms was not reported. For reasons not described, only a subset of women were included in the disease progression analysis (n=312), including only 60% of OC users after DO. In this analysis, disease progression did not differ significantly (p>.05) between four groups defined by OC use and/or pregnancy after DO (only OC use after DO, only pregnancy after DO, OC use and pregnancy after DO and neither OC use or pregnancy after DO).

4. Discussion

We identified four studies rated as having fair to poor quality that examined OC use among women with MS, all of which suggest that OCs do not negatively affect disease course [20–23]. Two retrospective cohort studies found no detrimental influence of at least 1 year of continuous OC use after DO on disability levels [20,23], both of which found less disability

among OC users compared with never users. Total duration of COC use after DO was also found to be significantly associated with lower disability in one study [20]. All four included studies examined the effect of OCs on some aspect of disease severity or progression with none finding a negative effect and two retrospective cohort studies suggesting a positive effect [20,23]. Three studies, including one RCT, examined the influence of OCs on relapse rates, none finding significant associations [20,22,23]. One RCT examined the effect of COC use among women taking interferon β−1a and found that the cumulative number of unique active brain lesions detected by MRI at 24 months was significantly lower among women taking 40-mcg COCs versus no COCs [22]. COCs were not harmful except that one woman taking low-dose COCs prematurely discontinued use due to a DVT that may or may not have been related to COC use. No studies were identified that examined the safety of other contraceptive methods or examined other outcomes of interest, including VTE or changes in bone mineral density, related to contraceptive use among women with MS.

This body of evidence has several limitations. OC use was self-reported by women and subject to recall error in two studies [20,21], and the type of OCs examined were not reported in two studies [21,23]. As some evidence from this review suggests that the total duration of OC use significantly reduces disability [20], it is limiting that two studies did not report on the total duration of OC use beyond the specified time period (e.g., 3 months, 1 year) [21,23]. In addition, the timing of OC use relative to outcome measurement was not reported in three studies, thus women may not have been using OCs at the time outcomes were assessed [20,21,23]. Further, the two retrospective cohort studies that reported beneficial effects of OCs may have observed lower disease disability and severity/progression among OC users because of a “healthy user” bias in which women with less severe disease chose to use OCs or needed contraception because they were healthy enough to engage in sexual activity. Additional studies would be needed to confirm the beneficial effects of OCs found in these studies. Other limitations of the studies in this body of evidence include samples of women from a single center [20,21,23], not describing the MS diagnostic criteria used [21,22] and not indicating if women were using therapeutic medications that may have impacted outcomes under investigation [21]. Last, the RCT that found beneficial effects of 40-mcg COCs among women on interferon β−1a may not be generalizable to women not taking this treatment, since it is unknown whether 40-mcg COCs enhance the effect of interferon β−1a or if interferon β−1a predisposes the immune system to potential positive effects of COCs.

Additional studies not meeting our inclusion criteria were identified that may provide relevant indirect evidence. Three case reports [31–33] were identified that describe episodes of cerebral venous thrombosis among women with MS. In one case report, two women aged 23 and 19 years taking OCs (type not reported) with last high dose corticosteroid use within 48 h and a lumbar puncture within 4–6 days experienced cerebral venous thrombosis [31]. OC use was considered a vascular risk factor, but the authors proposed that the lumbar puncture and high dose corticosteroids were the major contributory factors. In the second case report, one woman aged 46 years with no cerebrovascular risk factors other than COC use (35-mcg EE) was hospitalized where she was diagnosed as having MS and underwent lumbar puncture and received high doses of corticosteroids intravenously; the woman developed cerebral venous thrombosis and passed away [32]. The authors attributed the

outcome largely to the lumbar puncture which can slow venous flow and tear the venous sinuses predisposing one to develop a cerebral venous thrombosis, but also mentioned the possible role of high dose corticosteroids. In the third case report, a woman aged 35 years with a history of using OCs (type not reported) for approximately 8 years, no history of cigarette smoking and recent prednisone use experienced intracranial transverse and sigmoid sinus thromboses and, later, DVT of the calf [33]. In their concluding remarks, the authors discouraged COC use among MS patients with decreased mobility due to increased risk for DVT.

Six additional studies provide potentially relevant indirect evidence, five of which examined or described changes in MS symptoms related to cyclical hormonal changes [34–38] and one of which examined the effect of the pregnancy hormone estriol among women with MS [16]. Two prospective cohort studies, from the same institution but among different samples of COC users, examined MS symptoms over three cycles [34,38]. In the first cohort study (n=7), women reported significantly higher symptom scores for weakness, numbness and tiredness (out of 13 total symptoms) during the hormone-free interval compared with weeks COCs were taken daily [34]. In the second cohort study (n=22), women reported significantly higher symptom scores for weakness, vertigo, urinary symptoms and stiffness (out of 10 total symptoms) during the hormone-free interval compared with weeks COCs were taken daily [38]. Findings from both suggest a positive effect of the COC steroids on MS symptoms. Two cross-sectional studies by the same authors examined OC use among women with and without premenstrual exacerbation of MS symptoms [35,36]. Whereas the earlier report found significantly higher OC use among women reporting no influence of the premenstrual period on MS symptoms suggesting a protective effect [35], the later report found no difference in OC use between groups [36]. The fourth study, a case report, described the suppression of monthly exacerbations of MS symptoms through the use of norethynodrel (Enovid-E) for more than 2 years among a woman aged 36 years who only experienced exacerbations during onset of menstruation [37]. The last study providing indirect evidence was a cross-over trial examining the effect of estriol in 10 women with RRMS [16]. Compared with baseline, women treated with 8 mg/day of oral estriol for 6 months experienced significant decreases in gadolinium-enhancing lesions, a favorable immune response and improved cognition.

Evidence on the effect of pregnancy on MS disease course may also be relevant. MS typically stabilizes during pregnancy, with lower relapse rates versus prepregnancy, particularly during the third trimester when circulating levels of estrogens and progestins are highest; but aggravation of symptoms is often seen during the first 3 months postpartum when hormone levels drop [15]. The beneficial effect of pregnancy on MS disease course may also be related to changes in the immune system during pregnancy.

The exact mechanism through which hormones may exert a protective effect on MS disease course is not fully understood. In laboratory animals with experimental autoimmune encephalomyelitis, a spectrum of neurological disorders used to model MS [39], estrogens and progestins have shown antiinflammatory and neuroprotective effects [40,41]. It has also been suggested that estrogens could affect nerve conduction [15]. More research is needed to

better understand the effect of endogenous and exogenous hormonal exposures, including hormonal contraceptives, on MS prognosis.

No evidence was found examining the effect of combined hormonal contraceptives on VTE risk among women with MS. Data from population-based, matched cohort studies from the United Kingdom and Sweden suggest that compared with those without MS, MS patients have an approximately threefold increased risk of VTE [12] or DVT [13], with lower risk found among females than males in one study [VTE adjusted hazard ratio (AHR) = 2.28, 95% CI = 1.73, 3.00 for females vs. AHR=3.16, CI=2.18, 4.57 for males] [12]. VTE risk also varies by MS type, with increased risk of DVT among those with progressive forms of the disease [relative risk (RR) = 3.57, CI=1.95, 6.56 for PPMS, RR=3.41, CI=2.45, 4.75 for SPMS, and RR=2.16, CI=1.21, 3.87 for RRMS] [13]. Among MS patients (females and males combined), risk factors for VTE included history of varicose veins, a prior VTE, obesity and recent (past 6 months) major trauma, spasticity, disability and corticosteroid use [12]. In this study, immobility was not examined separately but was considered as part of disability and spasticity which both interfere with normal movement. Immobility is a known major risk factor for thrombosis [42] and likely plays an important role leading to the increased risk of VTE among MS patients, especially given the elevated risks of DVT among MS patients with progressive forms of the disease [13].

Another theoretical concern for which no evidence was found was the impact of progestin-only injectables, which may be associated with small but reversible changes in bone mineral density in the general population [43], on bone mineral density and fracture risk among women with MS. Bone health among MS patients may be compromised due to disease-related disability, immobility, use of corticosteroids and fracture risk high due to poor bone health and increased probability of falls secondary to weakness and ataxia [44]. Data from a population-based, matched-cohort study from the United Kingdom suggest that compared with controls, MS patients have a 1.2-fold increased risk of any fracture after adjustment, with higher risk for hip fracture (AHR=2.79, CI=1.83, 4.26) and osteoporotic fracture (AHR=1.35, CI=1.13, 1.62), defined as a fracture of the radius/ulna, vertebrae, femur, hip, humerus, pelvis or ribs [45]. Among females aged 18–49 years with MS specifically, the median 5-year risk of osteoporotic fracture was 1.6% [45].

In conclusion, evidence from one RCT rated as having fair quality, two retrospective cohort studies rated as having fair quality and one cross-sectional study rated as having poor quality suggests that use of COCs or OCs (type not specified) among women with MS does not worsen the clinical course of disease (body of evidence grading Level I, fair to Level II-3, poor). No evidence was identified that examined the safety of other contraceptive methods or examined other outcomes of interest (VTE, changes in bone mineral density) related to contraceptive use among women with MS. The evidence base would be strengthened by the development of additional studies with strong designs that examine a broader range of contraceptive methods and outcomes, report the timing of contraceptive use relative to outcome measurement and include women with different types of MS. The information in this review was presented to an expert panel in August 2015 at a meeting held by the CDC and will be incorporated into the forthcoming update of the US MEC.

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Table 1

Evidence table for OC use and clinical course of disease among women with MS

Author, year, support, country	Study design, population	Contraceptive use	Outcome	Results	Quality, strengths, weaknesses
Poser, 1979 [24] Poser, 1982 [21] German Research Foundation Germany	Cross-sectional Women with MS from an outpatient clinic (*n*=512) 387 of childbearing age at time of survey (20–50 years) 312 included in disease progression analysis	OC use after onset, at least 3 months continuously (*n*=151) 4 comparison groups in disease progression analysis: (a) only OC use after onset (*n*=58); (b) only pregnancy after onset (*n*=42); (c) OC use and pregnancy after onset (*n*=33); and (d) neither OC nor pregnancy after onset (*n*=179) Measured by participant survey	Worsening of symptoms; measured by self-report Disease progression or severity calculated by dividing disability measured by Kurtzke scale by years of disease duration; measured during medical exam and evaluated by computer	21/151 (14%) OC users after onset had worsening of symptoms Disease progression did not differ between groups (p>.05)	II-3, poor Strengths High participation rate (85%) Large sample size Disability assessed during medical exam and classified using objective scale Excluded women with acute bout at time of survey Included women too disabled to travel to clinic via home visitation Weaknesses Single center MS diagnosis criteria unknown Type of OC unknown OC use self-reported Timing of OC initiation and total duration of use unknown Timing of OC use relative to outcome assessment unknown Worsening of symptoms self-reported Proportion of non-OC users after onset with worsening of symptoms NR Only 91/151 (60%) OC users after onset were included in disease progression analysis Use of therapeutic medications NR
Sena, 2012 [23] Bayer Health Care and Biogen Idec Portugal	Retrospective cohort Women with RRMS before receiving DMT (*n*=132) Outpatient clinic at university hospital; women first examined 1995–2010 Age distribution of entire sample NR At least 2 years duration ofdisease; mean (SD) duration=6.2 (5.1) years None had been treated with steroids for at least 1 month	Never OC use (*n*=52) OC use only before onset, at least 1 year continuously (*n*=26) OC use after onset, at least 1 year continuously (*n*=54); 45/54 (83%) began OC use before onset Abstracted from clinic records	Disability measured by EDSS, severity measured by MSSS, annualized relapse rate; abstracted from clinic records	OC users after onset had significantly (p<.05) lower EDSS and MSSS values vs. never users after adjustment for age at DO, disease duration, smoking status and age at menarche OC users after onset had increased odds of having benign disease course (MSSS<2.5) vs. never and only before onset users combined after adjustment for confounders (AOR: 2.97, 95% CI: 1.24–6.54) No association between OC group and annualized relapse rates after adjustment for confounders	II-2, fair Strengths High participation rate among eligible women (100%) Large sample size MS diagnosed according to revised McDonald criteria Women were not on DMT Clinical outcomes abstracted from clinic records Disability and severity classified using objective scales OC use confirmed by prescription adherence for ≥12 continuous months Adjusted for wide range of confounders Weaknesses Single center Type of OC unknown Total duration of OC use unknown Timing of OC use relative to outcome assessment unknown
Gava, 2014 [20]	Retrospective cohort Women with RRMS at onset (n=174); 141 with RRMS; 33 with SPMS	Never COC use (n=63) COC use only before onset,	Disability measured by EDSS, severity measured by MSSS,	COC users before and after onset had less disability (EDSS=2.3±1.6) vs. never users (EDSS=3.4±2.2)	II-2, fair Strengths

Author, year, support, country	Study design, population	Contraceptive use	Outcome	Results	Quality, strengths, weaknesses
Source of support not stated Italy	RRMS; 33 with SPMS Academic medical center Age distribution of entire sample NR At least 1 year duration of disease; mean (SD) duration=14.3 (9.8)years 59% had ever used DMT Median duration of COC use=7 years, range=1–32 years	at least 1 year continuously (*n*=33) COC use before and after onset, at least 1 year continuously (*n*=44) COC use only after onset, at least 1 year continuously (*n*=34) Measured via patient interview	annualized relapse rate, progression to SPMS; abstracted from clinic records	(p<.05); COC users only after onset had less disability (EDSS=2.5±1.6) vs. never users, but NS Survival analysis found significantly lower probability of progression to SPMS in COC users before and after onset vs. never users (p=.015) and COC users only after onset vs. never users (p=.008), after adjustment for age, disease duration, DMT use, age at menarche, and parity Severity and annualized relapse rate did not differ between groups Among COC users before and after onset and COC users only after onset combined (*n*=78), total duration of COC use after onset was significantly (p= .0005) associated with lower disability but not severity	High participation rate among eligible women (100%) Large sample size MS diagnosed according to revised McDonald criteria Clinical outcomes abstracted from clinic records Disability and severity classified using objective scales Type of OC known (i.e., COC) Target sample size determined by power calculations Examined differences by total duration of COC use Adjusted for wide range of confounders in survival analysis Weaknesses Single center COC use self-reported Timing of OC use relative to outcome assessment unknown
Pozzilli, 2015 [22] Grants from Ateneo and Facolta, Sapienza University of Rome and the Italian Federation of Multiple Sclerosis Italy	RCT Women with RRMS(*n*=149) taking interferon β−1a subcutaneously 5 MS medical centers Mean age~30 years Mean disease duration~3–4 years Baseline disability [mean (range) EDSS=1.5 (0,5)] FU for 24 months	Group 1: no COC (*n*=50); 90% continued interferon β −1a treatment; 100% completed FU Group 2: EE 20 mcg + desogestrel 150 mcg (*n*=50); 88% continued interferon β−1a treatment; 76% completed COC use; 98% completed FU Group 3: EE 40 mcg + desogestrel 125 mcg (*n*=49); 92% completed interferon β−1a treatment; 73% completed COC use; 100% completed FU	Cumulative number of CUALs on brain MRI at weeks 48 and 96 (marker of inflammation), quantified by 2 trained physicians using semi-automated method; standard MRI protocol was followed Annualized relapse rate from week 0 to 96 Proportion of patients with sustained disability progression, defined as a sustained increase for 6 months of at least 1 point in the EDSS score or increase of≥1.5 points if baseline EDSS score was 0 Adverse events	Cumulative number of CUALs at week 96 (primary outcome) was 0.98 (95% CI 0.53, 0.91), 0.84 (95% CI 0.66,1.02), and 0.72 (95% CI 0.53, 0.91) for Groups 1,2 and 3, respectively; represents relative reduction of 14.1% between Group 2 vs. 1 (p=.24) and 26.5% between Group 3 vs. 1 (p=.04), after adjustment for age, number of gadolinium-enhancing lesions, and baseline disability; significant differences not observed at 48 week No significant differences in annualized relapse rate from week 0 to 96 between groups, after adjustment for age and number of relapses in prior 2 years (mean ± SD=0.33± 0.08, 0.44±0.09, and 0.32± 0.08 for Groups 1, 2 and 3, respectively No significant differences in sustained disability progression comparing Group 2 vs. 1 (HR=1.36, 95% CI=0.72, 2.58) or comparing Group 3 vs. 1 (HR=0.97, 95% CI=0.49, 1.92), after adjustment for age and baseline disability	I, fair Strengths Multicenter Large sample size Randomization computer-generated Allocation sequence concealed Physicians assessing outcomes blinded to group allocation 99% completed 96 weeks of FU High and comparable interferon β−1a treatment completion rates Disability classified using objective scale Clinical outcomes measured by brain MRI Lesions quantified by two physicians for concurrence Excluded women with relapses or steroid intake within prior 60 days and OC users within prior 30 days Type of OC known Target sample size determined by power calculations Intention-to-treat analysis performed for primary outcome Adjustment for wide range of confounders Long FU period Weaknesses MS diagnosis criteria unknown Moderate COC use completion rates Generalizability to women not taking interferon β −1a unknown

Author, year, support, country	Study design, population	Contraceptive use	Outcome	Results	Quality, strengths, weaknesses
				Rate of COC discontinuation due to adverse events was similar between Groups 2 and 3, but 1 patient in Group 2 prematurely discontinued COC use due to episode of DVT	COC adherence assumed Study not powered to detect differences in annualized relapse rate or sustained disability progression

R, hazard ratio; NR, not reported; NS, not statistically significant; SD, standard deviation; SPSM, secondary-progressive multiple sclerosis.